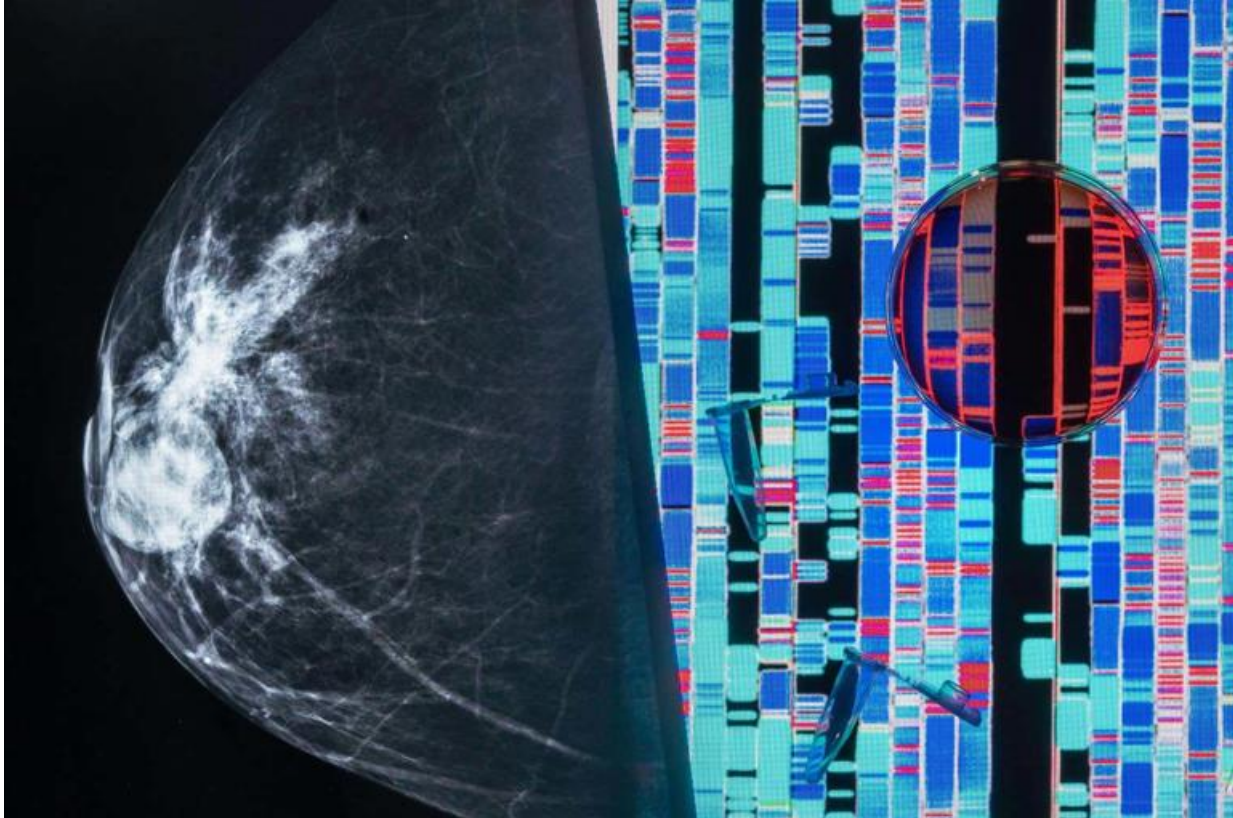


MEDICAL RESEARCH VOL 5

Cancer atlas reveals how tumors evolve inside the body



Mapping tumours and the genetic changes within them could help develop new cancer treatments Sipra Press/Alamy

We now have some of the most detailed maps ever made of several cancers, along with new tools and methods for analysing them. The findings come from an initiative to map cancers called the [Human Tumor Atlas Network](#), and provide clues about how cancers form, evolve and become resistant to treatment.

[Read more](#)

Why viewing cancer as an ecosystem could lead to better treatments

Cancer develops when genetic mutations spur cells to grow and proliferate uncontrollably. Much of what we know about the disease comes from genetically analysing tumours. Until recently, we could only do this by combining and

analysing all the genetic data in a tumour sample at once, making it impossible to identify individual cell types.

But tumours aren't monolithic. "They're complex, like ecosystems that consist of not just tumour cells, but also immune cells, endothelial cells and other support cells," says [Daniel Abravanel](#) at the Dana-Farber Cancer Institute in Boston.

Thanks to the advent of more sophisticated tools, a team of researchers has now been able to identify individual cells or determine their functions in tumours from nearly 2000 people with 20 different kinds of cancer.

As part of the work, [Li Ding](#) at Washington University in St. Louis, Missouri, and her colleagues mapped 131 tumour regions from 78 people with cancer types that show up in the breasts, the colon, the pancreas, the kidneys, the uterus and the bile ducts that connect the liver and gall bladder to the small intestine. They used a technique called single-cell sequencing to measure which genes were turned on or off in each cell of a tumour sample.

The researchers also viewed tissue samples under powerful microscopes to determine the location and structure of cells. Next, they built 3D models of tumours, showing how cells within them are organised and interact. They found that, within tumours, cancer cells form distinct clusters known as microregions. The researchers then grouped these areas based on similar genetic alterations, such as high or low immune cell activity. Evolution within the genetic activity of cells in microregions appears to be a major factor in cancers becoming resistant to treatments.

Cancer mystery as cases rise among younger people around the world

The number of people under 50 with cancer is increasing in many countries and for many different tumour types. Why this is occurring isn't entirely clear, but it may be due to some aspects of modern life

Further research from the Human Tumor Atlas Network suggests that multiple cells can sometimes coordinate to form colon cancer. "For decades, the consensus in the field has been that a tumour originates from a single cell," says [Doug Winton](#) at the University of Cambridge.

Winton and his colleagues used mice that were genetically engineered so their cells changed colour when they became cancerous. This made it possible to identify and track tumours as they formed in the guts of the animals. The researchers found that about 40 per cent of colon tumours originated from multiple cells, which cooperated to outcompete neighbouring cells.

A separate group of researchers led by [Ken Lau](#) at Vanderbilt University in Tennessee also [identified biomarkers](#) for monitoring tumour evolution. Naturally occurring mutations create permanent genetic changes in tissue, which allowed the researchers to reconstruct the sequence of events, creating a molecular timeline of each tumour's growth.

Using this approach, they analysed early precursors of colon cancer in mice and people and found that up to 30 per cent had a multicellular origin. The best predictor we currently have for determining whether a precancerous lesion in the colon will become cancerous is its size, says Lau. Understanding how colon cancer forms can improve our ability to screen precancerous lesions and detect cancer earlier, he says.

Read more

Are you truly healthy? These new tests provide the ultimate check-up

The cancer mapping project uncovered some surprises. Abravanel and his colleagues collected 67 tumour biopsies from 60 people with [metastatic breast cancer](#), meaning it had spread to other organs, such as the liver, brain and lungs. They found that samples collected from the same participant at different time points were genetically very similar. "You would expect to see different mutations evolve over time," says Abravanel.

As part of the project, researchers led by [Ben Raphael](#) at Princeton University [created an algorithm](#) that quantifies the proportion of cancerous and non-cancerous cells in a tumour and investigates how these cells interact, which can also help discern how a tumour is growing.

Together, these discoveries bring us a step closer to understanding how cancer forms and evolves, which, in turn, could improve treatment. Abravanel says this could help in his clinical practice as well: "We try as best we can to match the

right treatment to the right patient, but largely we aren't able to, for individual cases, pull out what the best therapy would be at that moment in time."

Journal reference

Nature [DOI: 10.1038/s41586-024-08087-4](https://doi.org/10.1038/s41586-024-08087-4)

Journal reference

Nature [DOI: doi.org/10.1038/s41586-024-08053-0](https://doi.org/10.1038/s41586-024-08053-0)

Unmasking the 'golden blood' type: the rare Rh-null that could be in one out of every six million

This rarest of blood types is defined by an unusual Rh factor that is neither negative nor positive. It is designated as Rh-null by scientists. Blood consists of various molecules, including proteins or blood group antigens. Using these, various systems can be established. To date, 32 combinations have been discovered.

Understanding basic blood groups and their significance

To understand better, let's go over the basic blood groups and what defines them. **The O blood group lacks any antigens while group A, B, and AB are successively characterized by antigen A, B, and AB.** Noteworthy are the antibodies, produced in response to antigens absent from the blood cells:

- Group O produces anti-A and anti-B antibodies,
- Group A generates anti-B antibodies,
- Group B forms anti-A antibodies,
- Group AB does not produce any antibodies.

Apart from antigen A and B, there's also the **antigen D**. This antigen is present in 85% of people (those with an Rh-positive blood group). Similarly, its absence characterizes the Rh-negative blood group. **Of the 61 known blood group antigens**, the negative/positive distinction refers solely to antigen D. During blood transfusion, people with Rh- factor can donate plasma to those with **both Rh+ and Rh- factors**. Those carrying a positive factor can only donate to individuals with the identical factor. Rh- is particularly sought after because it can be given to anyone, due to the absence of the aforementioned antigens.

Exploring the phenomenon of "Golden Blood"

"Golden blood" is not golden in literal terms, but it carries a unique characteristic that makes it fit for royalty. Specifically, **this type of blood lacks any of the 61 Rh antigens**. Its distinctive factor is indeterminable, thereby earning it the 'null' label. The first individual diagnosed with this condition, in 1961, was an Australian woman. Scientists speculate that **this blood type could be present in one person out of every six million!** So far, only 43 people have been confirmed to possess this blood type.

We know that blood characteristics are hereditary, and the same holds true in this case. Research points to the appearance of this condition being due to the **autosomal recessive inheritance pattern** (both parents pass on a copy of the mutated gene). Such individuals can donate blood to any group, but they can only receive blood from people with the same condition. Doctors thus advise them to donate and store blood for themselves in an emergency.

Microglia digest large Alzheimer's plaques by spitting enzymes at them, preclinical study finds

Microglia digest large Alzheimer's plaques by spitting enzymes at them, preclinical study finds

Immune cells in the brain called microglia can partially break down large amyloid plaques characteristic of Alzheimer's disease by latching on to them, forming a sort of external stomach and releasing digestive enzymes into the space, according to a preclinical study by Weill Cornell Medicine investigators. The findings could ultimately lead to therapies that boost the ability of microglia to break down amyloid plaques.

The study, [published](#) in *Cell Reports*, shows that the breakdown process, called digestive exophagy, may also help explain seemingly contradictory reports that microglial cells can spread plaques in Alzheimer's.

Microglia are scavengers that move around the brain, consuming small bits of cellular trash like microbes, dead cells and debris. They do this by wrapping themselves around the substance and encapsulating it in a vesicle. The vesicle then ferries the cargo to a membrane-bound organelle within the cell called a lysosome that is filled with digestive enzymes.

Researchers suspected that microglia could also break down amyloid plaques, but it was unclear how the cells could consume these massive aggregates, which are much bigger than they are.

"We found that the cells basically attach a lysosome onto a large plaque, and they expel enzymes into the space that can digest the amyloid," said Frederick Maxfield, M.S. '73, Ph.D. '77, the Vladimir Horowitz and Wanda Toscanini Horowitz Distinguished Professor in Neuroscience at Weill Cornell Medicine.

Thinking about how microglia could eat something very large in the brain reminded Maxfield of macrophages, which are immune cells that do a similar scavenging job throughout the rest of the body. In previous work, his lab found that when macrophages run into something too big to wrap around—such as a clump of lipoproteins in an atherosclerotic plaque—they form a kind of external stomach that digests the clump bit-by-bit with lysosomal enzymes.

To see whether microglia do the same thing, the team, led by Santiago Solé-Domènech, assistant professor of research in biochemistry, and Rudy Jaquet, a

Weill Cornell Graduate School of Medical Sciences doctoral student in the Maxfield lab at the time of the study, first turned to cultured mouse microglial cells.

In a series of experiments, they showed that when one of these cells touched a large amyloid plaque in a lab dish, it formed a partially sealed space around the aggregate, like macrophages do. "The microglial lysosomes secreted their contents, and they acidified the region to activate the enzymes that digest the amyloid deposits," Maxfield said.

Next, the team analyzed a mouse model of Alzheimer's disease. Co-author Marie-Ève Tremblay, a professor at the University of Victoria, used electron microscopy to image brain samples and saw pockets formed by microglial cells on plaques that are characteristic of digestive exophagy. She also observed a lysosomal enzyme in the space.

Microglia degrade plaques, but they are also known to contribute to the formation of plaques. This paradox was intriguing, and the researchers wondered if digestive exophagy could play a role in spreading Alzheimer's plaques to other parts of the brain.

In previous research, the team loaded cultured microglial cells with smaller bits of plaques, called amyloid fibrils. When the researchers did this, the cells took a long time to break them down in internal lysosomes, and they eventually spit out the difficult-to-digest pieces.

In the current study, the team also loaded microglia with amyloid fibrils, but they put the cells near big plaques. "We saw that the microglia would try to eat the plaques from the outside, but because they were already loaded with amyloid fibrils, they would secrete these smaller pieces toward the plaque," Sole-Domenech said.

Microglia cells can move quickly throughout the brain, so they can easily move to a different location after digesting a plaque. "So, if microglial cells start to do digestive exophagy on another large object, they could release those seeds of amyloid fibrils into a new area," Maxfield said.

Now that the team has observed digestive exophagy in mice, they will assess whether human cells also use this process. Human induced pluripotent stem cells can mature into many types of cells, including microglia, which would give the researchers the opportunity to conduct a wide range of experiments.

More information: Rudy G. Jacquet et al, Microglia degrade Alzheimer's amyloid-beta deposits extracellularly via digestive exophagy, *Cell Reports* (2024). DOI: [10.1016/j.celrep.2024.115052](https://doi.org/10.1016/j.celrep.2024.115052)

Provided by Cornell University

Study reveals gut bacteria's role in food addiction and obesity

Compulsive eating and [obesity](#) may be triggered by a specific gut bacteria, suggests a new study.

The breakthrough may lead to new treatments for the "growing" problem of food addiction and other eating disorders, say scientists.

An international research team has identified specific bacteria in the gut that are associated with both humans and mice developing an addiction to food that can lead to obesity.

The researchers also identified bacteria that play a beneficial role in preventing food addiction.

Professor Elena Martín-García of Pompeu Fabra University, Spain, said: "A number of factors contribute to food addiction, which is characterized by loss of control over food intake and is associated with obesity, other eating disorders and alterations in the composition of bacteria in the gut – the gut microbiome.

"Until now, the mechanisms underlying this behavioral disorder were largely unknown."

The research is due to be presented on Thursday at the Federation of European Neuroscience Societies (FENS) Forum in Vienna, Austria, and will be published simultaneously in the [journal Gut](#).

[Dr. Rafael Maldonado](#), who leads the Laboratory of Neuropharmacology at Pompeu Fabra University, said: "These results from our study may allow us to identify new biomarkers for food addiction and, most importantly, to evaluate whether the beneficial bacteria could be used as potential new treatments for this obesity-related behavior, which, at present, lacks any effective therapeutic approaches."

"Potential new treatments could involve using beneficial bacteria and dietary supplementation."

Prof. Martín-García used the Yale Food Addiction Scale (YFAS 2.0) to diagnose food addiction in mice and humans.

It contains 35 questions for people to answer, and these can also be grouped into three criteria for use in mice: persistent food-seeking, high motivation to obtain food, and compulsive behavior.

She and her colleagues investigated the gut bacteria in mice who were and were not addicted to food and found an increase in bacteria belonging to a group called the Proteobacteria phylum and a decrease in bacteria belonging to the Actinobacteria phylum in the food-addicted mice.

Those mice also had a decrease in the amount of another type of bacteria called Blautia from the Bacillota phylum.

The researchers used the YFAS to classify 88 patients into those who were addicted or not addicted to food.

Similar to the findings in mice, decreases in Actinobacteria phylum and Blautia were seen in those who were food-addicted and increases in Proteobacteria phylum.

Further analysis showed how the findings in humans correlated with those in mice.

Prof. Martín-García said: "The findings in both mice and humans suggested that specific microbiota could be protective in preventing food addiction.

"In particular, the strong similarities in the amount of *Blautia* underlined the potential beneficial effects of this particular gut bacteria.

"Therefore, we investigated the protective effects of oral administration of lactulose and rhamnose, which are non-digestible carbohydrates known as 'prebiotics' that can increase the amount of *Blautia* in the gut.

"We did this in mice and found that it led to an increase in the abundance of *Blautia* in mice faeces in parallel with dramatic improvements in food addiction.

"We saw similar improvements when we gave the mice a species of *Blautia* called *Blautia wexlerae* orally as a probiotic.

"The gut microbiota signatures in both mice and humans suggest possible non-beneficial effects of bacteria belonging to the Proteobacteria phylum and potential protective effects of increasing the abundance of Actinobacterial and Bacillota against the development of food addiction."

Prof. Martín-García says the findings show how bacteria in the gut influence brain function and vice versa.

She said: "We have demonstrated for the first time a direct interaction between the gut composition and brain gene expression, revealing the complex and multifactorial origin of this important behavioural disorder related to obesity.

"Understanding the crosstalk between alterations in behaviour and bacteria in the gut constitutes a step forward for future treatments for food addiction and related eating disorders."

Prof. Martín-García also described work investigating how microRNAs (miRNAs) – small, single-stranded molecules that regulate gene expression and contribute to almost any cellular process – are involved in food addiction.

She says changes in the expression of miRNAs may be involved in the mechanisms underlying the disorder.

The researchers used a technique called Tough Decoy (TuD) to inhibit specific miRNAs in the medial prefrontal cortex (mPFC) of brains of mice in order to produce mice that were vulnerable to developing food addiction.

They explained that the mPFC is the part of the brain involved in self-control and decision-making.

They found that inhibition of miRNA-29c-3p promoted persistence of response and enhanced the vulnerability of the mice to develop food addiction.

Inhibiting another miRNA called miRNA-665-3p promoted compulsive behaviour and vulnerability to food addiction.

Dr. Maldonado said: "These two miRNAs could act as protective factors against food addiction.

"This helps us to understand the neurobiology of the loss of eating control, which plays a crucial role in obesity and related disorders.

"To understand these mechanisms further, we are now exploring how the gut microbiota and miRNA expression in the brain interact in mice."

Chair of the FENS communication committee [Dr. Richard Roche](#) welcomed the findings.

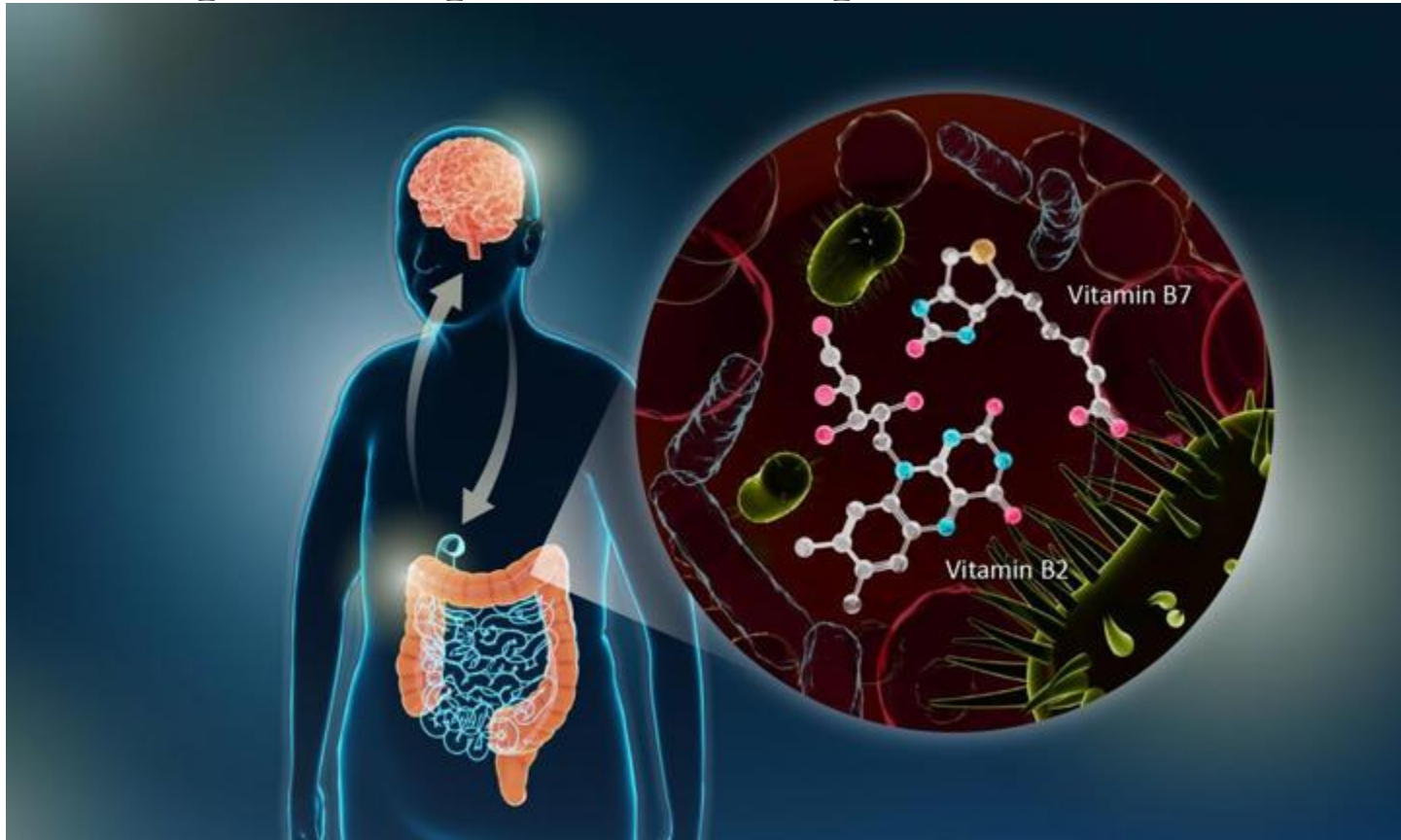
Dr. Roche, of Maynooth University, Ireland, who was not involved in the research, said: "Compulsive eating and food addiction is a growing problem worldwide.

"There are many factors that contribute to it, in particular the environment that people live in and the availability of certain types of food.

"However, we've known for some time that there are probably contributing factors for eating disorders and the research by Professor Martín-García and colleagues shows how the different types of bacteria in the gut have an impact on brain function and vice versa in humans and mice."

He added: "This understanding opens the way to developing potential new treatments for eating disorders, and we look forward to seeing more research in this area."

Link between gut microbiota and Parkinson's disease points to potential therapeutic route



In Parkinson's disease, a reduction in the gut bacteria of genes responsible for synthesizing the essential B vitamins B2 and B7 was found. Credit: Reiko Matsushita© Provided by Medical Xpress

A study led by Nagoya University Graduate School of Medicine in Japan has revealed a link between gut microbiota and Parkinson's disease (PD). The researchers found a reduction in the gut bacteria of genes responsible for synthesizing the essential B vitamins B2 and B7.

They also identified a relationship between the lack of these genes and low levels of agents that help maintain the integrity of the intestinal barrier. This barrier prevents toxins from entering the bloodstream, which causes the inflammation seen in PD. Their findings, [published](#) in *npj Parkinson's Disease*, suggest that treatment with B vitamins to address these deficiencies can be used to treat PD.

PD is characterized by a variety of physical symptoms that hinder daily activities and mobility, such as shaking, slow movement, stiffness, and balance problems. While the frequency of PD may vary between different populations, it is estimated to affect approximately 1-2% of individuals aged 55 years or older.

Various physiological processes are heavily influenced by the microorganisms found in the gut, which are collectively known as gut microbiota. In ideal conditions, gut microbiota produce SCFAs and polyamines, which maintain the intestinal barrier that prevents toxins entering the bloodstream. Toxins in the blood can be carried to the brain where they cause inflammation and affect neurotransmission processes that are critical for maintaining mental health.

To better understand the relationship between the microbial characteristics of the gut in PD, Hiroshi Nishiwaki and Jun Ueyama from the Nagoya University Graduate School of Medicine conducted a metanalysis of stool samples from patients with PD from Japan, the United States, Germany, China, and Taiwan.

They used shotgun sequencing, a technique that sequences all genetic material in a sample. This is an invaluable tool because it offers researchers a better understanding of the microbial community and genetic makeup of the sample.

They observed a decrease in the bacterial genes responsible for the synthesizing of riboflavin (vitamin B2) and biotin (vitamin B7) in patients diagnosed with PD. Riboflavin and biotin, derived from both food and gut microbiota, have anti-inflammatory properties, which may counteract the neuroinflammation seen in diseases like PD.

B vitamins play crucial roles in the metabolic processes that influence the production and functions of short-chain fatty acids (SCFAs) and polyamines, two agents that help maintain the integrity of the intestinal barrier, preventing toxins entering the bloodstream. An examination of fecal metabolites revealed decreases of both in patients with PD.

The findings indicate a potential explanation for the progression of PD. "Deficiencies in polyamines and SCFAs could lead to thinning of the intestinal mucus layer, increasing intestinal permeability, both of which have been observed in PD," Nishiwaki explained.

"This higher permeability exposes nerves to toxins, contributing to abnormal aggregation of alpha-synuclein, activating the immune cells in the brain, and leading to long-term inflammation.

"Supplementation therapy targeting riboflavin and biotin holds promise as a potential therapeutic avenue for alleviating PD symptoms and slowing disease progression."

The results of the study highlight the importance of understanding the complex relationship among gut microbiota, metabolic pathways, and neurodegeneration. In the coming years, therapy could potentially be customized based on the unique microbiome profile of each patient. By altering bacterial levels in the microbiome, doctors can potentially delay the onset of symptoms associated with diseases like PD.

"We could perform gut microbiota analysis on patients or conduct fecal metabolite analysis," Nishiwaki said. "Using these findings, we could identify individuals with specific deficiencies and administer oral riboflavin and biotin supplements to those with decreased levels, potentially creating an effective treatment."

More information: Hiroshi Nishiwaki et al, Meta-analysis of shotgun sequencing of gut microbiota in Parkinson's disease, *npj Parkinson's Disease* (2024). [DOI: 10.1038/s41531-024-00724-z](https://doi.org/10.1038/s41531-024-00724-z)

Provided by Nagoya University

Alzheimer's can be spread BETWEEN humans: Pioneering study reveals at least five people have 'caught' memory-robbing illness - as scientists warn hundreds more may be 'at risk'

- **Children were given growth hormones and later developed early-onset dementia**
- **Alzheimer's is caused by a toxic amyloid-beta protein building up in the brain**
- **Did you or anyone you know get the injections as a child? We want to hear from YOU - get in touch: Health@dailymail.com**

[Alzheimer's](#) can spread between humans, a groundbreaking study revealed today.

Experts have found evidence of at least five people 'catching' the memory-robbing disorder from now-banned hormone treatments.

The patients were among 1,848 people injected with growth hormones riddled with toxic amyloid-beta protein 'seeds', or prions, as children.

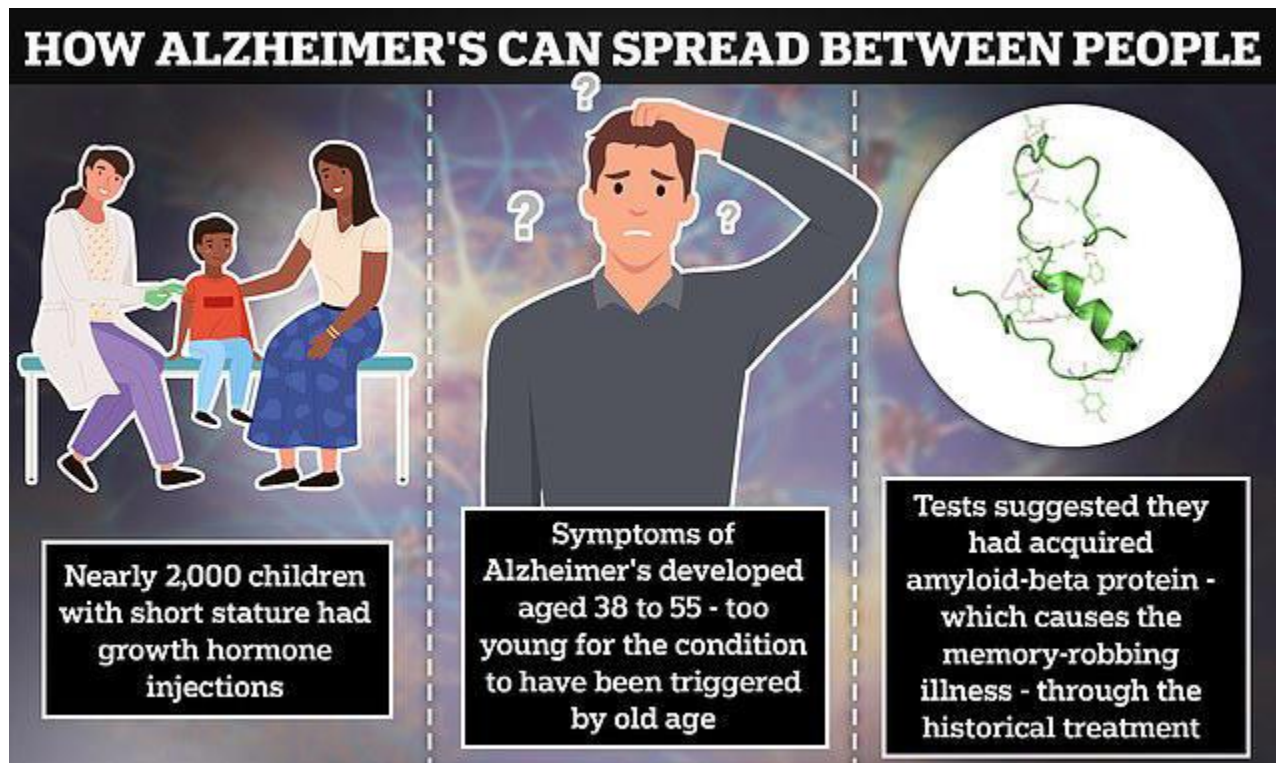
All five came down with the same rare early-onset form of the devastating dementia condition.

Others who received the same treatment are now considered 'at risk'.

Between 1958 and 1985, abnormally short children in the UK and the US were given hormones harvested from cadavers to help spur their growth.

The technique was then banned and doctors instead used synthetic hormones after it emerged that some batches were contaminated with prions that led to a fatal and incurable brain disorder called Creutzfeldt-Jakob disease (CJD). CJD itself is closely related to 'mad cow' disease.

Academics now believe other medical and surgical procedures might carry a risk of spreading Alzheimer's as prions — which accumulate in the brain and kill neurons — can survive hospital sterilisation methods.



Five patients were among 1,848 injected with growth hormones infected with toxic amyloid-beta protein 'seeds' as children. All five came down with the same rare early-onset form of the devastating dementia condition. Others who received the same treatment are now considered 'at risk' © Provided by Daily Mail

As prions accumulate in the brain, the NHS says plaque deposits may appear in the brain. Abnormal build-ups of proteins in and around neurons is thought to be what causes Alzheimer's.

Professor John Collinge, of University College London, said action must be taken to prevent accidental transmission in the future.

He said: 'These patients were given a specific and long-discontinued medical treatment which involved injecting them with material now known to have been contaminated with disease-related proteins.'

'We are now planning to look at ways of destroying prions from surgical equipment, as they can resist normal decontamination methods.'

Scientists create blood test for Alzheimer's

A pinprick blood test has been developed which hopes to determine a person's chances of developing dementia in the future.

The home-test kit, developed by the charity FoodfortheBrain.org, measures blood sugar, vitamin D, omega-3 and B vitamin status, as potentially modifiable risks for dementia.

People will then be given a risk score and diet advice on how to reduce it, as part of a global prevention study.

The charity hopes to enrol a million people worldwide, making it the largest 'citizen science' global prevention initiative.

Founder Patrick Holford said: 'Alzheimer's is a preventable, but not reversible disease. Less than one in a hundred cases are directly caused by genes.

'Prevention is entirely possible if you can identify who is at risk early enough and encourage the right diet and lifestyle changes.'

Higher levels of omega-3, from foods such as oily fish, and the sunshine vitamin, vitamin D, have also been linked to a lower risk of the disease.

Participants will be asked to take an online cognitive function test before being sent the Dementia Risk Index functional Test to do at home, which measures the levels of each risk factor. Both test scores will then be analysed and tracked over time.

Alzheimer's was previously believed to come in two forms — a 'sporadic' variant suffered by thousands of people over the age of 65, which is by far the most common, and a genetic early-onset type that runs in families.

The UCL scientists say they have now identified a third variant, which is slightly different from the others and very rare, which can be passed from one person to another.

Batches of the infected growth hormone were stored in a Department of Health archive as a dried powder.

UCL scientists were allowed to test the decades-old powder on mice and found it triggered the production of Alzheimer's-causing proteins.

However, Professor Collinge said the at-risk group is extremely small — made up of patients who have had certain neurosurgical procedures, tissue transplantation or organ donation.

He said: 'There is a risk group out there. Those who were given the infected growth hormone were all notified many years ago that they were at risk of developing CJD.

'There is now a possible risk of them developing Alzheimer's. But these risks are not possible to quantify at the moment.'

Researchers are currently monitoring the patients to study what is happening in their brains and catch any problems early.

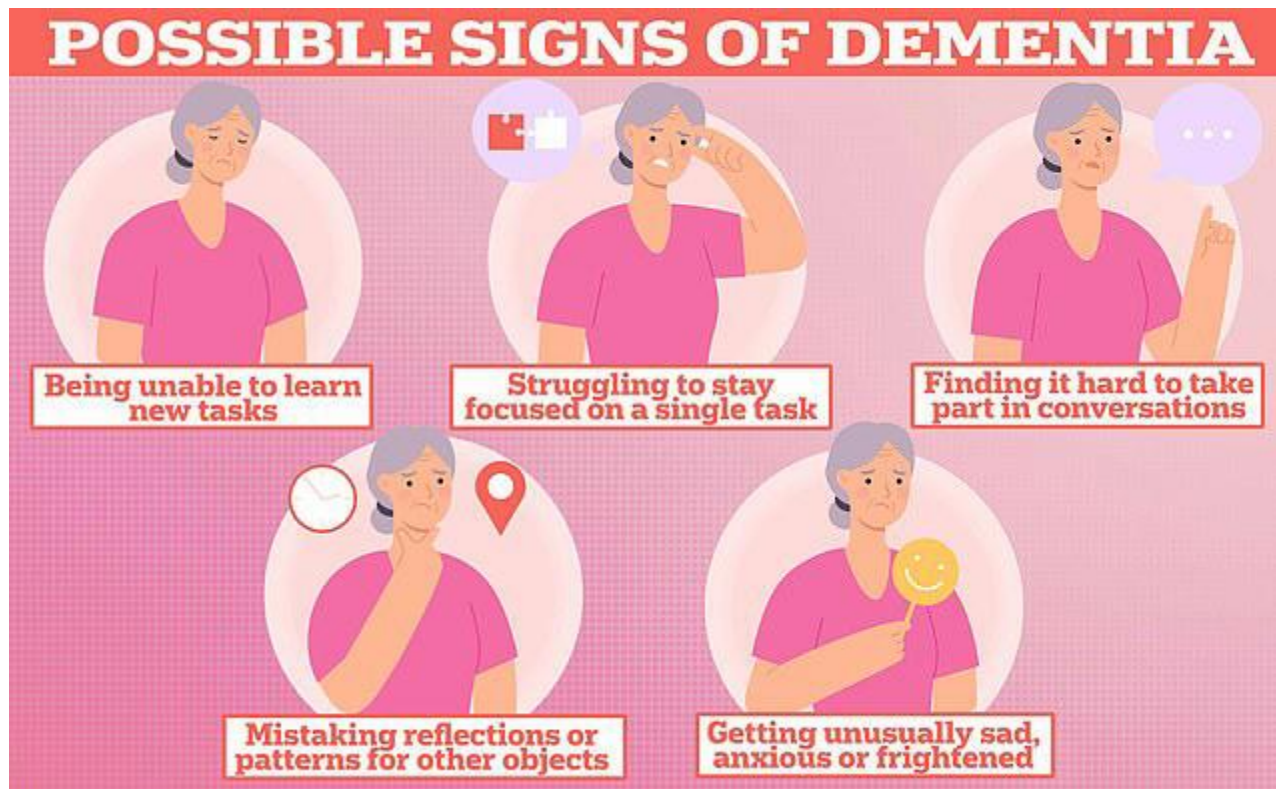
Professor Collinge added: 'I should emphasise these are very rare occurrences. You can't "catch" Alzheimer's, it is not transmissible in the sense of a viral or bacterial infection.

'These rare transmission routes are where people have been accidentally injected with infected human tissue extracts, and the majority of this relates to medical procedures that are no longer used.

'From a public health point of view, this will probably affect a relatively small number of patients.'

He added the new findings could help point researchers in the right direction for understanding and treating Alzheimer's in future.

Dr Susan Kohlhaas, executive director of research at Alzheimer's Research UK, said: 'A diagnosis of Alzheimer's disease can be devastating for all involved, and our hearts go out to the families that have been affected by these tragic circumstances.



But they can also be a sign of dementia — the memory-robbing condition plaguing nearly 1million Brits and 7million Americans© Provided by Daily Mail

'It's important to stress this is the only recorded instance of Alzheimer's transmission between humans.

'However, this study has revealed more about how amyloid fragments can spread within the brain, providing further clues on how Alzheimer's disease progresses and potential new targets for the treatments of tomorrow.

'We will continue to redouble our research efforts in our pursuit for a cure.'

The people described in the study had all been treated as children with a type of human growth hormone taken from dead donors (cadaver-derived human growth hormone or c-hGH).

But the treatment was withdrawn in 1985 after the CJD link emerged.

After that, c-hGH was replaced with a synthetic growth hormone that did not carry the risk of transmitting CJD.

Growth hormone donated by humans was prepared in different ways. All batches prepared using a method called HWP were infected with toxic prions, the experts found.

In theory, one dose of HWP could be enough to infect a patient with Alzheimer's disease-causing seeds, but it is not known how many definitely received the HWP variety.

Most patients were given various types of preparation during their treatment.

Around 900,000 Brits are currently living with dementia, of which Alzheimer's is the most common form.

What is Alzheimer's and how is it treated?

Alzheimer's disease is a progressive, degenerative disease of the brain, in which build-up of abnormal proteins causes nerve cells to die.

This disrupts the transmitters that carry messages, and causes the brain to shrink.

More than 5 million people suffer from the disease in the US, where it is the 6th leading cause of death, and more than 1 million Britons have it.

WHAT HAPPENS?

As brain cells die, the functions they provide are lost.

That includes memory, orientation and the ability to think and reason.

The progress of the disease is slow and gradual.

On average, patients live five to seven years after diagnosis, but some may live for ten to 15 years.

EARLY SYMPTOMS:

- Loss of short-term memory
- Disorientation

- Behavioral changes
- Mood swings
- Difficulties dealing with money or making a phone call

LATER SYMPTOMS:

- Severe memory loss, forgetting close family members, familiar objects or places
- Becoming anxious and frustrated over inability to make sense of the world, leading to aggressive behavior
- Eventually lose ability to walk
- May have problems eating
- The majority will eventually need 24-hour care

HOW IT IS TREATED?

There is no known cure for Alzheimer's disease.

However, some treatments are available that help alleviate some of the symptoms.

One of these is Acetylcholinesterase inhibitors which helps brain cells communicate to one another.

Another is memantine which works by blocking a chemical called glutamate that can build-up in the brains of people with Alzheimer's disease inhibiting mental function.

As the disease progresses Alzheimer's patients can start displaying aggressive behaviour and/or may suffer from depression. Drugs can be provided to help mitigate these symptoms.

Other non-pharmaceutical treatments like mental training to improve memory helping combat the one aspect of Alzheimer's disease is also recommended.

Source: [Alzheimer's Association](#) and the [NHS](#)

Gut microbe imbalances could predict a child's risk for autism, ADHD and speech disorders years before symptoms appear

Early screening for neurodevelopmental disorders such as autism is important to ensure children [have the support](#) they need to gain the [essential skills](#) for daily life. The American Academy of Pediatrics recommends that all children be [screened for developmental delays](#), with additional screening for those who are preterm or have a low birth weight.

However, the U.S. Preventive Services Task Force has [called for more research](#) into the effectiveness of current autism screening practices. Primarily based on milestone checklists and symptoms, autism diagnoses also currently rely on [observations of behavior](#) that often manifests after crucial developmental stages have passed.

Researchers and clinicians are working to develop simple, reliable tools that could identify early signs or risk factors of a condition before symptoms are obvious. While early screening can lead to the risk of overdiagnosis, understanding a child's developmental needs can help guide families toward resources that address those needs sooner.

[We are researchers who study the](#) role the microbiome plays in a variety of conditions, such as mental illness, autoimmunity, obesity, preterm birth and others. In our recently published research on Swedish children, we found that microbes and the metabolites they produce in the guts of infants—both found in poop and cord blood—[could help screen for a child's risk](#) of neurodevelopmental conditions such as autism. And these differences can be detected as early as birth or within the first year of life. These markers were evident, on average, over a decade before the children were diagnosed.

Microbes as biomarkers

Biomarkers are biological indicators—such as genes, proteins or metabolites in blood, stool or other types of samples—that signal the presence of a condition at a certain point in time. There are [no known biomarkers for autism](#). Efforts to find biomarkers have been largely hindered by the fact that [autism has many potential pathways](#) that lead to it, and researchers tend to ignore how these causes may work [together as a whole](#).

One potential biomarker for neurodevelopmental conditions such as autism are [gut microbes](#). The connection between the gut and brain, or the [gut-brain axis](#), is an area of considerable interest among scientists. Gut microbes play significant roles in health, including in immunity, neurotransmitter balance, digestive health and much more.

A lot of work has been done around mapping what a ["typical" microbiome looks like](#) based on age and organ system. Researchers have shown that the microbiome is personalized enough that it can [distinguish two people or two households](#) even better than genetics, with differences in colonization starting very [early in life](#).

The microbiome undergoes [immense changes during childhood](#). It shapes and is shaped by the [immune system](#) and influenced by [life changes and events](#). It is also [influenced by factors](#) like genetics, environment, lifestyle, infection and medications.

Gastrointestinal symptoms such as diarrhea, pain and constipation are common in children with autism and ADHD, with as many as 30% to 70% of autism patients also diagnosed with [functional gastrointestinal disorders](#). Untreated GI issues can also lead to additional [sleep and behavioral disorders](#) among these children. A small pilot study found that children with autism showed improvements in gastrointestinal and autism-related symptoms after [having healthy microbes transferred](#) into their guts, with some benefits lasting [up to two years](#).

Most studies on the microbiome and neurodevelopmental conditions, however, are restricted to people who are already diagnosed with [ADHD](#), [autism](#) or other conditions, and these studies often show mixed results. These limitations raise an important question: Does the microbiome play a direct role in the development of autism and other neurodevelopmental conditions, or are changes in microbiome composition a consequence of the conditions themselves?

Some investigations have proposed that the microbiome has [little or no association with future autism](#). However, these studies have a notable limitation: They don't examine microbial imbalances prior to diagnosis or symptom onset. Instead, these studies focus on children already diagnosed with autism, comparing them to their siblings and unrelated neurotypical children. In most cases, dietary data and samples are collected several years after diagnosis, meaning the study cannot test for whether microbial imbalances cause autism.

Microbes matter

We wondered whether studying the bacteria residing in small children before they are diagnosed or show symptoms of autism or other conditions could give us a clue into their neurodevelopment. So, we examined the cord blood and stool collected at approximately 1 year of age from participants of an ongoing study called [All Babies in Southeast Sweden](#), which follows the health of approximately 17,000 children born between 1997 and 1999 and their parents. We have followed these children since birth, nearly 1,200 of whom were later diagnosed with a neurodevelopmental disorder by age 23.

We found [significant differences](#) in bacterial composition and metabolite levels that developed before symptoms of neurodevelopmental conditions—such as gastrointestinal upset, crankiness and sleep problems—as well as formal medical diagnoses. These differences spanned many conditions, including autism, ADHD and speech disorders.

Next, we linked bacteria to neurotransmitters—chemical signals that help brain cells communicate—and vitamins such as riboflavin and vitamin B in the child's stool. Given [previous research](#) on children and adults already diagnosed with a neurodevelopmental disorder, we expected to find differences in the microbiome composition and health between those with and without neurodevelopmental conditions.

But we were surprised to discover just [how early these differences emerge](#). We saw variability in the microbes and metabolites that affect immune and brain health, among others, in the stool collected from the diapers of children around 1 year of age and in umbilical cord blood collected at birth.

The imbalance in microbial composition—what microbiologists call [dysbiosis](#)—we observed suggests that incomplete recovery from repeated antibiotic use may greatly affect children during this vulnerable period. Similarly, we saw that repeated ear infections were linked to a [twofold increased likelihood](#) of developing autism.

Children who both repeatedly used antibiotics and had microbial imbalances were significantly more likely to develop autism. More specifically, children with an absence of [Coprococcus comes](#), a bacterium linked to mental health and quality of life, and increased prevalence of [Citrobacter](#), a bacterium known for antimicrobial resistance, along with repeated antibiotic use were two to four times more likely to develop a neurodevelopmental disorder.

[Antibiotics are necessary](#) for treating certain bacterial infections in children, and we emphasize that our findings [do not suggest avoiding their use](#) altogether. Parents should use antibiotics if they are prescribed and deemed necessary by their pediatrician. Rather, our study suggests that repeated antibiotic use during early childhood may signal underlying immune dysfunction or disrupted brain development, which can be influenced by the gut microbiome. In any case, it is important to consider whether children could benefit from treatments to restore their gut microbes after taking antibiotics, an area we are actively studying.

Another microbial imbalance in children who later were diagnosed with neurodevelopmental disorders was a decrease in [Akkermansia muciniphila](#), a bacterium that reinforces the lining of the gut and is linked to neurotransmitters important to neurological health.

Even after we [accounted for factors](#) that could influence gut microbe composition, such as how the baby was delivered and breastfeeding, the relationship between imbalanced bacteria and future diagnosis persisted. And these imbalances preceded diagnosis of autism, ADHD or intellectual disability by 13 to 14 years on average, refuting the assumption that gut microbe imbalances arise from diet.

We found that [lipids and bile acids were depleted](#) in the cord blood of newborns with future autism. These compounds provide nutrients for beneficial bacteria, help maintain immune balance and influence neurotransmitter systems and signaling pathways in the brain.

Microbiome screening at well-child visits

Microbiome screening is not common practice in well-child visits. But our findings suggest that detecting imbalances in beneficial and harmful bacteria, especially during critical periods of early childhood development, can provide essential insights for clinicians and families.

There is a long way to go before such screening becomes a standard part of pediatric care. Researchers still need validated methods to analyze and interpret microbiome data in the clinic. It's also unclear how bacterial differences change across time in children around the world—not just which bacteria are present or absent, but also how they may be shaping immune responses and metabolism. But our findings reaffirm the growing body of evidence that the early gut microbiome plays a key role in shaping neurodevelopment.

30 medicinal plants that'll change your life forever





Coriander -

It contains substances that protect the gastric mucosa and the intestines, facilitating digestion and relieving stomach cramps. It's also effective against anxiety.

© Shutterstock



Cinnamon -

Its essential oils act against various micro-organisms and fungi. It helps in inflammatory processes and also against gas and poor digestion.



Valerian -

The plant has powerful anti-stress properties. Its anxiolytic action is due to a substance that acts on the central nervous system.



Aloe vera - The plant acts in cell multiplication, accelerating healing and also working as an antiseptic. It's can be used to combat dandruff and lice.



Chamomile - A widely-used herb to soothe the nervous system and cramps. It has anti-inflammatory properties and it helps in the elimination of gas and stimulates the appetite. Its benefits to skin hydration have been proven.



Watercress -

It's a diuretic, anti-inflammatory and can be used to treat oral thrush, gingivitis and acne. It also aids digestion and soothes coughing.



Rosemary -

Its active ingredients treat migraines, help with memory loss and low immunity, and even reduce rheumatic and joint pain.



Lavender -

Lavender has over 150 compounds that can help fight insomnia and lack of appetite. The flowers help with coughing, bronchitis, burns and migraines.



Arnica -

Widely used as a cream to relieve rheumatic pain and tendinitis, it's also used to treat skin problems like acne and boils.



Boldo -

Rich in boldine, a substance produced by the liver that breaks down fats. This makes it effective in improving digestion and liver function.



Guarana -

Rich in caffeine and theobromine; substances that act on the central nervous system, making it effective against stress as well as beneficial for the body in general.



Marigolds - This famous flower has excellent healing properties and is used in the treatment of rashes, light burns, sunburns, fungi and acne.



Peppermint -

The plant relieves digestive colic, reduces inflammation in the bronchi, fights fatigue, liver, gas and digestive problems.



Pepper -

It facilitates digestion, relieves pain and has the power to accelerate the metabolism, helping in weight loss.



Cymbopogon citratus -

Widely used for treating anxiety, its tea is also good for stomach problems and gas. It also has analgesic and anti-rheumatic properties.



Dandelion -

Famous for being effective against digestive disorders, the plant also acts as a diuretic and laxative. It also stimulates the appetite.



Cloves - Its oil is used in dentistry as an analgesic and antiseptic. It's also effective against inflammation and swelling.



Aniseed -

Also known as Anis, the plant is very used against gas, stomach problems, cramps and migraines.



Eucalyptus - It's a powerful and effective expectorant for respiratory problems such as asthma and bronchitis. Plus, it's also effective in lowering fever and fighting sciatic nerve pain



Licorice - It's an effective antiseptic and anti-inflammatory root used against lung problems and coughs. It's also used in cases of allergic reactions, bronchitis and arthritis.



Lemon balm -

Also known as Melissa, this plant is famous for the calming effect of its essential oils. It's also analgesic and antispasmodic. What's more, it helps fighting against colic and gas.



Carqueja -

Its essential oils act on liver cells by increasing bile production, aiding liver function and digestion.



Garlic - It's rich in vitamins A, B1, B2 and C, as well as minerals such as sulfur and iodine. It has the power to lower cholesterol, boost the immune system and alleviate circulatory problems. And if that's not enough, it also has expectorant and antiseptic properties.



Comfrey - It's widely used to treat ulcers and helps in controlling diabetes. It has compounds that help in the regeneration of tissue, acting as a great healing aid.



Bay leaf -

In addition to having antiseptic and soothing properties, it's also used to aid digestive and muscle problems, relieving pain and bruising.



Mallow -

Its leaves are anti-inflammatory, so its tea is recommended for gastric ulcers and it also helps treating skin problems.



Surinam Cherry -

Rich in vitamin C, the fruit is widely used for its soothing and anti-inflammatory properties, and to alleviate respiratory problems.



Tamarind -

In addition to acting as a natural laxative, it's also used to treat infections caused by fungi.



Thyme -

It has an expectorant effect, helps relieve symptoms of coughing and bronchitis and also acts as an antiseptic.

Doctor warns of five medications known to raise dementia risk

Common prescription medications could be increasing your risk of dementia, a doctor has warned.

The disorder blights the lives of millions worldwide, slowly robbing them of their memories and independence.

Yet, four in ten cases of the memory robbing disorder could be prevented with simple lifestyle changes, according to research.

There are some factors such as smoking and drinking that can increase the risk of developing dementia — but so can some medication.

Dr Zain Hasan, a US-based anesthetist, told his 635,000 followers on [TikTok](#) that there are five medications that could cause dementia — including some antidepressants, painkillers and antihistamines.

The first drug he included in his warning was antihistamine medication used to help ease the symptoms of allergies, as well as anticholinergics, also used to treat allergies.

These medications, some of which are available over the counter, are used to treat hayfever, eczema, hives and conjunctivitis, which causes red and itchy eyes.

However, Dr Hasan said long-term use has been linked to dementia.

One 2015 US [study](#) tracked the brain health of more than 3,400 participants over 65 years between 1994 and 2012.

Researchers found there was a link between increased doses of anticholinergics and those that developed dementia.

Another medication that is thought to cause dementia is opiates, often used as painkillers after surgery, serious injury or for [cancer](#) patients.

Dr Hasan said: 'This is pretty common knowledge but if you take any opiates like morphine regularly they affect your brain, they cause sedation and anything that causes sedation for a long period of time can probably end up causing dementia.'

A 2024 [study](#), which looked at data of more than 21,000 patients, found opiate users had a 15 per cent higher risk of developing dementia.

Another medication was omeprazole, which is widely used to treat indigestion and heartburn.

He said: 'If you take omeprazole regularly it can increase the amount of beta-amyloid in your brain, which can lead to dementia.'

'It works as a proton pump inhibitor, it decreases acid inside your stomach. It is actually surprising to me, I had no idea it was linked to dementia.'



Dr Zain Hasan, a US-based anesthetist, told his 635,000 followers on TikTok that there are five medications that could cause dementia — including antidepressants, painkillers and antihistamines

A type of sedative drug used to treat anxiety, insomnia and seizures called benzodiazepines — such as Valium and Xanax — are thought to raise dementia risk if taken over a long period of time.

Dr Hasan said: 'It makes sense, it goes into your central nervous system it numbs your entire brain, it helps with anxiety, it helps with [alcohol](#) withdrawal.'

'If you take them for a long period of time especially to help you sleep at night, they can induce dementia.'

Several studies have shown a link between the drug and dementia. In one benzodiazepine [study](#) a team of researchers from France and Canada selected 2,000 people with Alzheimer's disease and 7,000 without it.

Researchers found those who had taken benzodiazepines for three to six months had a 32 per cent greater risk of developing Alzheimer's, and those taking one for more than six months had an 84 per cent greater risk than those who hadn't taken one.

Dr Hasan also highlighted that taking tricyclic antidepressants (TCAs) — a less commonly prescribed mental health drug compared to SSRIs — could also cause dementia.

He explained that the theme for all these medications is they directly impact your brain, with the exception of omeprazole.

'They all affect your brain they cross the blood brain barrier, anything that sedates your brain for a long period of time including anesthesia can cause dementia,' Dr Hasan warns.

He urged those who are taking these medications to always speak to a doctor before stopping, especially medications like opioids and benzodiazepines.

Dr Hasan also suggested those who are 'scared or worried about dementia in the future' to speak with a doctor about the risks.

There are currently estimated to be 982,000 people with dementia in the UK. This number is expected to rise to 1.4 million by 2040.

An estimated 6.7million Americans age 65 and older are living with Alzheimer's dementia today. This number could grow to 13.8 million by 2060.

Alzheimer's disease is the most common type of dementia, affecting between 50 and 75 per cent of those diagnosed.

Chemical found in breakfast foods linked to brain damage in new study

A pesticide that has been found in breakfast cereals, oats and orange juice may be able to cause dementia symptoms in weeks.

Weed-killer glyphosate, which is the [active ingredient in RoundUp](#), has long been linked to cancers and nerve damage. But much of the earlier research has focused on looking at people that interact with it every day like farm workers.

The new study, performed on mice, suggests even small amounts of exposure can have long-lasting effects.

Experts found rodents who were given for about three months saw [Alzheimer's](#)-like changes to their brains which persisted for months.

Upon dissecting the brains, the researchers saw the chemical itself had gotten into the delicate tissue of the brain, where it likely caused inflammation, which caused nerves and brain tissue to decay, leading to the changes they observed after six months.

Patrick Pirrotte, a study author and director at City of Hope said: 'These findings highlight that many chemicals we regularly encounter, previously considered safe, may pose potential health risks.

Foods that were found to contain glyphosate include Quaker oatmeal, Cheez-It and Tropicana orange juice, according to a separate analysis by Sokolove law, a personal injury and illness law firm.



A 2023 analysis from personal injury and illness law firm Sokolove Law compiled a list of products that had tested positive for glyphosate in the past. Outside the food items, they also said the chemical was detected in cotton products and bottled water.

Previous studies have mainly focused on dosing mice with high levels of glyphosate. Only certain humans, like farm or factory workers, are commonly exposed to high levels of the herbicide, the average person likely is exposed to much smaller amounts of the chemical daily, if at all

According to the US Geological Survey, about 300million pounds of the chemical are used in the country each year, on products like corn, soybeans, oats, alfalfa, cotton and wheat.

From there, it can accumulate in soil, water or stick to crops as they're processed into food items.

The [CDC](#) estimates that about 81 percent of Americans had been exposed to glyphosate as of 2014.

Studies of this sort led the International Agency for Research on Cancer to classify glyphosate as 'possibly carcinogenic to humans', but the chemical is still approved for use by the EPA and considered safe.

It's banned or restricted in European countries like Germany, Portugal and Spain.

Few studies have examined what impact lower levels of long-term exposure to the chemical might have.

That's what the new research set out to examine. The paper included researchers from Arizona State University and City of Hope, a private research center in California and appears in the [Journal of Neuroinflammation](#).

They fed mice two levels of glyphosate: one high level and one low level that would be closer to the levels humans contact the pesticide.

The mice were fed their dose every day for 13 weeks, and then researchers stopped adding glyphosate to their diet, and merely observed them for six months.

Consistent with older research, even six months after the researchers stopped feeding the mice the pesticide, the high-levels of glyphosate caused the mice to develop brain inflammation and Alzheimer's-like changes.

However, the researchers found that there were similar, yet less pronounced, changes in the brains of the mice who were fed low doses of the chemical.

Chemical found in breakfast foods linked to brain damage in new study

The researchers write that this inflammation could lead to the symptoms seen in dementia, where healthy brain cells become clogged with sticky plaques that lead to mass cell death and eventually, memory loss.

This could help explain why we've seen an uptick in memory-robbing conditions in recent decades, Dr Velazquez claimed.

Glyphosate has been used since the 1950s. It became more popular in 1996, when techniques for genetic modification became more advanced, allowing scientists to manufacture crops that were resistant to it.

Professor Pirrotte said: 'Herbicides are used heavily and ubiquitously around the world.'

Because of how common these are, Dr Velazquez said: 'our goal is to identify environmental factors that contribute to the rising prevalence of cognitive decline and neurodegenerative diseases in our society'.

Roughly 7million Americans are living with Alzheimer's - and that number is expected to grow to 13million by 2050, according to the Alzheimer's Association.

This projected growth makes it essential for science to investigate many possible causes for the disease, the study authors said.

Samantha Bartholomew, a PhD candidate at ASU who authored the study, said: 'My hope is that our work drives further investigation into the effects of glyphosate exposure, which may lead to a reexamination of its long-term safety and perhaps spark discussion about other prevalent toxins in our environment that may affect the brain'.

Still, they cautioned, since the research was conducted in mice, it's not certain that what's observed in this study will be the same in humans. More research is needed.

Two herbicides detected in up to 98% of children may cause learning and social difficulties, study warns

The two most widely used herbicides in the world may cause learning problems and poor memory and social skills in children, a study has warned.

Using urine samples and test performance scores from adolescents, researchers found that traces of glyphosate, the most heavily applied herbicide in the US, and common weed killer 2,4D, were linked to worse brain function.

Researchers from the University of [California](#) San Diego found that glyphosate was present in 98 percent of the 520 samples.

People may be exposed to the chemicals by eating contaminated food or drinking water, and it is thought the substances affect the pathways in the brain linked to memory and learning.

Other [research](#) has found that glyphosate is in up to 90 percent of wheat-based products such as pizza, crackers and pasta.

Over the last two decades, there has been a [substantial rise in chronic diseases and mental health disorders](#) in young adults worldwide.

'Exposure to neurotoxic contaminants in the environment could play a part of this increase,' said senior study author Dr Jose Ricardo Suarez, associate professor at UC San Diego.



[View gallery](#)

Exposure to glyphosate, the most heavily applied herbicide in the US, and common weed killer 2,4D, was linked to worse brain function among adolescents.

The researchers measured the concentrations of two popular herbicides in urine samples: glyphosate and 2,4-dichlorophenoxyacetic acid, better known as 2,4D.

The urine samples were collected in 2016 from 519 children aged between 11 and 17 living in the agricultural county of Pedro Moncayo, Ecuador.

Herbicides are the most commonly used class of pesticides worldwide, often used to kill weeds.

[Elevated PFAS levels linked to higher cancer, low birth weight rates](#)



[Cities with the highest levels of toxic 'forever chemicals' in tap water also have above-average rates of disease and pregnancy complications, a DailyMail.com analysis suggests.](#)

Glyphosate, used in crops such as corn and soy, is a nonselective herbicide, meaning it kills all vegetation in an area rather than just weeds.

It was detected in 98 percent of participant samples.

2,4D, a herbicide used to kill leafy weeds, was detected in 66 percent of the urine samples.

The researchers also examined the adolescents' performance in five areas: attention and inhibitory control (how well you can stop impulses), memory and learning, language, spatial awareness, and social perception.

They did this by looking through the test scores from 2016 on things like how quickly the children could understand a set of instructions, how well they could remember faces and how quickly they could solve shape puzzles.

Higher amounts of 2,4D in urine were linked to worse scores in the tests for attention and inhibitory control, memory and learning, and language.

Glyphosate concentration in urine was only connected to lower scores in social perception.

The most common glyphosate product is Roundup weed killer, made by Monsanto.

There have been significant increases in glyphosate and 2,4D use following the introduction of genetically modified, glyphosate-resistant "Roundup-ready" crops in 1996 and 2,4D-resistant crops in 2014, the study authors said.

Bayer, the owner of the chemical manufacturing company, has long maintained that exposure to the weed killer has no negative impacts on human health.

The study was published Wednesday in the journal [Environmental Health Perspectives](#).

Scientists raise alarm over arsenic contamination: Metal increasingly found in tap water causes cancer and is rife in Arizona, Nevada and New Mexico

- **Arsenic is used in pesticides but over-exposure can cause cancer stem cells**
- **The toxic metal is rife in the Southwest due to low rainfall and over pumping**

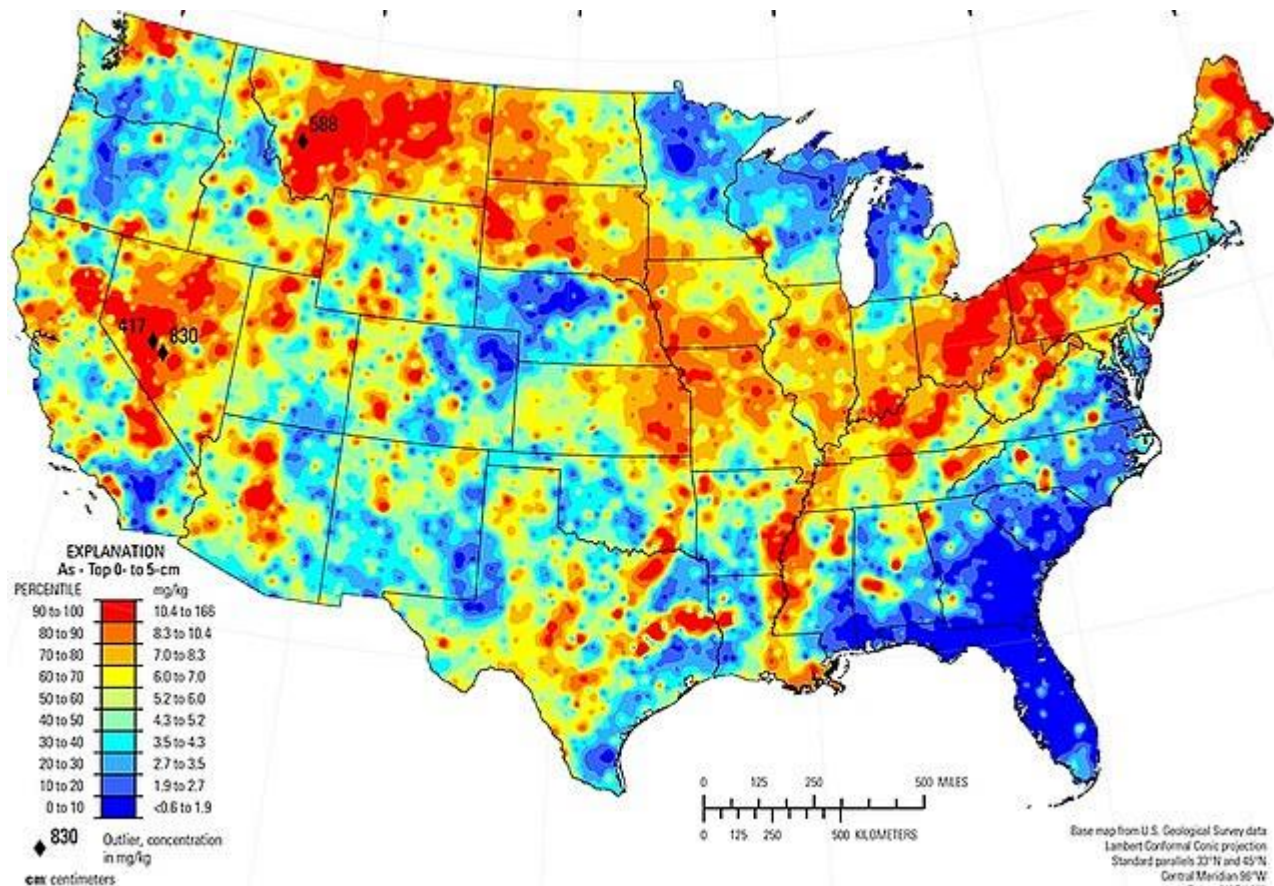
Scientists have raised the alarm over yet another cancer-causing toxin contaminating food and water which they call an 'urgent health threat'.

Arsenic, a metal naturally found in the Earth's crust, is used in pesticides and processes like cement manufacturing — but it is increasingly ending up in groundwater, where it ends up in drinking water wells.

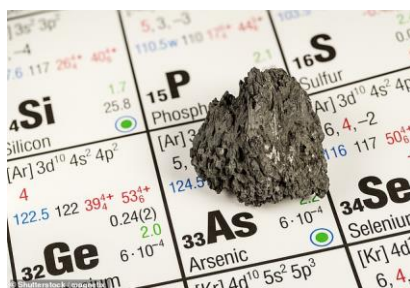
Repeated exposure can damage DNA, weaken the immune system and lead to the formation of cancer cells, as well as high blood pressure and heart disease.

While attention has been given to the dangers of lead and [PFAS contamination](#) in recent years, scientists at Florida International University warn that arsenic is not commanding the same attention, despite posing a similar risk to health.

Some 31 states had levels of arsenic in drinking water above the legal limit between 2017 and 2019, according to the Environmental Working Group.



Data from 2017 showing the concentration of arsenic across the US in the top 5cm of soil. The highest levels are in the north, southwest and north east of America, which could be due to lower amounts of rainfall



Arsenic is a naturally occurring element in the Earth's crust and is used in pesticides and processes like cement manufacturing

A 2019 Consumer Reports investigation even found that bottled water brands sold in America had levels of arsenic that exceeded the legal limit — which the Food and Drug Administration (FDA) says is 10 parts per billion (ppb).

Other studies of multiple popular baby food brands also found arsenic at levels higher than the legal limit. Some evidence suggests this can lead to lower IQ scores in children.

[Writing in the Conversation](#), the Florida scientists said: 'Since many countries are still affected by high levels of arsenic, we believe arsenic exposure is a global public health issue that requires urgent action.'

They added: 'People who live in areas with naturally high levels of arsenic in the soil and water are at particular risk.'

'In the US, for example, that includes regions in the Southwest such as Arizona, Nevada and New Mexico.'

A [study](#) by the American Chemical Society published in 2017 found that up to 2.1 million people are exposed to arsenic through their drinking water.

The hotspots they identified included New England (predominantly Maine and New Hampshire), the upper Midwest, the southwest (most notably Nevada, southern Arizona, southern and central California, and isolated regions in all western states), and southern Texas.

[Elevated PFAS levels linked to higher cancer, low birth weight rates](#)



[Cities with the highest levels of toxic 'forever chemicals' in tap water also have above-average rates of disease and pregnancy complications, a DailyMail.com analysis suggests.](#)

Your body can absorb arsenic through multiple routes, such as inhalation and skin contact, but the primary source of arsenic exposure is contaminated drinking water and food.

Research suggests that it damages DNA, stops cells from communicating with one another and impairs the immune system, creating the perfect environment for cancers to grow.

Arsenic in soil and rock can dissolve into groundwater and get into drinking water wells. The chemical can enter food when used by farmers as a pesticide and fertilizer.

Chronic exposure to arsenic raises the risk of developing multiple types of cancer.

Research indicates arsenic can damage DNA, interfere with cell signaling pathways and disrupt the immune system, which can all lead to cancer.

Arsenic exposure has also been connected to the formation of cancer stem cells — cells in tumors that cause cancer to grow and spread.

Like normal stem cells in the body, cancer stem cells can turn into many different kinds of cells.

The point in a stem cell's development where it gets the genetic mutation to turn into a cancer stem cell is still unknown.

But Cristina Andrade-Feraud, PhD Candidate, and Diana Azzam, Assistant Professor of Environmental Health Sciences at the Florida International University, are trying to change that.

They are using cells from the same organ at varying stages of cellular development to identify how the origins of cells impact the formation of cancer stem cells.

The duo warned in their article that 'preventing chronic arsenic exposure is critical to reducing the burden of arsenic-related health effects.'

Exposure to even low levels of arsenic in the long term may cause issues such as high blood pressure, skin thickening and discoloration, problems with blood vessels, nerve numbness or pain and heart disease, as well as cancer.

In the short term, exposure to high levels of arsenic in drinking water can lead to stomach pain, nausea, vomiting, headaches and diarrhea.

The Great Forever Chemical Cover-up: Most studies that link PFAS to serious health problems 'are flying under the radar', scientists warn - amid growing evidence manufacturers suppressed true dangers of toxins

- Studies detailing health harms of PFAS do not get the public attention they merit
- Researchers say more people need to know about cancers, birth defect risks
- READ MORE: [EXCL: PFAS linked to wave of cancer and illness in North Carolina](#)

A small fraction of the most compelling evidence pointing to the harms posed by forever chemicals, including birth defects and elevated [cancer](#) risk, gets the public attention it deserves.

Per- and polyfluoroalkyl substances, or PFAS, have been lurking in drinking water and the air we breathe for decades. A product of large-scale manufacturing and industry, the substances will persist for at least that long due to the glacial pace at which they degrade in the environment.

The so-called 'forever chemicals' remain in the bloodstream and organs for years at a time before clearing out of the body via urination, and because the chemicals are ever-present in daily life, from lining on nonstick cookware to run off from pesticides into the water supply, the body is continuously bombarded with them.

A DailyMail.com investigation earlier this month [revealed far higher-than-average](#) rates of cancer cases and deaths as well as pregnancy complications in the majority of counties whose drinking water contains high levels of PFAS chemicals.

But researchers at the Green Science Policy Institute found that of the most substantial scientific explorations into health outcomes of people who steadily breathe in or drink concentrations of PFAS chemicals, just eight percent come with a press alert to garner much-needed media attention.



The cities depicted on the map are just a handful of many that have been identified as having higher concentrations of PFAS in the public water supply and private wells

The institute's findings come just over a month after it was revealed that executives at DuPont and 3M, two of the largest PFAS manufacturers in the US, were first alerted to health risks in 1961, but [failed to raise the alarm until the 1990s](#).

Rebecca Fuoco, the director of science communications at the Green Science Policy Institute said: 'New studies finding strong associations between forever chemicals and serious harms like preterm birth and cancer are flying under the radar.'

'Research tucked away in scientific journals has limited reach, and therefore, impact.'

The authors of the statement posited that researchers may be wary to engage in 'non-scholarly communications' such as exchanges with the media.

Authors also said researchers may be hesitant to add to the growing body of evidence pointing to the many harms of PFAS exposure for fear of their research being 'inaccurate or over-hyped,' though when that happens it's typically because the associated press release was poorly written or misconstrued the findings.

Evidence pointing to the myriad dangers associated with exposure over a long period of time to PFAS has been steadily mounting over the past decade.

[Elevated PFAS levels linked to higher cancer, low birth weight rates](#)



Cities with the highest levels of toxic 'forever chemicals' in tap water also have above-average rates of disease and pregnancy complications, a DailyMail.com analysis suggests.

When PFAS enter the body, they settle in the bloodstream, kidneys, and the liver.

A 2007 estimate from the Centers for Disease Control and Prevention puts the total share of Americans with PFAS in their blood at a staggering 98 percent.

However, too few scientific studies detailing these dangers received the media attention that researchers say is necessary to convince authorities and responsible parties such as pesticide manufacturers to address the problem.

Typically, when research bodies such as large academic institutions reach substantial scientific conclusions that will have widespread public health implications, they issue press releases to garner media attention to get the word out.

And the press alerts get the job done for the most part - studies that came with media releases received 20 times more attention than the studies that did not, meaning a lot of useful information regarding public health went unrecognized.

Dr Linda Birnbaum, former head of the National Institute for Environmental Health Sciences who co-authored the Green Policy Institute's statement, said: 'I urge scientists and their institutions to embrace media outreach as a critical part of the research process.

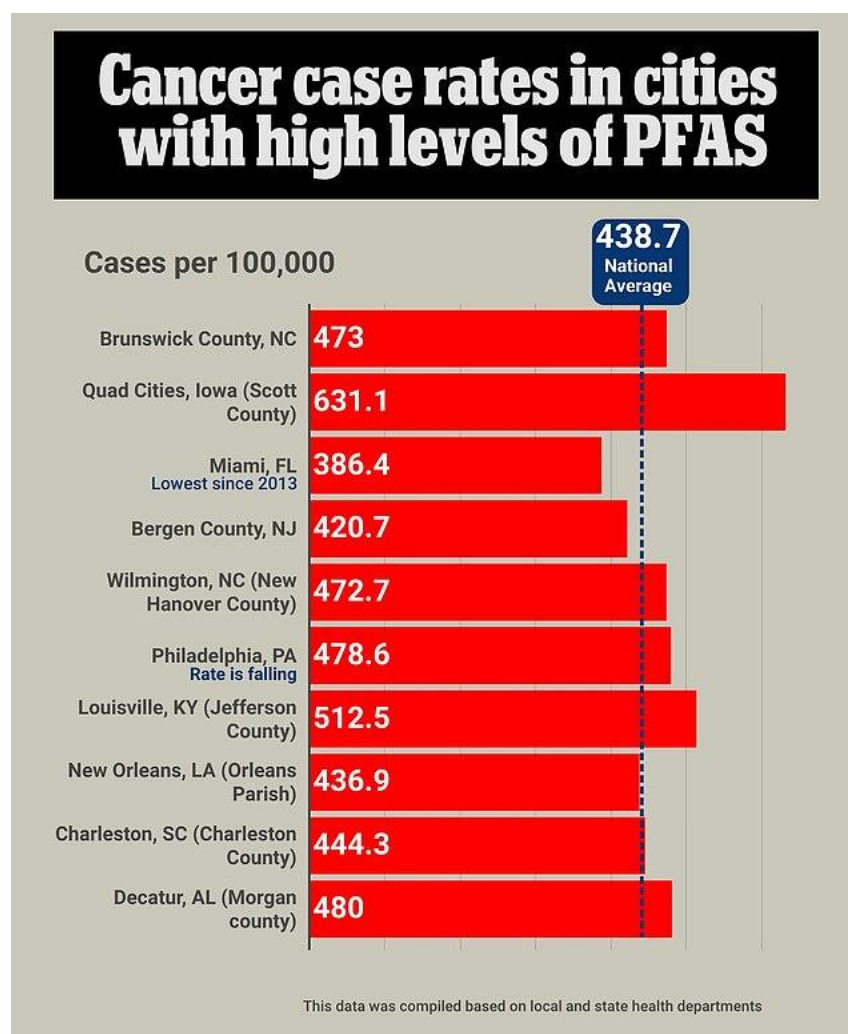
'As scientists, we hold the key to information that can inform better policies, medical practices, industry innovation, and more. It's our responsibility to unlock that potential by sharing our research with a wide audience.'

Absent federal rules for restricting levels of forever chemicals in drinking water, almost half of all drinking water sources in the US have been shown to contain at least one type of PFAS.

This is becoming increasingly evident in places like Brunswick County, North Carolina, where the tap water has some of the highest concentrations of PFAS nationwide due in large part to pollution from a nearby DuPont chemical plant.

A DailyMail.com investigation found that tap water in Brunswick County contains 155 times the amount of PFOA deemed safe (1.09 parts per trillion). The state average, for reference, is 0.945ppt.

Experts are pointing the finger at a chemical plant in Fayetteville, which they say has been dumping poisonous chemicals into the Cape Fear River Basin - which serves as the primary drinking water supply for over 1.5 million North Carolinians - since the 1980s.



+3

[View gallery](#)

Cancer diagnoses in most of the towns designated by the Environmental Working Group for having high levels of PFAS in water are above the national average rate of about 439 cases per 100,000 people

PFAS are omnipresent in modern life. Some of the estimated 12,000 PFAS chemicals are used to give nonstick cookware its trademark quality, repel water from raincoats, and comprise the fire extinguishing foam used by firefighters.

Neighborhoods with the highest PFAS levels in drinking water

Concentrations are measured in parts per trillion (PPT)

1. Brunswick County, N.C. at 185.9ppt
2. Quad Cities, Iowa at 109.8ppt
3. Miami, Fla. at 56.7ppt
4. Bergen County, N.J. at 51.4ppt
5. Wilmington, N.C. at 50.5ppt
6. Philadelphia, Pa. at 46.3ppt
7. Louisville, Ky. at 45.2ppt
8. New Orleans, La. at 41.8ppt
9. Charleston, S.C. at 33.3ppt
10. Decatur, Ala. at 24.1ppt

Information courtesy of a separate report by the Environmental Working Group

The chemicals also often line the packaging of some foods which can then absorb some of the toxins.

Washing dishes lined with PFAS and blanketing crops with PFAS-laden pesticides creates runoff that seeps into drinking water sources.

DuPont was the center of a PFAS-related controversy last month when it agreed, alongside two other chemical companies, to settle pollution complaints for about \$1.2 billion.

Even while many manufacturers have phased out the use of certain PFAS, such as PFOA, the chemicals have exceedingly long half-lives, in some instances, of up to a decade.

A substance's half life is the time it takes for half of the initial amount of a chemical to degrade or disappear.

For instance, perfluorooctanoic acid (PFOA), one of the most studied PFAS chemicals, is estimated to have a half-life ranging from several years to more than a decade in the environment before breaking down.

Earlier this month, researchers from the US Geological Survey, a federally-run investigation, tested water sources at more than 700 locations across the country for per- and polyfluoroalkyl substances (PFAS).

They found that 45 percent of drinking water sources contained at least one PFAS - with highest concentrations in the Great Plains, the Great Lakes, the Eastern Seaboard and Central/Southern California.

The team's testing was limited to 32 types of PFAS out of more than 12,000 that exist, meaning thousands of the chemicals could have gone undetected. If that's the case, it may indicate that the problem is even larger than the study conveys.

Study reveals lasting effects of common herbicide on brain health



Glyphosate, one of the most widely used herbicides, is sprayed on crops worldwide. A new study in mice suggests glyphosate can accumulate in the brain, causing damaging effects linked with Alzheimer's disease. Credit: Jason Drees

The human brain is an incredibly adaptable organ, often able to heal itself even from significant trauma. Yet for the first time, new research shows even brief contact with a common herbicide can cause lasting damage to the brain, which may persist long after direct exposure ends.

In a new study, Arizona State University researcher Ramon Velazquez and his colleagues at the Translational Genomics Research Institute (TGen), part of City of Hope, demonstrate that mice exposed to the herbicide glyphosate develop significant brain inflammation, which is associated with neurodegenerative disease. The findings suggest the brain may be much more susceptible to the damaging effects of the herbicide than previously thought. Glyphosate is one of the most pervasive herbicides used in the U.S. and worldwide.

The research, which appears today in the [*Journal of Neuroinflammation*](#), identifies an association between glyphosate exposure in mice and symptoms of neuroinflammation, as well as accelerated Alzheimer's disease-like pathology. This study tracks both the presence and impact of glyphosate's byproducts in the brain long after exposure ends, showing an array of persistent, damaging effects on brain health.

Glyphosate exposure in mice also resulted in premature death and anxiety-like behaviors, which replicates findings by others examining glyphosate exposure in rodents. Further, the scientists discovered these symptoms persisted even after a 6-month recovery period during which exposure was discontinued.

Additionally, the investigation demonstrated that a byproduct of glyphosate—aminomethylphosphonic acid—accumulated in brain tissue, raising serious concerns about the chemical's safety for human populations.

"Our work contributes to the growing literature highlighting the brain's vulnerability to glyphosate," Velazquez says. "Given the increasing incidence of cognitive decline in the aging population, particularly in rural communities where exposure to glyphosate is more common due to large-scale farming, there is an urgent need for more basic research on the effects of this herbicide."

Velazquez is a researcher with the ASU-Banner Neurodegenerative Disease Research Center at the ASU Biodesign Institute and an assistant professor with the School of Life Sciences. He is joined by first author Samantha K. Bartholomew, a Ph.D. candidate in the Velazquez Lab, other ASU colleagues, and co-senior author Patrick Pirrotte, associate professor with the Translational Genomics Research Institute (TGen) and researcher with the City of Hope Comprehensive Cancer Center in California.

According to the Centers for Disease Research, farm laborers, landscape workers, and others employed in agriculture are more likely to be exposed to glyphosate through inhalation or skin contact. Additionally, the new findings suggest that ingestion of glyphosate residues on foods sprayed with the herbicide potentially poses a health hazard. Most people living in the U.S. have been exposed to glyphosate during their lifetime.

"My hope is that our work drives further investigation into the effects of glyphosate exposure, which may lead to a reexamination of its long-term safety and perhaps spark discussion about other prevalent toxins in our environment that may affect the brain," Bartholomew says.

The team's findings build on [earlier ASU research](#) that demonstrates a link between glyphosate exposure and a heightened risk for neurodegenerative disorders.

The previous study showed that glyphosate crosses the blood-brain barrier, a protective layer that typically prevents potentially harmful substances from entering the brain. Once glyphosate crosses this barrier, it can interact with brain tissue and appears to contribute to neuroinflammation and other harmful effects on neural function.

The EPA considers certain levels of glyphosate safe for human exposure, asserting that the chemical is minimally absorbed into the body and is primarily excreted unchanged. However, recent studies, including this one, indicate that glyphosate, and its major metabolite aminomethylphosphonic acid, can persist in the body and accumulate in brain tissue over time, raising questions about existing safety thresholds and whether glyphosate use is safe at all.

Herbicide may attack more than weeds

Glyphosate is the world's most heavily applied herbicide, used on crops including corn, soybeans, sugar beets, alfalfa, cotton and wheat. Since the introduction of glyphosate-tolerant crops (genetically engineered to be sprayed with glyphosate without dying) in 1996, glyphosate usage has surged, with applications predominately in agricultural settings.

The U.S. Geological Survey notes approximately 300 million pounds of glyphosate are used annually in the United States alone. Although glyphosate levels are regulated on foods imported into the United States, enforcement and specific limits can vary. Due to its widespread use, the chemical is found throughout the food chain. It persists in the air, accumulates in soils, and is found in surface and groundwater.

Despite being considered safe by the EPA, the International Agency for Research on Cancer classifies glyphosate as "possibly carcinogenic to humans," and emerging research, including this study, points to its potential role in worsening neurodegenerative diseases by contributing to pathologies, like those seen in Alzheimer's disease.

The chemical works by inhibiting a specific enzyme pathway in plants that is crucial for producing essential amino acids. However, its impact extends beyond the intended weed, grass and plant targets, negatively affecting the biological systems in mammals, as demonstrated by its persistence in brain tissue and its role in inflammatory processes.

"Herbicides are used heavily and ubiquitously around the world," says Pirrotte, associate professor in TGen's Early Detection and Prevention Division, director of the Integrated Mass Spectrometry Shared Resource at TGen and City of Hope, and senior author of the paper. "These findings highlight that many chemicals we regularly encounter, previously considered safe, may pose potential health risks. However, further research is needed to fully assess the public health impact and identify safer alternatives."

Is glyphosate safe to use at all?

The researchers hypothesized that glyphosate exposure would induce neuroinflammation in control mice and worsen neuroinflammation in Alzheimer's model mice, causing elevated Amyloid- β and tau pathology and worsening spatial cognition after recovery. Amyloid- β and Tau are key proteins that comprise plaques and tau tangles, the classic diagnostic markers of Alzheimer's disease. Plaques and tangles disrupt neural functioning and are directly linked to memory loss and cognitive decline.

The experiments were conducted over 13 weeks, followed by a six-month recovery period. The main metabolite, aminomethylphosphonic acid, was detected in the brains of both normal and transgenic mice with Alzheimer's pathology. Transgenic mice are genetically modified to carry genes that cause them to develop Alzheimer's-like symptoms as they age. This allows researchers to study the progression and effects of the disease in a controlled laboratory setting.

The researchers tested two levels of glyphosate exposure: a high dose, similar to levels used in earlier research, and a lower dose that is close to the limit used to establish the current acceptable dose in humans.

This lower dose still led to harmful effects in the brains of mice, even after exposure ceased for months. While reports show that most Americans are exposed to glyphosate daily, these results show that even a short period could potentially cause neurological damage.

Glyphosate caused a persistent increase in inflammatory markers in the brain and blood, even after the recovery period. This prolonged inflammation could drive the progression of neurodegenerative diseases, including Alzheimer's, indicating even temporary glyphosate exposure can lead to enduring inflammatory processes that affect brain health.

The data emphasizes that glyphosate exposure may be a significant health concern for human populations. The researchers stress the need for continued vigilance and intensified surveillance of glyphosate neurological and other long-term negative health effects.

"Our goal is to identify environmental factors that contribute to the rising prevalence of cognitive decline and neurodegenerative diseases in our society," Velazquez says. "By unveiling such factors, we can develop strategies to minimize exposures, ultimately improving the quality of life for the growing aging population."

More information: Glyphosate exposure exacerbates neuroinflammation 1 and Alzheimer's disease-like 2 pathology despite a 6-month recovery period in mice, *Journal of Neuroinflammation* (2024). [DOI: 10.1186/s12974-024-03290-6](https://doi.org/10.1186/s12974-024-03290-6)

Provided by Arizona State University

This Probiotic Could Be A Missing Link Between Our Gut and Our Mental Health



THOM LEACH / SCIENCE PHOTO LIBRARY/Science Photo Library/Getty Images

The connection between the brain and the gut has long intrigued scientists. [Plenty of research](#) suggests that the trillions of bacteria living in our guts influence our mental health. But the mechanisms underlying this connection,

and the specific microbes at play, have been difficult to parse. But research out this week might have pinned down one key player.

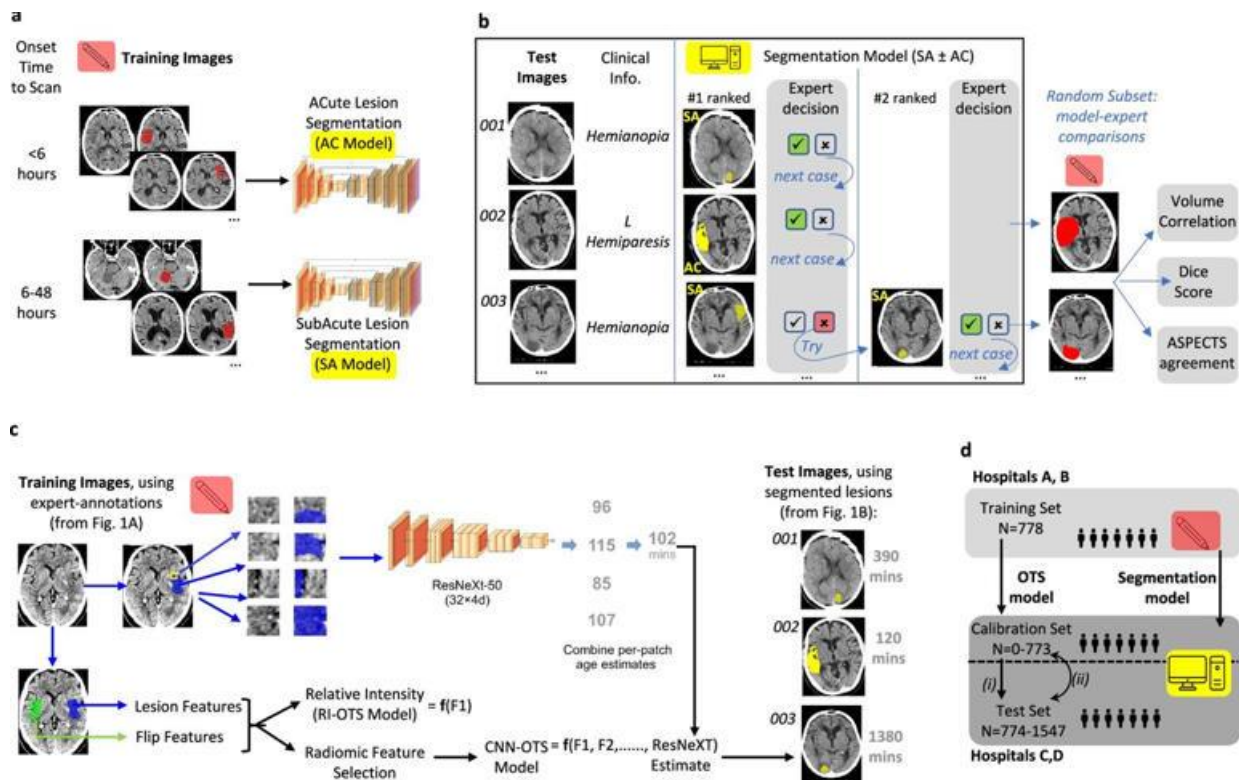
A [paper published today](#) in the journal *Cell Metabolism* identified circadian rhythm as a key connection linking the gut microbiome and mental health. The research, performed by a team from University College Cork and APC Microbiome Ireland, homes in on how our gut bacteria influence both our internal clocks as well as how our body responds to stress. The team identified specific gut bacteria that seems to be connection to both the body's circadian rhythm as well as the release of a particular stress hormone.

"Our research has revealed an important link between the gut microbiota and how the brain responds to stress in a time-specific way," senior author [John Cryan](#), a professor of anatomy and neuroscience at University College Cork in Ireland, [said in a press release](#). "The gut microbiome doesn't just regulate digestion and metabolism; it plays a critical role in how we react to stress, and this regulation follows a precise circadian rhythm."

Using mice, the team examined how an altered gut microbiome interferes with the animals' internal clocks and stress hormones during a day's time. Throughout the day, they collected samples in mice whose microbiomes had been depleted by antibiotic treatment. They found that depletion of gut microbiota led to hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, which is the system of brain structures and glands that regulate stress response.

The team also looked for specific strains of microbiota in healthy control mice to see which bacteria fluctuated with the body's diurnal rhythm. *Limosilactobacillus reuteri* displayed significant variation throughout the day, which correlated with the secretion of stress hormones known as glucocorticoids.

Because this was a mouse study, much more research will be needed to understand both this link, and how the results might translate into humans. It is also a step forward in creating new therapeutic approaches for the gut-brain axis. Understanding this complex connection could lead to the development of microbial-based therapies for conditions that often involve the circadian rhythm, such as depression. The identification of *L. reuteri* also creates a potential candidate for future psychobiotic interventions.



AI stroke brain scan readings found to be twice as accurate as current method

Methods overview. Credit: npj Digital Medicine (2024). DOI: 10.1038/s41746-024-01325-z

New AI software can read the brain scans of patients who have had a stroke to more accurately pinpoint when it happened and help doctors work out whether it can be successfully treated.

It is hoped that the new technology will ultimately enable faster and more accurate emergency treatment of patients in a hospital setting. Knowing the time

the stroke started is important because standard treatments only work in the very early stages post-stroke—and may otherwise cause secondary damage.

The software, devised by researchers from Imperial College London, Technical University of Munich, and Edinburgh University, addresses two of the most difficult challenges in assessing stroke patients—identifying the onset time of the stroke and whether the damage can be reversed. The software has been found to be twice as accurate as the current method—a visual assessment of the scan by a medical professional, who considers how dark a stroke area appears on CT scans of the brain.

A stroke occurs when the blood supply to part of the brain is blocked or reduced, preventing brain tissue from getting oxygen and nutrients. Brain cells then start to die quickly.

As time progresses, some treatments become ineffective or may even cause more problems. Yet finding out when the stroke happened is very difficult. Some strokes may start while the patient is asleep and some patients may have difficulties communicating because of the stroke symptoms.

Dr. Paul Bentley at Imperial's Department of Brain Sciences, who led the [study](#) published in *npj Digital Medicine*, said, "For the majority of strokes caused by a blood clot, if a patient is within 4.5 hours of the stroke happening, he or she is eligible for both medical and surgical treatments.

"Up to six hours, the patient is also eligible for a surgical treatment, but after this time point, deciding whether these treatments might be beneficial becomes tricky, as more cases become irreversible. So it's essential for doctors to know both the initial onset time, as well as whether a stroke could be reversed."

Patients who arrive at hospital with a suspected stroke immediately undergo a CT brain scan, which doctors review to assess how dark the affected areas, or lesions, in the brain are. Darker lesions mean the stroke has progressed further. From this they make an estimate of the time the stroke happened in the past, and whether it may be reversible, and use this to make treatment decisions.

But because all brains are unique, it is very hard to predict with accuracy when the stroke started. Even if doctors know an approximate chronological start time,

an individual's blood flow or blood vessel structure may mean the stroke is progressing more quickly or slowly than average.

The AI algorithm was developed in partnership with Professor Daniel Rueckert (Imperial College London and Technical University of Munich) and Edinburgh University. The model was trained on a dataset of 800 brain scans where the stroke time was known. As well as automatically extracting the relevant area from the brain scan, the algorithm reads and analyses the identified lesions, producing a time estimate.

When it was tested on almost 2,000 different patients, researchers found the AI software was twice as accurate as using a standard visual method. They believe this is because it includes additional features from the scans, such as texture, and accounts for variations within the lesion and background. It wasn't only good at estimating the chronological time of the stroke, but also the biological age of the lesions, by which is meant whether they may be reversible.

Dr. Bentley, who is also a consultant neurologist at Imperial College Healthcare NHS Trust, which has one of eight hyper acute stroke units in London, explained, "Having this information at their fingertips will help doctors to make emergency decisions about what treatments should be undertaken in stroke patients. Not only is our software twice as accurate at time-reading as current best practice, but it can be fully automated once a stroke becomes visible on a scan."

Lead author Dr. Adam Marcus said, "We estimate that up to 50% more stroke patients could be treated appropriately with treatments because of our method. We aim to deploy our software in the NHS, possibly by integrating with existing AI-analytic software that is already in use in hospital trusts."

More information: Adam Marcus et al, Deep learning biomarker of chronometric and biological ischemic stroke lesion age from unenhanced CT, *npj Digital Medicine* (2024). [DOI: 10.1038/s41746-024-01325-z](https://doi.org/10.1038/s41746-024-01325-z)

Provided by Imperial College London

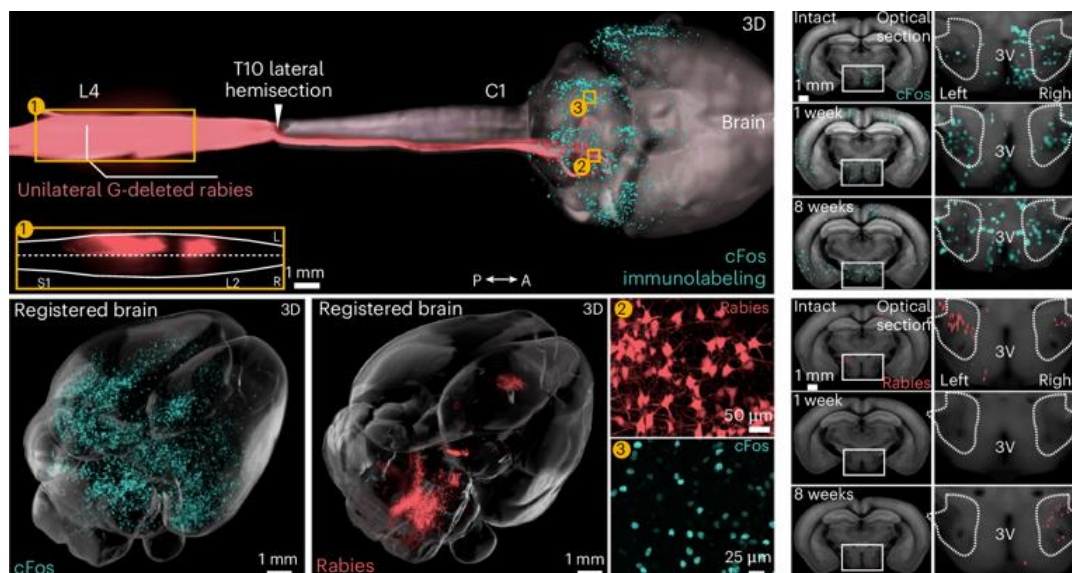
Breakthrough deep brain stimulation therapy restores walking after spinal cord injury

A spinal cord injury (SCI) disrupts communication between the brain and [spinal cord](#), leading to partial or complete paralysis. But recent breakthroughs suggest an unexpected brain region could play a critical role in restoring mobility.

By targeting the lateral hypothalamus (LH) with deep brain stimulation (DBS), researchers have demonstrated significant recovery in walking ability for individuals with partial SCI. This novel approach, backed by detailed neurological mapping and clinical trials, promises to transform treatment for paralysis.

Scientists at [EPFL](#) and [Lausanne University Hospital](#) (CHUV), under the leadership of Grégoire Courtine and Jocelyne Bloch, developed a space-time brain atlas that maps active neurons involved in walking recovery. To their surprise, this atlas highlighted the LH—a region traditionally associated with functions like arousal and feeding, not locomotion.

Their work revealed that glutamatergic neurons in the LH (LHVglut2) are crucial for regaining walking ability after incomplete SCI. Activating these neurons reorganized spinal cord projections, enhancing motor recovery.



The team translated these findings into a pioneering DBS therapy targeting the LH. The results were striking. In animal models, DBS immediately improved walking, and over time, it fostered long-lasting recovery by strengthening residual neural pathways.

Encouraged by these preclinical outcomes, the researchers conducted a pilot [clinical trial](#) involving two participants with incomplete SCI. Both showed immediate and sustained improvements in mobility, even after the stimulation was turned off.

Clinical Trial Brings Hope to SCI Patients

Wolfgang Jäger, a 54-year-old participant, described his transformation following the treatment. Injured in a 2006 skiing accident, he had been confined to a wheelchair for years. After receiving DBS, Jäger regained the ability to take steps, a freedom he had long missed.

"Last year on vacation, I walked down and back to the sea using the stimulation," he shared. Beyond walking, his independence in daily tasks improved significantly. "I can now reach things in my kitchen cupboards," Jäger added, highlighting the therapy's profound impact on quality of life.

The DBS procedure involves [implanting electrodes](#) into specific brain regions to modulate neural activity. While DBS has been used for decades to treat disorders like Parkinson's disease and essential tremor, applying it to restore walking is unprecedented. By targeting the LH, the team tapped into a previously unrecognized neural pathway critical for locomotor recovery.

The discovery of the LH's role in walking recovery marks a milestone in neuroscience. Through detailed brain-wide mapping, researchers identified the LH as a key player in mobilizing spinal cord-projecting neurons. These findings challenge traditional views on motor control and underscore the brain's capacity for adaptation.

"This research demonstrates the brain's central role in recovery from paralysis," said Courtine, a professor of neuroscience at EPFL and co-director of

the [NeuroRestore center](#). "We discovered how to engage residual connections and augment recovery in people with spinal cord injury."

The breakthrough was made possible by advanced imaging tools at the Wyss Center, which provided high-resolution maps of neuronal activity. These tools allowed the team to pinpoint the LH's involvement in walking, a previously overlooked function of this brain region.

Combining DBS and Spinal Stimulation for Enhanced Outcomes

The study's findings go beyond immediate mobility improvements. The therapy reorganized residual [neural pathways](#), enabling durable recovery. This suggests DBS does more than stimulate movement—it may catalyze long-term changes in brain and spinal cord networks.

Future research aims to combine DBS with spinal implants that have already shown promise in restoring movement after SCI. "Integrating our brain and spinal stimulation approaches could offer a comprehensive recovery strategy," said Courtine. Such combined therapies could enhance motor recovery and offer new hope for patients with SCI.

DBSLH mediates long-term improvements in walking in humans with SCI. (CREDIT: Nature Medicine)© The Brighter Side of News

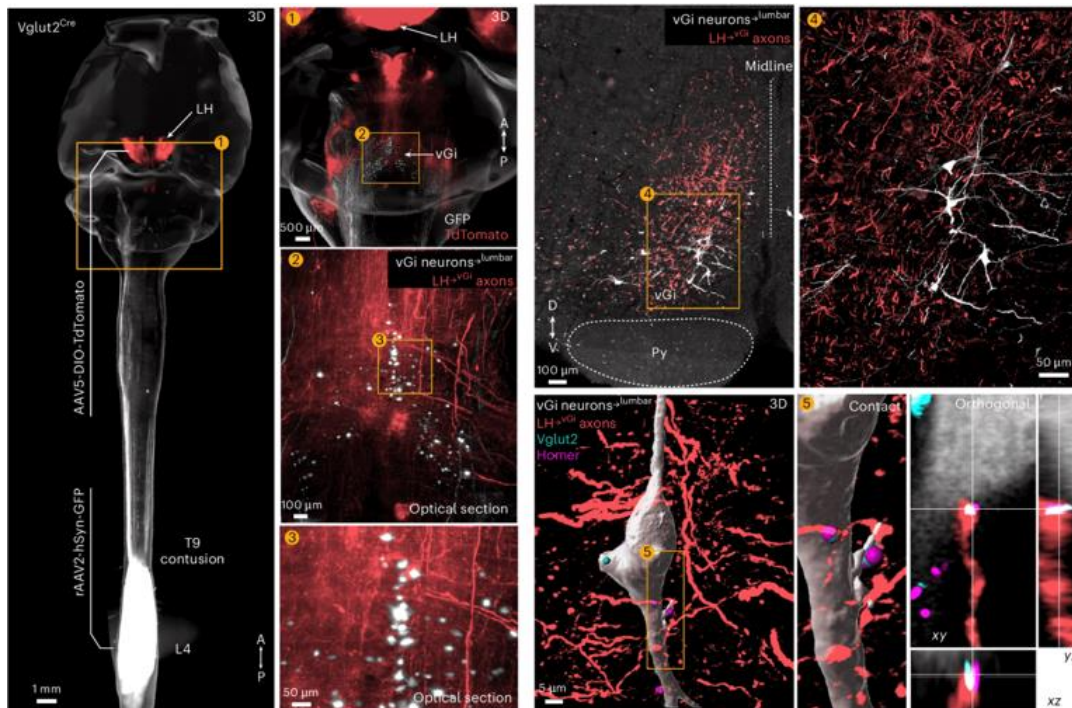
The success of DBS therapy hinged on surgical precision and patient feedback. Using advanced brain imaging, Bloch, a neurosurgeon at CHUV and co-director of .NeuroRestore, guided the electrode implantation process. Patients remained awake during the surgery, providing real-time feedback.

"When the [electrode](#) was in place, the first patient immediately said, 'I feel my legs,'" Bloch recounted. "As we increased the stimulation, she said, 'I feel the urge to walk!' It was a breakthrough moment."

This feedback validated the team's novel approach and underscored the LH's critical role in walking recovery. Bloch emphasized the importance of these discoveries for understanding brain functions and advancing neurosurgical techniques.

Future Directions and Challenges

While the results are promising, further studies are necessary to establish the safety and efficacy of DBS targeting the LH. Researchers are investigating potential effects on [body weight](#), hormonal profiles, psychological health, and autonomic functions.



Neurons in the vGi relay signals from LHvGlut2 neurons. (CREDIT: Nature Medicine)© The Brighter Side of News

As clinical trials expand, the focus will shift to optimizing protocols and exploring broader applications for DBS in treating other forms of paralysis.

“This foundational work shows the unexpected potential of targeting specific [brain regions](#) to restore neurological functions,” said Jordan Squair, a lead author of the study. The team’s innovative methodologies could inspire new treatments for a range of conditions affecting the nervous system.

The implications of this research extend beyond [restoring mobility](#). It represents a shift in how we understand and treat SCI. By leveraging cutting-edge technologies and interdisciplinary collaboration, researchers are uncovering the brain's hidden potential to heal and adapt.

For patients like Jäger, these breakthroughs translate into newfound independence and hope—a reminder of the power of science to transform lives.

How immune cells 'sniff out' pathogens: Signaling study could speed up the search for new drugs



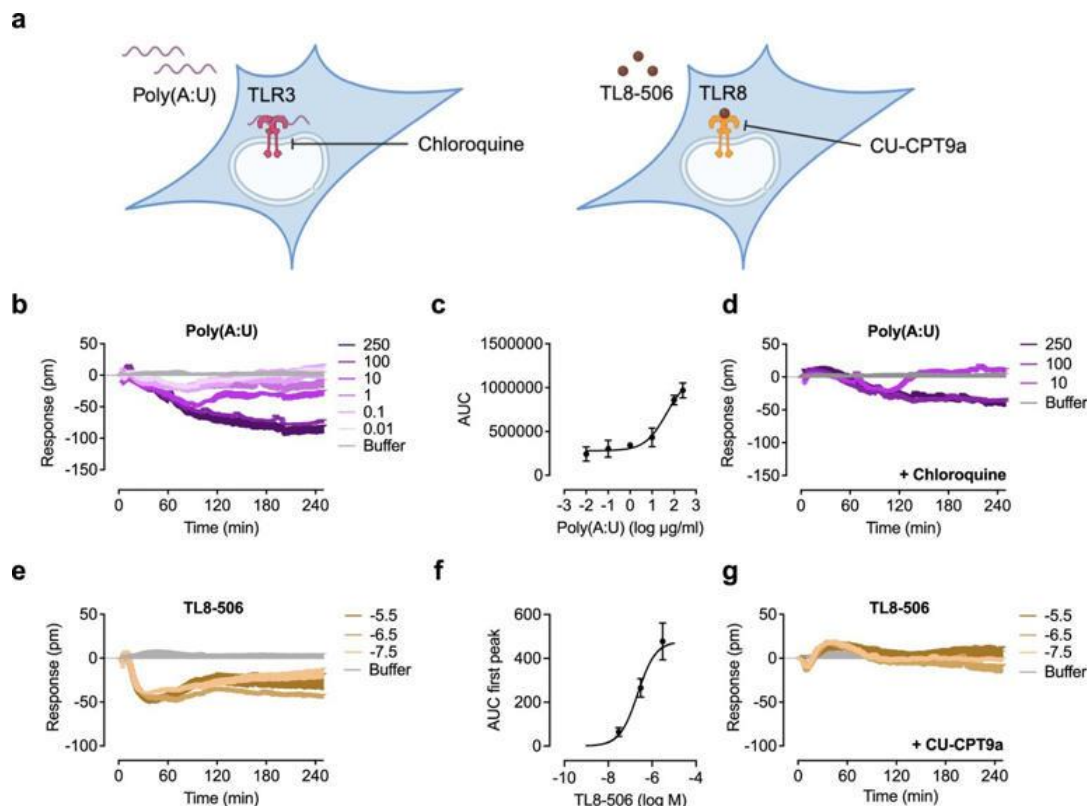
Felicitas Lauber (left), Dr. Janine Holze (center) and Professor Günther Weindl (right) used an innovative method to observe immune receptors at work. Credit: Katrin Limani/University of Bonn

Immune cells are capable of detecting infections just like a sniffer dog, using special sensors known as Toll-like receptors, or TLRs for short. But what signals activate TLRs, and what is the relationship between the scale and nature of this activation and the substance being detected?

In a recent study, researchers from the University of Bonn and the University Hospital Bonn (UKB) used an innovative method to answer these questions. The approach that they took might help to speed up the search for drugs to combat infectious diseases, cancer, diabetes or dementia. Their findings have been [published](#) in *Nature Communications*.

TLRs are found in great numbers on the surface of many of our cells, particularly those in the mucous membranes and those of our immune system.

They work like the olfactory receptors in our nose, being activated when they encounter a specific chemical signal. The alarm that they trigger starts a series of reactions inside the cells. When scavenger cells "sniff out" a bacterium, for instance, they initiate a process known as phagocytosis by engulfing and digesting it, while other immune cells release special messengers that call for reinforcements and thus provoke inflammation.



Optical biosensor decodes signaling of endosomal TLRs. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-53770-9

TLRs activated by danger signals

There are several groups of TLRs, each of which responds to different smells. "These are molecules that have crystallized into important danger signals over the course of evolution," explains Professor Günther Weindl from the Pharmaceutical Institute at the University of Bonn. Among them are lipopolysaccharides (LPS), which form integral parts of a bacterium's cell wall.

"What we don't yet know for certain in many cases is what responses are prompted by a signal being detected," says Weindl, who is also a member of the Transdisciplinary Research Areas (TRAs) Life & Health and Sustainable Futures. "For instance, it's quite possible that different molecules stimulate the same TLR but trigger different responses."

Researchers usually attempt to answer this question by marking molecules in a different color, which tells them, for example, when the receptor switches on a certain signaling pathway in which these molecules play an important role. However, this method is very time-consuming and laborious and requires the observer to be very familiar with the signaling pathways already.

"Instead, we trialed a different technique that doesn't require any color-coding and that's already been used successfully to shed light on how other receptors work," Weindl says. "We've now used this method for the first time to study TLRs." The process is based on the fact that cells tend to change their form when they come into contact with a signal molecule in order, for example, to gear themselves up to "swallow" a bacterium or transform into infected tissue.

Changing the wavelength to make TLR activation visible

This change of form can be seen very easily by placing the cells on a specially coated transparent plate and shining a broadband light source on them from below. Certain regions (wavelengths) of the light spectrum are reflected where the light meets the coating—which ones in particular will depend on the processes and changes under way inside the cell.

"We were able to demonstrate that these changes in the reflected wavelengths kick in just a few minutes after adding the signal molecule," says Weindl's colleague Dr. Janine Holze. "We also brought cells into contact with *E. coli* and *Salmonella* lipopolysaccharides.

"Although both components of the cell wall stimulate the same TLR, the reflected spectrum changed in a different way after introducing the *E. coli* LPS than after adding their *Salmonella* counterparts." This suggests that the same receptor is

activated by different molecules in different ways and then triggers specific responses depending on the signal.

Says Weindl, "This method thus permits a much more nuanced explanation than before of how the receptors work as well as simplifying the search for potential drugs with a highly specific profile of action." Possible uses include strengthening the immune response so that the body's own defense forces can fight cancer cells more effectively.

With diseases such as diabetes, rheumatism or Alzheimer's, by contrast, the aim is to weaken specific aspects of the immune response that could otherwise damage healthy tissue, and the new method may well take researchers one step further toward this goal.

More information: Janine Holze et al, Label-free biosensor assay decodes the dynamics of Toll-like receptor signaling, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-53770-9](https://doi.org/10.1038/s41467-024-53770-9)

Provided by University of Bonn

How bacteria attach their cloaks of invisibility to immune defenses

Bacteria have different strategies for protecting themselves. Some bacterial pathogens surround themselves with a shell made of many sugar chains that lie close together, also known as capsular polymers. This protects the bacteria from drying out and physical stress. In addition, the capsule makes the pathogens invisible to our body's own defenses, so to speak, and helps them to survive in the body.

Preventing the capsule from being built would weaken the bacteria significantly. Enzymes that build such capsules are therefore potential targets for drugs and valuable biotechnological tools for the production of vaccines. Despite their

importance, it is still unknown how the capsule polymers—which differ greatly depending on the type of bacteria—are attached to the bacterial membrane.

Anchor chain' and enzymes decoded

A fatty acid molecule is located in the membrane itself as an "anchor." The intermediate piece, i.e. the linker connecting the anchor and the capsule, has now been identified by an international team led by Dr. Timm Fiebig, head of the "Microbial Glycobiology and Vaccine Development" working group at the Institute of Clinical Biochemistry at the Hannover Medical School (MHH). The researchers have not only succeeded in precisely describing this so-called linker in a larger group of bacterial pathogens, but also in characterizing the enzymes called transition transferases that produce the linker.

With the initial description, these are now available as potential target structures for the development of antibacterial agents and as synthesis tools for vaccine development. The work has been [published](#) in the journal *Nature Chemical Biology*.

Capsule-forming enzymes extend the chain of links

The so-called capsular polymerases, which produce the different polysaccharide capsules, also play an important role in the formation of the chain.

"The polymerase recognizes the linker and can extend it," explains Dr. Fiebig. The researchers were also able to clarify this step in the capsular biosynthetic pathway. Using a special chromatography device, they were able to purify the enzymes and the linker, examine their structure and reproduce the capsule synthesis in a test tube.

"This showed that the transition transferases stimulate the capsule polymerase to form particularly long sugar chains, which presumably protect the bacterium even more effectively," the biochemist notes. The Fiebig group has already been able to demonstrate how the capsular polymerases build up the bacterial capsule in earlier studies, including for the bacterium *Haemophilus influenzae* type b (Hib), which causes infections of the upper and lower respiratory tract, but also more serious diseases such as middle ear infection, meningitis or blood poisoning.

Starting point for new antibacterial drugs

In addition to the potential biotechnological use of the enzymes, the work is also important for basic research into the production of capsules.

"On the one hand, we were able to show that transition transferases occur in conserved regions of the bacterial genome, i.e. their genes are always found in the same place in the genome, regardless of the bacterial species," explains Dr. Christa Litschko, a scientist at the institute and the first author of the study.

"On the other hand, we have discovered that the linker is structurally different from the capsular polymer, contrary to previous assumptions." These observations will help to find further candidates of this enzyme class that create connections between the outer membrane of the bacterium and its capsule.

Since different types of bacteria can use the same method to produce the anchor chain, this could be a starting point for drugs that, like antibiotics, can be used against several strains of bacteria. In their research, the scientists have found similarities in the design and construction of the linker in various pathogens that can cause meningitis and urinary tract infections, for example.

"By inactivating the enzymes that build the linker, we could prevent the attachment and formation of the capsule shell, leaving the bacterium defenseless against attack by the immune system," emphasizes Dr. Fiebig. "However, a lot of research is still needed before we get there."

More information: Christa Litschko et al, Transition transferases prime bacterial capsule polymerization, *Nature Chemical Biology* (2024). [DOI: 10.1038/s41589-024-01664-8](https://doi.org/10.1038/s41589-024-01664-8)

Provided by Hannover Medical School

Caterpillar fungus could be the surprising ingredient that stops cancer

NOTTINGHAM, United Kingdom — In a remarkable discovery, researchers have uncovered the key behind a traditional Asian medicine's potential to combat cancer. The compound in question, **cordycepin**, is produced by a caterpillar fungus and has long been touted for its health benefits, but its precise effects on the body have remained elusive – until now.

The study, published in the journal [FEBS Letters](#), was led by Dr. Cornelia de Moor from the University of Nottingham's School of Pharmacy. Her team used advanced techniques to analyze the impact of cordycepin on thousands of genes across multiple cell lines. Their findings reveal that this fungal compound works by interrupting the very signals that [drive uncontrolled cell growth](#) – a hallmark of cancer.

"We have been researching the effects of Cordycepin on a range of diseases for a number of years and with each step we get closer to understanding how it could be used as an [effective treatment](#)," explains Dr. de Moor in a university release. "One of the exciting things to have been happening is that it has become easier and less expensive to do these very large experiments, so we were able to examine thousands of genes at the same time."



A caterpillar infected with Cordyceps militaris, the pretty orange fungus that produces Cordycepin. (Credit: Daniel Winkler – Mushroaming)

The researchers discovered that once inside the cell, cordycepin is converted into a molecule that closely resembles the cell's primary energy carrier, ATP. This cordycepin-based compound then [directly interferes](#) with the cell's growth-promoting pathways, potentially slowing the rapid division seen in cancer cells.

Importantly, this mechanism of action suggests cordycepin derivatives could offer a less damaging alternative to many current cancer treatments, which often take a [heavy toll on healthy cells](#) and tissues.

"Our data confirms that cordycepin is a good starting point for novel cancer medicines and explains its beneficial effects," says Dr. de Moor.

The caterpillar fungus, known as *Cordyceps militaris*, has long been prized in [traditional Chinese and Tibetan medicine](#) for its supposed restorative and invigorating properties. Now, modern science is beginning to unravel the secrets behind this fungus's medicinal potential.

While much work remains to be done, these findings represent an important step forward in the development of new, more targeted cancer therapies. By harnessing the power of nature's own compounds, researchers hope to one day provide patients with effective treatments that minimize harmful side-effects. The road ahead may be long, but the promise of this mushroom-derived molecule has renewed hope in the fight against cancer.

Paper Summary

Methodology

The study aimed to see how cordycepin, a compound derived from fungi, affects cell signaling related to growth. Researchers used various cell types, including cancer cell lines, to see how cordycepin influenced pathways known to drive cell growth and survival. They treated cells with cordycepin, sometimes alongside other compounds like pentostatin (to prevent cordycepin's breakdown), then observed changes in gene expression and protein activity. Techniques like western blotting, RNA sequencing, and cell growth assays helped confirm the effects.

Key Results

Cordycepin slowed down cell growth by disrupting two major signaling pathways, PI3K/mTOR and MEK/ERK. These pathways are crucial for cell division and survival, especially in cancer cells. The compound also reduced the cells' ability to repair wounds (important in cancer spread) and even shrank tumors in animal models. The effects were more pronounced when paired with pentostatin, indicating that preventing cordycepin breakdown increased its potency.

Study Limitations

The study doesn't fully explain how cordycepin disrupts the specific pathways, and results may vary depending on cell types. Also, the study primarily used lab-grown cells and a single animal model, which might not fully replicate how cordycepin would work in human patients. There are also questions about potential side effects that weren't covered.

Discussion & Takeaways

The findings suggest cordycepin could be a valuable tool in cancer treatment, as it targets key pathways that many cancer cells rely on. By blocking multiple growth signals, cordycepin may reduce the chances of drug resistance, which is a major issue with some cancer therapies. Its effectiveness could improve when used alongside other treatments that prevent its breakdown. However, more studies, particularly on humans, are needed to validate these results.

Funding & Disclosures

The study received funding from sources including the University of Nottingham, Versus Arthritis, and other research scholarships. Collaborations involved various institutions, including the University of Dundee and the MRC Toxicology Unit. The study authors disclosed financial support and the contributions of researchers and students who assisted in pilot and supporting experiments.

Ketamine treats depression better than other meds. Researchers finally know why

BUFFALO, N.Y. — In recent years, ketamine — long known for its misuse as a psychedelic party drug — has become a “life-saving” medicine for people battling major depression. Patients praise the drug for producing fast and long-lasting results in low doses. Now, researchers at the University of Buffalo have unlocked the mystery behind ketamine’s effects on the brain at various doses, along with its tremendous impact on mental health.

Their study, published in [Molecular Psychiatry](#), describes where and what receptor ketamine binds to in the brain to provide its anti-depressant effects in as little as a few hours. The research also sheds light on how depression develops in the brain and the potential for other psychedelics to help with other brain conditions.

From Party Drug to Depression Treatment: Ketamine’s Evolution

Ketamine has an interesting history. It first started in the 1960s when doctors used it as an anesthetic. However, ketamine enhances the senses and can make someone experience hallucinations and a feeling of being disconnected from the body at higher doses. This potential for abuse gave ketamine a bad reputation as more people experienced ketamine abuse, and variations of it started showing up as a [popular party drug](#).

Then, in the 2000s, researchers showed evidence of low doses of ketamine quickly relieving symptoms of major depression and suicidal thoughts. Traditional antidepressants take months for people to feel the effects—time that people with suicidal ideation may use to act on their thoughts. Ketamine [almost instantly silences](#) those suicidal thoughts, and its antidepressant action can last for several days and up to a week. There are now ketamine clinics nationwide where the drug is given intravenously to treat depression.

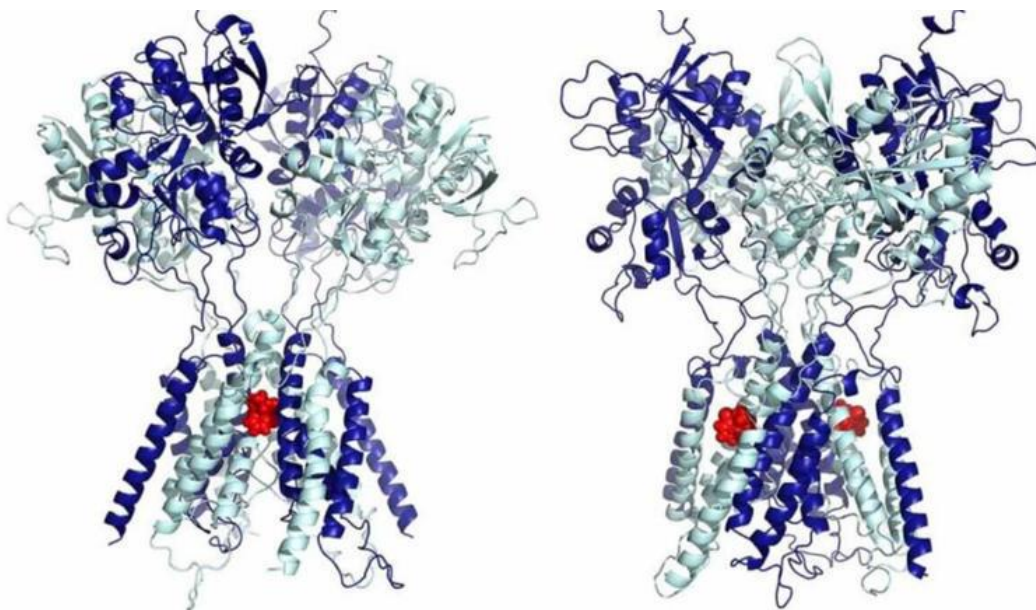
Like a lock and key, ketamine binds to the brain via *N-methyl-D-aspartate* (NMDA) receptors. NMDA receptors are all over the brain and are

essential in maintaining consciousness. The study came about from an observation by Sheila Gupta, a UB undergraduate at the time who would go on to co-author the paper.

“Sheila noticed that when applied onto NMDA receptors that were chronically active, ketamine had a stronger inhibitory effect than expected based on the literature,” says Dr. Gabriela K. Popescu, a professor of biochemistry at the University of Buffalo and senior study author, in a press release. “We were curious about this discrepancy.”

A Surprising Scientific Discovery

The study showed that low-dose ketamine alters the activity of certain NMDA receptors, which could contribute to its [hallucinatory effects](#). It’s also the reason drugs that affect all NMDA receptors produce severely harmful psychiatric side effects that distort a person’s reality.



These images demonstrate the different binding sites in NMDA receptors that the UB team has discovered are responsible for ketamine’s distinct clinical effects, as an anesthetic at high doses and as an anti-depressant at very low doses. The image on the left shows ketamine bound in the central pore of the receptor, which results in anesthetic action; the one on the right shows ketamine bound in the lateral sites, which results in anti-depressive action. (Image credit: Jamie Abbott)

The Buffalo team’s observation was unusual, considering past research into ketamine’s effects on the brain. Years ago, scientists added ketamine to NMDA

receptors to study the anesthetic's [antidepressant effect](#). The drug made little difference.

"This observation caused many experts to turn their attention to receptors located outside synapses, which might be mediating ketamine's antidepressive effects," Popescu explains. The discovery prompted the team to look for other mechanisms than a direct current block, which many scientists assume is how ketamine exerts its effect on the brain.

"Because we track activity from a single receptor molecule over an extended period of time, we can chart the entire behavioral repertoire of each receptor and can identify which part of the process is altered when the receptor binds a drug or when it harbors a mutation," Popescu adds.

At low doses, the authors found ketamine does not work on the main current but currents already activated in the background. It did not affect synaptic receptors, which only activate in short electrical bursts.

"This results in an immediate increase in excitatory transmission, which in turn lifts depressive symptoms," says Popescu. "Moreover, the increase in excitation initiates the formation of new or stronger synapses, which serve to maintain higher excitatory levels even after ketamine has cleared from the body, thus accounting for the [long-term relief](#) observed in patients."

When you give a little ketamine, it plugs up two spots on NMDA receptors. The binding slows down extra-synaptic receptors to relieve depression symptoms. The areas where ketamine binds to the receptor can only hold so much, so higher doses of ketamine cause a spillage from the area and into the pore, blocking synaptic currents and creating an anesthetic effect.

Understanding Ketamine's Dual Action

A 3D model of the NMDA receptor was created to help researchers predict where ketamine would bind. "The simulations show that at high concentrations, which is how it is used as an anesthetic, [ketamine](#) indeed lodges itself in the central ion-conducting pore of the receptors, where it stops ionic current from flowing through the receptor," says Popescu.

Meanwhile, ketamine acts differently at low amounts. It binds itself to two symmetrical sites on the side of the pore. The action does not block the current but slows receptors down, so the current is only slightly inhibited.

According to Popescu, finding the exact site where ketamine attaches to the NMDA receptor can help in finding drugs that work in a similar manner. The next step is to identify these drugs and see if they work as well as ketamine without causing [potential addiction](#).

Paper Summary

Methodology

The researchers used a combination of laboratory techniques to study ketamine's effects on NMDA receptors. They performed whole-cell recordings to measure electrical currents through these receptors in cells, used molecular modeling to predict where ketamine might bind, and conducted single-channel recordings to examine how individual receptors behaved. They tested different concentrations of ketamine and its enantiomers, ranging from 0.002 to 10 microMolar, and examined how various mutations in the receptor affected ketamine's ability to reduce receptor activity.

Results

The study revealed that ketamine has two distinct effects on NMDA receptors. At higher concentrations (micromolar range), it blocks the receptor's central pore. At lower concentrations (nanomolar range), it binds to a previously unknown site on the side of the receptor, causing the receptor to become less active through a different mechanism. The R(+) form of ketamine showed stronger interactions with this side site than the S(-) form, and mutations of specific amino acids in this region affected ketamine's ability to reduce receptor activity at low concentrations.

Limitations

The study was conducted using isolated cells and purified proteins, which may not fully represent how ketamine works in the complex environment of the

human brain. The researchers also note that ketamine's effects can vary depending on factors like pH, membrane composition, and voltage, which could affect its clinical effectiveness in different patients or brain regions.

Discussion and Takeaways

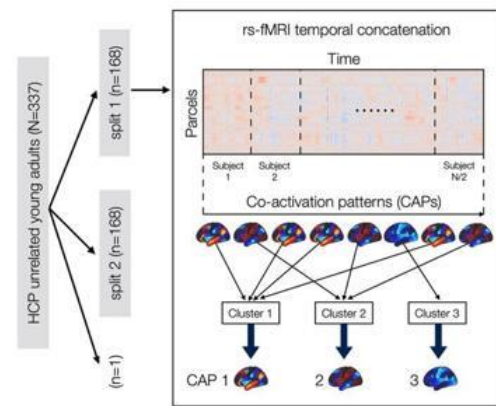
This research provides a molecular explanation for why ketamine's antidepressant effects occur at lower doses than its anesthetic effects and why similar drugs don't work as antidepressants. The discovery of a new binding site could lead to the development of more targeted treatments for depression and other neurological conditions. The findings also help explain why ketamine's effects might vary between individuals based on factors like brain pH and cell membrane composition.

Funding and Disclosures

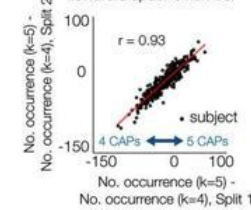
The research was funded by multiple National Institutes of Health grants (R35NS132248, R01MH118298, and R01NS108750). The authors declared no competing interests.

Biomarkers for psychiatric illness? Study gets researchers one step closer

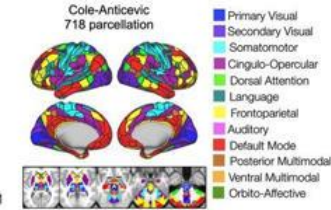
A Overview: reproducible CAP analysis with shuffled split-half resampling



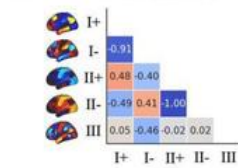
B Individual's preference toward a specific number



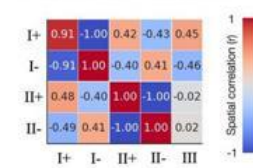
D Resting state networks



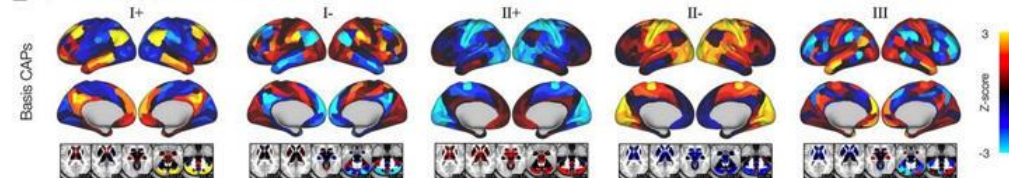
C 5-CAP basis set



4-CAPs and 5-CAPs basis sets



E Spatial topography of five basis CAPs



F Spatial similarity of five basis CAPs to pre-defined resting state networks

A reproducible set of CAPs in the whole-brain rs-fMRI involve recurring mixed representations of canonical resting-state networks. Credit: PLOS Biology (2024). DOI: 10.1371/journal.pbio.3002808

A key challenge in the effort to link brain activity with behavior is that brain activity, measured by functional magnetic resonance imaging (fMRI), for instance, is extraordinarily complex. That complexity can make it difficult to find recurring activity patterns across different people or within individuals.

In a new study, Yale researchers were able to take fMRI data, reduce its complexity, and in doing so, uncover stable patterns of activity shared across more than 300 different people. The findings, researchers say, are a promising step forward in uncovering biomarkers for psychiatric disorders.

The study was [published](#) Sept. 24 in the journal *PLOS Biology*.

"Because human brain activity is so complex, it can be unreliable, particularly when you're aiming for reproducibility," said Kangjoo Lee, lead author of the

study and an associate research scientist in the Department of Psychiatry at Yale School of Medicine. "In this study, we wanted to capture features of brain activity that were linked to features of human behavior and were also consistent across different people."

To do this, the researchers used fMRI data from 337 healthy young adults, each of whom underwent four 15-minute fMRI scans.

"These images, which were taken during a resting state, were essentially snapshots of brain activity," said Lee. "So over time, we were able to observe moment-to-moment changes in brain activity."

Each snapshot represented activity occurring throughout the brain in a particular moment, which included many different brain networks engaged in many different processes, contributing to the data's complexity.

To reveal shared patterns in the data, the researchers applied an approach called data dimension reduction, which, Lee says, essentially takes high-dimensional, complex data like brain activity and reduces it to a lower dimensional space. The idea is similar to representing the complex pattern of a dance sequence through a small number of basic movements.

After reducing the complexity of the data, the researchers uncovered three shared patterns of brain activity that were "highly recurring across participants and within participants," Lee said.

Further, while these patterns were found among all participants, there were also differences among the individuals. For instance, the researchers observed differences in terms of which of the three states different individuals spent the most time, how long they lingered in particular states, and which states people transitioned between.

The findings suggest these types of patterns could reveal information about something shared across different people—such as a behavior—as well as individual differences related to those behaviors or how they change over time.

The researchers are now considering how this approach could be applied to psychiatric disorders.

"Here we looked at healthy adults, but if we ran a similar analysis in a clinical population, we may find recurring brain patterns that are shared among that population but not among healthy individuals," said co-senior author John Murray, a former professor of psychiatry and physics at Yale, now a professor at Dartmouth College. "Therefore, these shared patterns could represent biomarkers of psychiatric illness that are useful in clinical settings."

The current study lends support to that idea. The researchers found that the patterns in which people spent more time and the patterns that they transitioned to were associated with cognitive function, emotion regulation, and alcohol and substance use.

"Uncovering recurring brain patterns in clinical populations could tell us something about the neural activity associated with specific symptoms and how it differs between individuals," said Lee.

More information: Kangjoo Lee et al, Human brain state dynamics are highly reproducible and associated with neural and behavioral features, *PLOS Biology* (2024). [DOI: 10.1371/journal.pbio.3002808](https://doi.org/10.1371/journal.pbio.3002808)

Provided by Yale University

Brain circuits tied to depression's "negativity effect" uncovered

A recent study conducted by scientists in France and published in [Translational Psychiatry](#) offers new insights into how depression affects the brain's processing of positive and negative experiences. The research found that during depressive episodes, specific brain circuits become hyperactive in response to negative stimuli, while those involved in perceiving positive stimuli

are less active. This shift in brain activity may contribute to the pessimistic outlook commonly seen in individuals with depression. Understanding how depression affects the brain's interpretation of everyday experiences is important for developing more effective treatments. Depression is marked by a "negativity bias," where people interpret situations and sensory experiences—such as sights, sounds, and smells—in an excessively negative way.

Scientists know this bias plays a significant role in reinforcing depressive symptoms, but they don't fully understand the brain mechanisms behind it. The new study aimed to explore the brain circuits involved in this bias, focusing on the amygdala, a brain region known for its role in processing emotions.

"Negative emotional biases alter the perception of emotional stimuli in individuals with depression. As a result, pleasant stimuli lose their hedonic value, while negative stimuli become even more negative," said study authors Chantal Henry (a professor of psychiatry at Paris Cité University) and Mariana Alonso (a research associate at Institut Pasteur), who are both affiliated with the [Emotional Circuits](#) research group.

"These biases lead to the development and maintenance of depressive symptoms and are assessed by various tests in humans. However, there are very few tests in animals to measure emotional bias in a translational way. Importantly, restoring these biases is essential for recovering from a depressive state, making it crucial to understand their mechanisms."

To investigate this, the researchers used both human participants and a mouse model of depression. In the human part of the study, the team recruited 48 adults with bipolar disorder, 23 of whom were currently experiencing a depressive episode. They also included 11 individuals without a history of mental illness as a control group. All participants completed an "odor test," a test designed to assess how they rated different smells. Using this method, the researchers could determine whether the participants had a negativity bias in their perception of odors, especially for those in a depressive state.

"The olfactory preference test we developed is simple but allows us to study essential emotional processes involved in the onset and maintenance of depression," Henry and Alonso explained.

In parallel, the scientists created a similar depressive state in mice by giving them a chemical (corticosterone) that induces depression-like behavior. They then used an odor preference test, where the mice were exposed to neutral, pleasant, and unpleasant odors, and their behaviors were observed. Researchers monitored the time the mice spent near each odor, assessing whether depressive mice displayed a similar negativity bias.

To further understand the brain mechanisms involved, the scientists used imaging techniques on the mice to examine changes in brain circuits, focusing on two specific pathways in the amygdala: the basolateral amygdala-to-nucleus accumbens pathway and the basolateral amygdala-to-central amygdala pathway. The first pathway is generally associated with positive experiences, while the second is associated with negative experiences.

The researchers found significant differences between the depressed and non-depressed groups, both in humans and in mice. Depressed individuals and depressive-like mice rated or responded more negatively to odors, even to neutral or positive ones. This negativity bias was associated with heightened activity in the brain circuits responsible for processing negative experiences. In the mice, researchers observed that the basolateral amygdala-to-central amygdala circuit was more active in those with depressive-like symptoms, while the pathway associated with positive experiences was less active.

The mice treated with the antidepressant fluoxetine showed a reduction in negativity bias, suggesting that these brain pathways are indeed tied to depressive symptoms. When specific neurons in the basolateral amygdala-to-nucleus accumbens pathway were activated in the depressive mice, their negativity bias diminished, and they responded more positively to neutral and pleasant smells. However, this manipulation did not change their negative response to unpleasant odors, suggesting that additional brain pathways might be required to fully address this bias in depressive states.

"Using an olfactory test, we demonstrated the presence of a negative emotional bias in mice with a depressive phenotype (which mimics some symptoms of human depression), closely resembling what is observed in depressed patients (pleasant odors are less pleasant, and unpleasant odors are more aversive)," Henry and Alonso told PsyPost. "We showed that this bias is linked to an imbalance in the activation of specific neurons within a small brain area, the

amygdala, which generates emotions. By manipulating these neurons in mice, we were able to correct this bias by increasing attractiveness of positive odors, and induce recovery from the depressive phenotype, demonstrating that it represents a critical target for understanding the action of antidepressants."

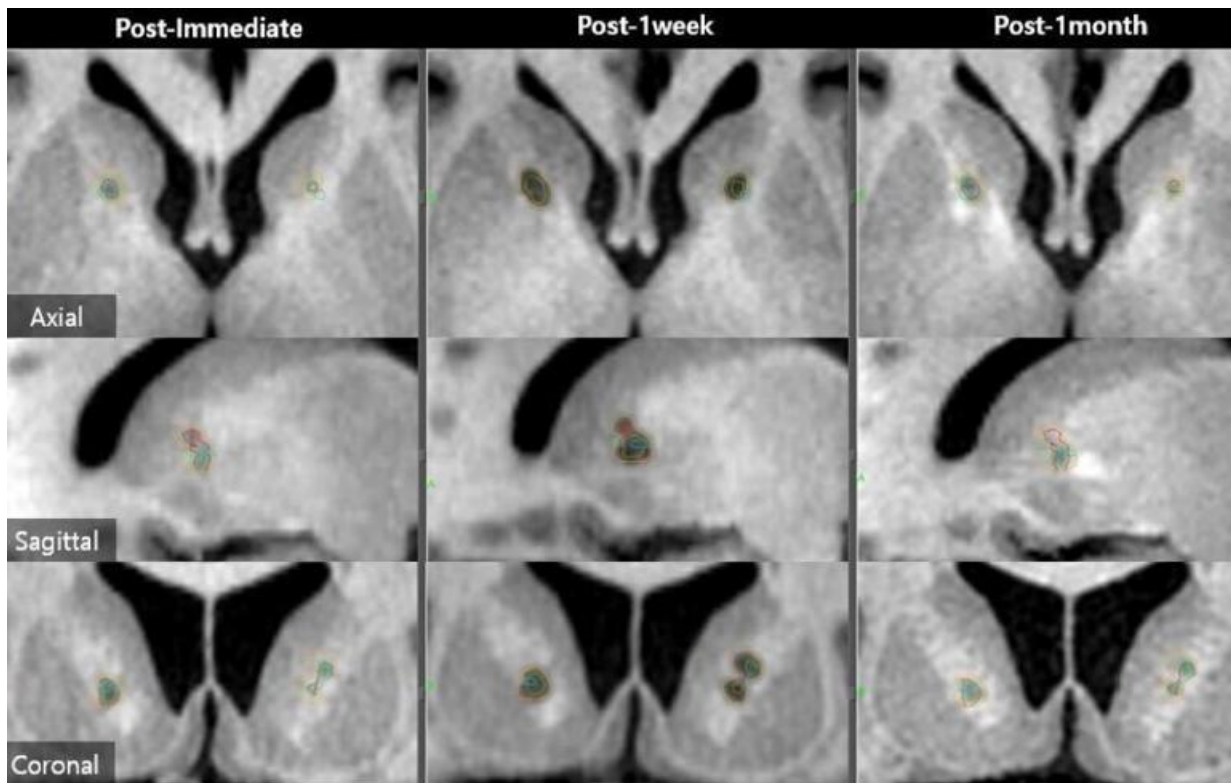
While the study sheds light on how certain brain circuits contribute to negativity bias, it has some limitations. The odor tests used in both humans and mice were a simple way to measure emotional responses but might not capture the full complexity of depressive symptoms. Also, while the mouse model of depression is helpful for studying some aspects of the illness, it cannot replicate the full experience of depression in humans, particularly in cases of bipolar disorder. Future studies could explore additional brain circuits that might contribute to depressive symptoms, as well as examine whether similar biases occur with visual or auditory stimuli.

Long-term, this research could help scientists develop more targeted therapies for depression. By focusing on the specific brain circuits associated with negative and positive perception, researchers hope to create treatments that reduce negativity bias in individuals with depression, offering new ways to alleviate symptoms for patients who do not respond to traditional antidepressants.

"Around 30% of patients with depression are resistant to conventional medical treatment with antidepressants," Henry and Alonso said. "Our goal is to pursue this research to improve our understanding of the mechanisms at the cellular and molecular levels, in order to identify more precise molecular targets exhibiting antidepressant properties."

The study, "[Disrupted basolateral amygdala circuits supports negative valence bias in depressive states](#)," was authored by Mathilde Bigot, Claire-Hélène De Badts, Axel Benchetrit, Éléonore Vicq, Carine Moigneu, Manon Meyrel, Sébastien Wagner, Alexandru Adrian Hennrich, Josselin Houenou, Pierre-Marie Lledo, Chantal Henry, and Mariana Alonso.

Study highlights novel non-invasive brain surgery for lasting relief from severe obsessive-compulsive disorder



Periodic changes of MRgFUS capsulotomy lesion size. Credit: Molecular Psychiatry (2024). DOI: 10.1038/s41380-024-02799-9

When conventional non-invasive treatments for psychiatric diseases fail, clinicians inevitably have to consider brain surgery. However, brain surgery for psychiatric diseases has long been taboo among the general public due to the infamous history of lobotomy. Thankfully, advancements in brain surgery in recent years are changing the narrative.

Bilateral capsulotomy, more commonly known as deep brain stimulation, is a form of brain surgery that has been garnering attention in treating treatment-resistant or refractory obsessive-compulsive disorder (OCD). Patients with

refractory OCD experience a debilitating degree of repetitive behaviors and thoughts that they are unable to control, thus downgrading their quality of life.

A group of researchers from South Korea demonstrated that a novel non-invasive bilateral capsulotomy called magnetic resonance-guided focused ultrasound (MRgFUS) capsulotomy is efficacious and safe in treating refractory OCD for up to two years. MRgFUS capsulotomy non-invasively and precisely ablates tissues in the brain region of interest. However, the sustained efficacy of this treatment option was unclear.

Recently, the same research group conducted a long-term follow-up study of 10 years involving patients with refractory OCD who underwent MRgFUS capsulotomy. They reported that MRgFUS capsulotomy is an efficacious and safe treatment option for refractory OCD, with high patient satisfaction, even at 10 years, establishing its lasting positive effects in patients. Their findings were published in [Molecular Psychiatry](#) on October 28, 2024.

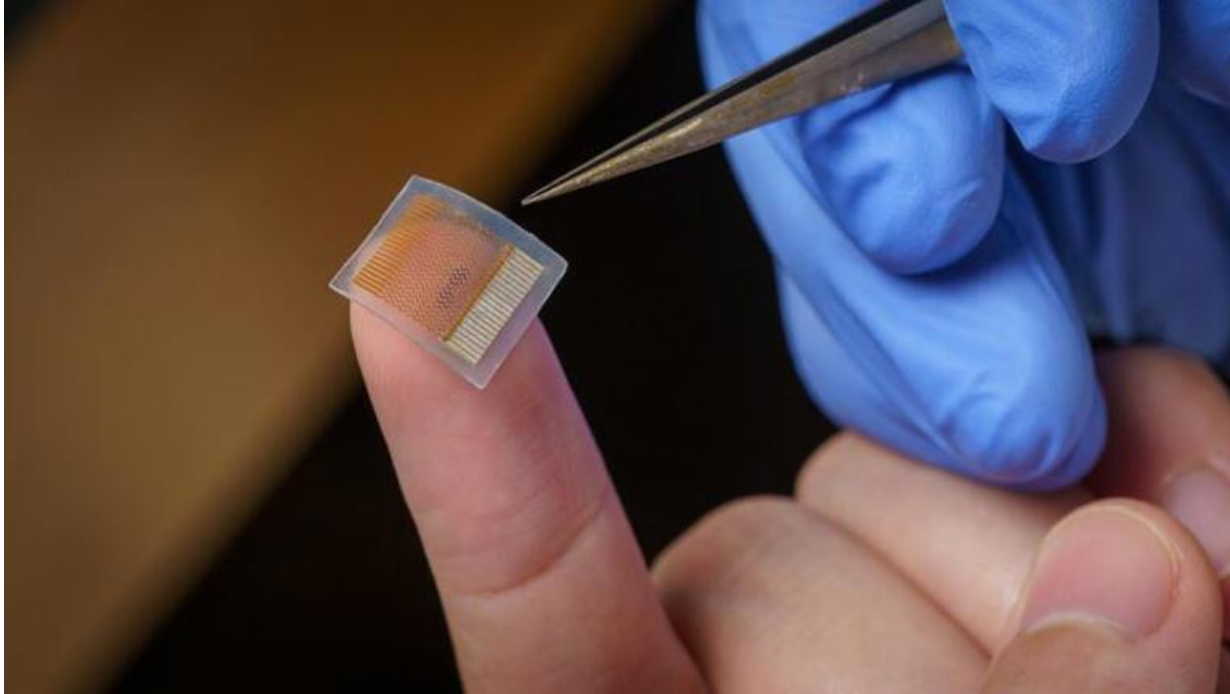
This study has achieved multiple milestones in OCD research, offering hope to many patients experiencing refractory OCD. Accordingly, Dr. Jin Woo Chang from Korea University Anam Hospital who is a lead researcher in the study, says, "These studies involve the world's first clinical trial for OCD with MRgFUS. The current study is also the world's first long-term follow-up study for OCD after treatment."

Interestingly, the application of MRgFUS capsulotomy may not be just limited to refractory OCD. Dr. Chang says, "The results from our clinical trial also imply the potential role of MRgFUS in managing other common psychiatric diseases, such as refractory depression, due to its simplicity and safety."

With the clinical application of MRgFUS capsulotomy on the horizon, Dr. Chang concludes, "With the rapid development of new surgical techniques like MRgFUS, it is possible to cure psychiatric diseases without additional complications. I am convinced this new technology will offer a new lease of life for those suffering and struggling from serious psychiatric problems."

More information: Kyung Won Chang et al, Long-term clinical outcome of a novel bilateral capsulotomy with focused ultrasound in refractory obsessive-compulsive disorder treatment, *Molecular Psychiatry* (2024). [DOI: 10.1038/s41380-024-02799-9](#) Provided by Korea University College of Medicine

This wearable ultrasound patch measures blood pressure



A wearable ultrasound patch for continuous and noninvasive blood pressure monitoring marks a major milestone in wearable technology research. The soft, stretchy patch provides real-time readings of blood pressure deep within the body, offering a simple, reliable alternative to current clinical methods. © David Baillot / UC San Diego

A new wearable ultrasound patch that is a continuous, noninvasive blood pressure monitor could improve the quality of clinical and in-home cardiovascular health monitoring, according to the researchers at University of California San Diego who developed and tested it on more than 100 patients.

Details of the technology and its testing were published in [Nature Biomedical Engineering](#).

“Traditional blood pressure measurements with a cuff, which are limited to providing one-time blood pressure values, can miss critical patterns. Our wearable patch offers a continuous stream of blood pressure waveform data, allowing it to reveal detailed trends in blood pressure fluctuations,” study co-first author Sai Zhou, who recently earned his doctorate in materials science and

engineering from the UC San Diego Jacobs School of Engineering, said in a written statement.

The postage-stamp-sized device is soft and stretchy and adheres to the skin. The researchers said that wearing it on the forearm offers precise, real-time readings of blood pressure deep in the body. He said the silicone-based patch has an array of little transducers between stretchable copper electrodes. The transducers transmit and receive ultrasound waves that can track changes in the blood vessel diameters, which are then converted to blood pressure values.

The device when tested was comparable in its results to both a blood pressure cuff and an arterial line, which is a sensor inserted into the artery to continuously monitor blood pressure, per a news release on the work. The arterial line is the gold standard for blood pressure monitoring in intensive care units and operating rooms, but it's invasive and can be painful. Nor can patients with an arterial line move around freely. Their movement is restricted.

The patch, comparable in its results, overcomes those issues.

The researchers reengineered an earlier patch made in the lab of Sheng Xu, a professor in the Aiso Yufeng Li Family Department of Chemical and Nano Engineering at the university. They made a pair of improvements to bolster the performance. First, they packed the transducers closer together so they'd have broader coverage to do a better job of targeting smaller arteries such as the brachial and radial arteries. They also reduced vibrations to improve signal clarity and tracking accuracy of the arterial walls.

Testing the device

The device was tested in different ways with 117 different patients doing a variety of activities in different settings. In one test, seven participants wore the patch while cycling, raising an arm or leg, meditating, eating and doing other tasks. In 85 subjects, the patch was tested as they changed positions, including transitioning from sitting to standing.

In all cases, the results closely matched those of blood pressure cuffs. But they also matched findings from arterial lines used in patients in intensive care when

the patches were used with 21 patients in a cardiac catheterization lab or who were admitted to intensive care after surgery.

The researchers hailed the findings, saying they showcase “its potential as a noninvasive alternative.”

“A big advance of this work is how thoroughly we validated this technology, thanks to the work of our medical collaborators,” said Xu. “Blood pressure can be all over the place depending on factors like white coat syndrome, masked hypertension, daily activities or use of medication, which makes it tricky to get an accurate diagnosis or manage treatment. That’s why it was so important for us to test this device in a wide variety of real-world and clinical settings. Many studies on wearable devices skip these steps during development, but we made sure to cover it all.” The researchers are planning large-scale clinical trials. They also want to validate a wireless, battery-powered version for long-term use.

Cognitive behavioral therapy enhances brain circuits to relieve depression

Cognitive behavioral therapy, one of the most common treatments for depression, can teach skills for coping with everyday troubles, reinforce healthy behaviors and counter negative thoughts. But can altering thoughts and behaviors lead to lasting changes in the brain?

New research led by Stanford Medicine has found that it can—if a therapy is matched with the right patients. In a study of adults with both depression and obesity—a difficult-to-treat combination—cognitive behavioral therapy that focused on problem solving reduced depression in a third of patients. These patients also showed adaptative changes in their brain circuitry.

Moreover, these neural adaptations were apparent after just two months of therapy and could predict which patients would benefit from long-term therapy.

The findings add to evidence that choosing treatments based on the neurological underpinnings of a patient's depression—which vary among people—increases the odds of success.

The same concept is already standard practice in other medical specialties.

"If you had chest pain, your physician would suggest some tests—an electrocardiogram, a heart scan, maybe a blood test—to work out the cause and which treatments to consider," said Leanne Williams, Ph.D., the Vincent V.C. Woo Professor, a professor of psychiatry and behavioral sciences, and the director of Stanford Medicine's Center for Precision Mental Health and Wellness.

"Yet in depression, we have no tests being used. You have this broad sense of emotional pain, but it's a trial-and-error process to choose a treatment, because we have no tests for what is going on in the brain."

Williams and Jun Ma, MD, Ph.D., professor of academic medicine and geriatrics at the University of Illinois at Chicago, are co-senior authors of the [study](#) published Sept. 4 in *Science Translational Medicine*. The work is part of a larger clinical trial called RAINBOW (Research Aimed at Improving Both Mood and Weight).

Problem solving

The form of cognitive behavioral therapy used in the trial, known as problem-solving therapy, is designed to improve cognitive skills used in planning, troubleshooting and tuning out irrelevant information. A therapist guides patients in identifying real-life problems—a conflict with a roommate, say—brainstorming solutions and choosing the best one.

These cognitive skills depend on a particular set of neurons that function together, known as the cognitive control circuit.

Previous work from Williams' lab, which identified [six biotypes](#) of depression based on patterns of brain activity, estimated that a quarter of people with depression have dysfunction with their cognitive control circuits—either too much or too little activity.

The participants in the new study were adults diagnosed with both major depression and obesity, a confluence of symptoms that often indicates problems with the cognitive control circuit. Patients with this profile generally do poorly on antidepressants: They have a dismal response rate of 17%.

Of the 108 participants, 59 underwent a year-long program of problem-solving therapy in addition to their usual care, such as medications and visits to a primary care physician. The other 49 received only usual care.

They were given fMRI brain scans at the beginning of the study, then after two months, six months, 12 months and 24 months. During the brain scans, the participants completed a test that involves pressing or not pressing a button according to text on a screen—a task known to engage the cognitive control circuit. The test allowed the researchers to gauge changes in the activity of that circuit throughout the study.

"We wanted to see whether this problem-solving therapy in particular could modulate the cognitive control circuit," said Xue Zhang, Ph.D., a postdoctoral scholar in psychiatry who is the lead author of the study.

With each brain scan, participants also filled out standard questionnaires that assessed their problem-solving ability and depression symptoms.

Working smarter

As with any other depression treatment, problem-solving therapy didn't work for everyone. But 32% of participants responded to the therapy, meaning their symptom severity decreased by half or more.

"That's a huge improvement over the 17% response rate for antidepressants," Zhang said.

When researchers examined the brain scans, they found that in the group receiving only usual care, a cognitive control circuit that became less active over the course of the study correlated with worsening problem-solving ability.

But in the group receiving therapy, the pattern was reversed: Decreased activity correlated with enhanced problem-solving ability. The researchers think this may be due to their brains learning, through the therapy, to process information more efficiently.

"We believe they have more efficient cognitive processing, meaning now they need fewer resources in the cognitive control circuit to do the same behavior," Zhang said.

Before the therapy, their brains had been working harder; now, they were working smarter.

Both groups, on average, improved in their overall depression severity. But when Zhang dug deeper into the 20-item depression assessment, she found that the depression symptom most relevant to cognitive control—"feeling everything is an effort"—benefited from the more efficient cognitive processing gained from the therapy.

"We're seeing that we can pinpoint the improvement specific to the cognitive aspect of depression, which is what drives disability because it has the biggest impact on real-world functioning," Williams said.

Indeed, some participants reported that problem-solving therapy helped them think more clearly, allowing them to return to work, resume hobbies and manage social interactions.

Fast track to recovery

Just two months into the study, brain scans showed changes in cognitive control circuit activity in the therapy group.

"That's important, because it tells us that there is an actual brain change going on early, and it's in the time frame that you'd expect brain plasticity," Williams said. "Real-world problem solving is literally changing the brain in a couple of months."

The idea that thoughts and behaviors can modify brain circuits is not so different from how exercise—a behavior—strengthens muscles, she added.

The researchers found that these early changes signaled which patients were responding to the therapy and would likely improve on problem-solving skills and depression symptoms at six months, 12 months and even one year after the therapy ended, at 24 months. That means a brain scan could be used to predict which patients are the best candidates for problem-solving therapy.

It's a step toward Williams' vision of precision psychiatry—using brain activity to match patients with the therapies most likely to help them, fast-tracking them to recovery.

"It's definitely advancing the science," Zhang said. "But it's also going to transform a lot of people's lives."

Researchers from University of Washington, University of Pittsburgh School of Medicine and The Ohio State University also contributed to the work.

More information: Xue Zhang et al, Adaptive cognitive control circuit changes associated with problem-solving ability and depression symptom outcomes over 24 months, *Science Translational Medicine* (2024). DOI: [10.1126/scitranslmed.adh3172](https://doi.org/10.1126/scitranslmed.adh3172)

Provided by Stanford University Medical Center

Startling Findings: High-Fructose Corn Syrup Linked to Cancer Growth

BY WASHINGTON UNIVERSITY IN ST. LOUIS DECEMBER 11, 2024 [NO COMMENTS](#) 8 MINS READ

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Recent research indicates that the liver converts fructose, increasingly used in modern diets, into nutrients that promote tumor growth in several cancers, suggesting new dietary strategies and therapeutic approaches to combat cancer.

The liver converts dietary fructose into nutrients that feed tumor growth, linking high-fructose consumption to cancer progression. This finding highlights both dietary caution and potential new cancer treatments.

Fructose consumption has risen significantly over the past five decades, primarily due to the extensive use of high-fructose corn syrup as a sweetener in beverages and ultra-processed foods. Recent research from [Washington University in St. Louis](#) reveals that dietary fructose promotes tumor growth in animal models of melanoma, breast cancer, and cervical cancer. However, the study, published on Dec. 4 in the journal *Nature*, indicates that fructose does not directly fuel tumors.

Instead, WashU scientists discovered that the liver converts fructose into usable nutrients for cancer cells, a compelling finding that could open up new avenues for care and treatment of many different types of cancer.

“The idea that you can tackle cancer with diet is intriguing,” said Gary Patti, the Michael and Tana Powell Professor of Chemistry in Arts & Sciences and a professor of genetics and of medicine at the School of Medicine, all at WashU.



Gary Patti, the Michael and Tana Powell Professor of Chemistry in Arts & Sciences and a professor of genetics and of medicine at the School of Medicine, all at WashU. Credit: WashU

“When we think about tumors, we tend to focus on what dietary components they consume directly. You put something in your body, and then you imagine that the tumor takes it up,” Patti said. “But humans are complex. What you put in your body can be consumed by healthy tissue and then converted into something else that tumors use.”

“Our initial expectation was that tumor cells metabolize fructose just like glucose, directly utilizing its atoms to build new cellular components such as DNA. We were surprised that fructose was barely metabolized in the tumor types we tested,” said the study’s first author, Ronald Fowle-Grider, a postdoctoral fellow in Patti’s lab. “We quickly learned that the tumor cells alone don’t tell the whole story. Equally important is the liver, which transforms fructose into nutrients that the tumors can use.”

Using metabolomics — a method of profiling small molecules as they move through cells and across different tissues in the body — the researchers concluded that one way in which high levels of fructose consumption promote tumor growth is by increasing the availability of circulating lipids in the blood. These lipids are building blocks for the cell membrane, and cancer cells need them to grow.

“We looked at numerous different cancers in various tissues throughout the body, and they all followed the same mechanism,” Patti said.

The corn syrup era

Scientists have long recognized that cancer cells have a strong affinity for glucose, a simple sugar that is the body's preferred carbohydrate-based energy source.

In terms of its chemical structure, fructose is similar to glucose. They are both common types of sugar, with the same chemical formula, but they differ in how the body metabolizes them. Glucose is processed throughout the whole body, while fructose is almost entirely metabolized by the small intestine and liver.

Both sugars are found naturally in fruits, vegetables, dairy products and grains. They are also added as sweeteners in many processed foods. Fructose, in particular, has penetrated the American diet over the last few decades. It is favored by the food industry because it is sweeter than glucose.

Prior to the 1960s, people consumed relatively little fructose compared with today's numbers. A century ago, an average person consumed just 5-10 pounds of fructose per year. To put it in familiar terms, that is roughly equal to the weight of a gallon of milk. In the 21st century, that number has increased to be as high as the equivalent of 15 gallons of milk.

"If you go through your pantry and look for the items that contain high-fructose corn syrup, which is the most common form of fructose, it is pretty astonishing," said Patti, who is also a research member of the Siteman Cancer Center, based at Barnes-Jewish Hospital and WashU Medicine, and the Center for Human Nutrition at WashU Medicine.

"Almost everything has it. It's not just candy and cake, but also foods such as pasta sauce, salad dressing and ketchup," he said. "Unless you actively seek to avoid it, it's probably part of your diet."

Cancer's appetite for fructose

Given the rapid rise in the consumption of dietary fructose over recent decades, the WashU researchers wanted to know more about how fructose impacts the growth of tumors.

Patti and Fowle-Grider began their investigation by feeding tumor-bearing animals a diet rich in fructose, then measuring how quickly their tumors grew. The researchers found that added fructose promoted tumor growth without changing body weight, fasting glucose, or fasting insulin levels.

"We were surprised to see that it had a rather dramatic impact. In some cases, the growth rate of the tumors accelerated by two-fold or even higher," Patti said. "Eating a lot of fructose was clearly very bad for the progression of these tumors."



Ronald Fowle-Grider, postdoctoral

fellow in chemistry, Washington University in St. Louis. Credit: WashU

But the next step in their experiments initially stumped them. When Fowle-Grider attempted to repeat a version of this test by feeding fructose to cancer cells isolated in a dish, the cells did not respond. “In most cases, they grew almost as slowly as if we gave them no sugar at all,” Patti said.

So, Patti and Fowle-Grider went back to looking at changes in the small molecules in the blood of animals fed high-fructose diets. Using metabolomics, they identified elevated levels of a variety of lipid species, including lysophosphatidylcholines (LPCs). Additional dish tests showed that liver cells that were fed fructose release LPCs.

“Interestingly, the cancer cells themselves were unable to use fructose readily as a nutrient because they do not express the right biochemical machinery,” Patti said. “Liver cells do. This allows them to convert fructose into LPCs, which they can secrete to feed tumors.”

A defining characteristic of cancer is uncontrolled proliferation of malignant cells. Each time a cell divides, it must replicate its contents, including membranes. This requires a substantial amount of lipids. While lipids can be synthesized from scratch, it is much easier for cancer cells to simply take lipids up from their surrounding environment.

“Over the past few years, it’s become clear that many cancer cells prefer to take up lipids rather than make them,” Patti noted. “The complication is that most lipids are insoluble in blood and require rather complex transport mechanisms. LPCs are unique. They might provide the most effective and efficient way to support tumor growth.”

Avoiding fructose

Interestingly, over the same period of time when human fructose consumption has surged, a number of cancers have become increasingly more prevalent among people under the age of 50. This raises the question whether the trends are linked. With \$25 million in support from Cancer Grand Challenges, Patti recently teamed up with Yin Cao, an associate professor of surgery at WashU Medicine, and other investigators from around the world, none of whom were involved in this study, to investigate possible connections.

“It will be exciting to better understand how dietary fructose influences cancer incidence. But one take-home message from this current study is that if you are unfortunate enough to have cancer, then you probably want to think about avoiding fructose. Sadly, that is easier said than done,” Patti said.

Aside from dietary intervention, the study authors said that this research could help us develop a way to prevent fructose from driving tumor growth therapeutically, using drugs.

“An implication of these findings is that we do not have to limit ourselves to therapeutics that only target disease cells,” Patti said. “Rather, we can think about targeting the metabolism of healthy cells to treat cancer. This has worked with mice in our study, but we would like to take advantage of our observations and try to improve the lives of patients.”

The study authors are working with clinical partners at WashU Medicine to explore a clinical trial related to fructose in the diet.

Reference: “Dietary fructose enhances tumour growth indirectly via interorgan lipid transfer” by Ronald Fowle-Grider, Joe L. Rowles III, Isabel Shen, Yahui Wang, Michaela Schwaiger-Haber, Alden J. Dunham, Kay Jayachandran, Matthew Inkman, Michael Zahner, Fuad J. Naser, Madelyn M. Jackstadt, Jonathan L. Spalding, Sarah Chiang, Kyle S. McCommis, Roland E. Dolle, Eva T. Kramer, Sarah M. Zimmerman, George P. Souroullas, Brian N. Finck, Leah P. Shriver, Charles K. Kaufman, Julie K. Schwarz, Jin Zhang and Gary J. Patti, 4 December 2024, *Nature*.

[DOI: 10.1038/s41586-024-08258-3](https://doi.org/10.1038/s41586-024-08258-3)

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Cannabis Use Linked to Epigenetic Changes, Study Finds



Using cannabis may cause changes in the human body's epigenome, a study of over 1,000 adults suggests. The [epigenome](#) functions like a set of switches, activating or deactivating genes to change how our bodies function.

"We observed associations between cumulative marijuana use and multiple epigenetic markers across time," [explained](#) epidemiologist Lifang Hou from Northwestern University when the research was published in 2023.

[Cannabis](#) is a [commonly used substance in the United States](#), with 49 percent of people trying it at least once, Hou and a team of US researchers report in their [published paper](#).

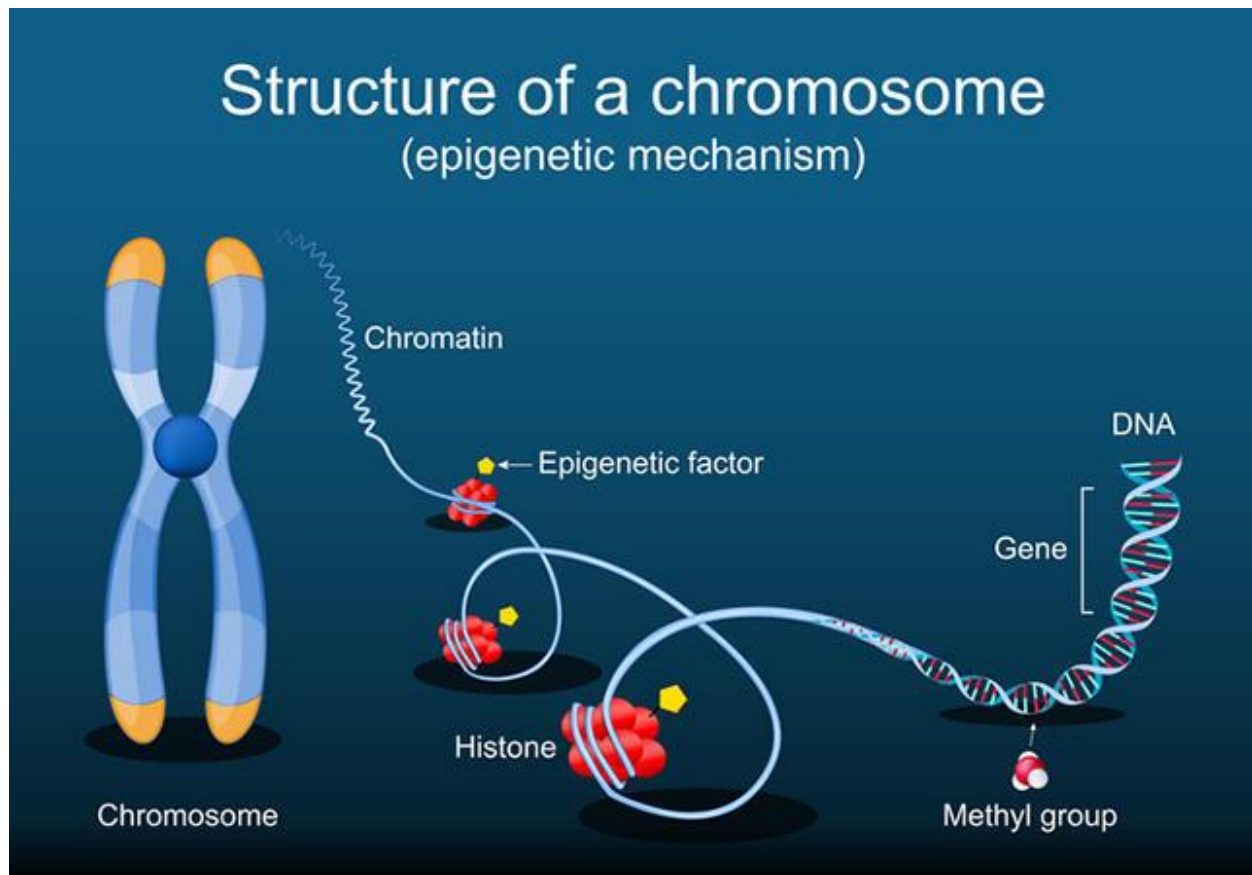
Some US states and [other countries](#) have made cannabis legal, but we still don't fully understand its [effects on our health](#).

The researchers studied around 1,000 adults who had participated in a long-term previous study where they had been asked about their cannabis use over a 20-year period.

Study participants provided blood samples on two occasions during that time, at the 15- and 20-year points. They were aged between 18 and 30 at baseline, or 'year 0'.

Using these blood samples from five years apart, Hou and her team looked at the [epigenetic changes](#), specifically [DNA methylation](#) levels, of people who had used cannabis recently or for a long time.

The addition or removal of [methyl groups](#) from DNA is one of the most studied epigenetic modifications. Without changing the genomic sequence, it changes the activity of genes, because it's harder for cells to read the genome instruction manual with these molecular changes in their way.



When epigenetic factors, which can come from other genes or the environment inside a cell or beyond, recruit a methyl group, it changes the expression of our genes. (ttsz/iStock/Getty Images)

Environmental and lifestyle factors can trigger these methylation changes, which can be [passed onto future generations](#), and blood [biomarkers](#) can provide information about both recent and historical exposures.

"We previously identified associations between marijuana use and the aging process as captured through DNA methylation," Hou [said](#).

"We wanted to further explore whether specific epigenetic factors were associated with marijuana and whether these factors are related to health outcomes."

Environmental and lifestyle factors can trigger methylation changes, which can be passed on to future generations.

The comprehensive data on the participants' cannabis use allowed them to estimate cumulative use over time as well as recent use and compare it with DNA methylation markers in their blood for analysis.

They found numerous DNA methylation markers in the 15-year blood samples, 22 that were associated with recent use, and 31 associated with cumulative cannabis use. In the samples taken at the 20-year point, they identified 132 markers linked to recent use and 16 linked to cumulative use.



The buds of a cannabis plant contain the most cannabinoids. (Esteban López/Unsplash)

"Interestingly, we consistently identified one marker that has previously been associated with tobacco use," Hou [explained](#), "suggesting a potential shared epigenetic regulation between tobacco and marijuana use."

Multiple epigenetic changes associated with cannabis use had previously been linked to things like [cellular proliferation](#), [hormone signaling](#), infections, neurological disorders like [schizophrenia](#) and [bipolar disorder](#), and [substance use disorders](#).

It's important to note that this study doesn't prove that cannabis directly causes these changes or causes health problems.

"This research has provided novel insights into the association between marijuana use and epigenetic factors," [said](#) epidemiologist Drew Nannini from Northwestern University.

"Additional studies are needed to determine whether these associations are consistently observed in different populations. Moreover, studies examining the effect of marijuana on age-related health outcomes may provide further insight into the long-term effect of marijuana on health."

The study has been published in [Molecular Psychiatry](#).

Cooking oil linked to cancer in young Americans by new study

oil© Getty

A recent surge of [colon cancers in young Americans](#) could be down to [consuming](#) certain types of cooking oil, according to a new government-funded study.

Eating large amounts of seed oils including sunflower, canola, corn, and grapeseed [has previously been linked to inflammation in the body, but evidence has been lacking](#).

This new study analyzed the tumors of more than 80 patients with colon cancer, and found seed oils may raise the risk of one of the fastest-growing forms of cancer.

The tumors were found to contain high levels of bioactive lipids, which are microscopic fatty compounds that occur when the body breaks down seed oils.

Published in the medical [journal Gut](#), the research looked at 81 tumor samples in people aged between 30 to 85. It found that they had significantly higher levels of the lipids caused by seed oils than healthier fats in their cancerous tumors.

The lipids are thought to promote inflammation, thus helping cancers grow, and they also prevent the body from fighting cancerous tumors.

The researchers urge people to swap the seed oils for other oils with omega-3 fatty acids, like olive and avocado oil.

President-Elect Donald Trump's nominee for secretary of the Department of Health and Human Services, Robert F Kennedy Jr, previously claimed that Americans are being "unknowingly poisoned" by seed oils.

It is important to mention that America's main cancer and heart disease bodies have said there is no evidence that moderate amounts of seed oils within a balanced diet contribute to cancer. There has been a growing movement against them within the wellness community, but some health professionals have disputed this.

Dr. Christopher Gardner, a professor of medicine at Stanford University School of Medicine in California and a nutrition scientist at the Stanford Prevention Research Center, spoke to the website heart.org in August this year.

He said, "People are cooking with these oils, not drinking them. In a situation where you need some kind of fat for cooking or food preparation, you can use plant oils or you can use butter or lard.

"Very consistently, all the data say butter and lard are bad for our hearts. And studies show swapping out saturated fats and replacing them with unsaturated fats lowers the risk for heart disease."

Some estimates suggest that the average American consumes almost 100 pounds of seed oils per year, putting it up 1,000-fold from what it was in the 1950s.

Cooking oils used by millions linked to cancer in second study in week

Swedish researchers claim [vegetable oils are better for heart](#)

[Cancer](#) patients who cut seed oil out of their diet may be able to slow their tumors, according to a new study.

By studying 100 men with early-stage prostate cancer over one year, researchers found those who ate less foods with vegetable oil and more foods like salmon had slower growing cancer than people who ate a normal western diet.

Seed oils - which include canola oil, corn oil and cottonseed oil - are high in omega-6 fats which some studies suggest may increase inflammation, making it easier for cancer to take over your system.

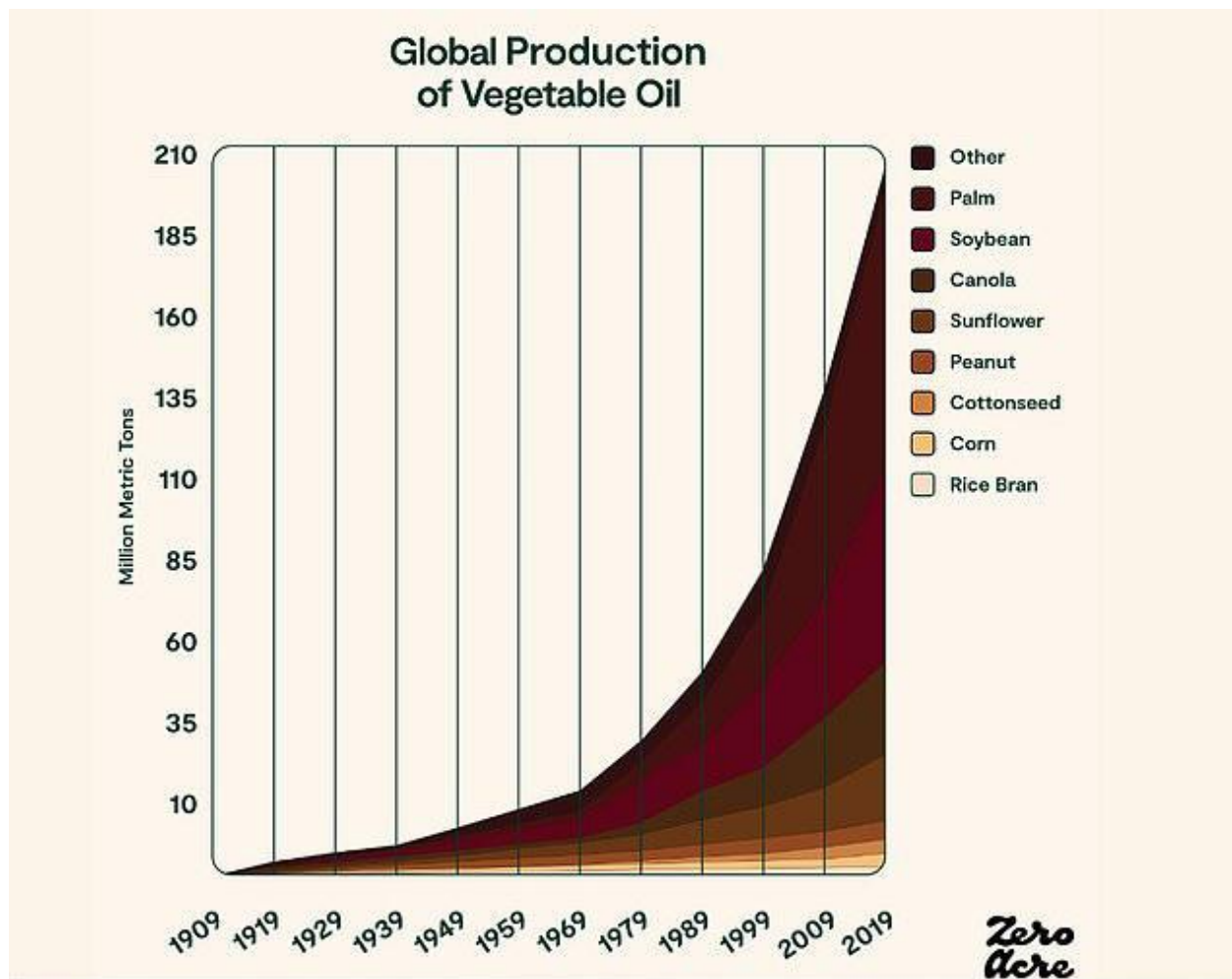
By contrast, oils found in fish are high in omega-3 fats, which are thought to protect against inflammation and support the immune system.

Dr William Aronson, a professor of urology at UCLA school of medicine who led the study, said: 'Our findings suggest that something as simple as adjusting your diet could potentially slow cancer growth and extend the time before more aggressive interventions are needed.'

The leading US medical bodies all say that seed oils are safe and are not linked to cancer or other diseases.

But public opinion, partially lead by figures like Robert F Kennedy Jr, has been scrutinizing the popular ingredient, who say the oils are 'driving the obesity epidemic'.

The new study comes just days after research from [University of South Florida](#) published earlier this week linked seed oils to the increase in colon cancer cases in young people.



Cooking oils used by millions linked to cancer in second study in week

In that study, the researchers suggested that the fats found in seed oils may promote inflammation, which can damage tissue, making it more easy for tumors to grow.

These lipids are believed to be dangerous in two ways - they promote inflammation which helps cancers grow and they prevent the body from fighting the tumors.

Roughly [70 percent of patients](#) are diagnosed with prostate cancers in the early stages of the disease, before surgery, radiation or chemotherapy may be necessary.

About 60 percent of those opt to treat their cancer through monitoring, according to the [National Cancer Institute](#).

That means that lifestyle changes that can prevent further tumor growth, such as changing diet, may be key.

The [American Cancer Society](#) estimates that there will be 299,010 cases of prostate cancer diagnosed in 2024 - which means about 201,000 will have early stage disease that they may opt to monitor, instead of treat.

In the new study, the researchers looked at 100 different men with this stage of prostate cancer.

The report, which was published in the journal of Clinical Oncology, focused specifically on the types fat they ate.

The Western diet is traditionally high in fats called omega-6s, which are found naturally in foods like corn, sunflower seeds as well as in vegetable oils.

American diets are also traditionally low in fats called omega-3s, which are found in fish, nuts and flaxseeds, are considered more healthy.

According to the researchers, previous studies of prostate cancer conducted in animals had found that lowering omega-6 intake and raising omega-3 intake could slow the rate that the cancer grew and became more aggressive.

So they assigned half of the participants to a diet low in omega-6 and high in omega-3, and left the other half to their normal habits.

This included slashing their intake of fried foods, chips and baked goods and loading up on foods like tuna and salmon. They ate roughly the same amount of calories, with varying amounts of fat and other nutrients.

After one year, they took a sample of their prostate tumors and analyzed them for chemical signs that give researchers an idea of how much a cancer has grown and changed.

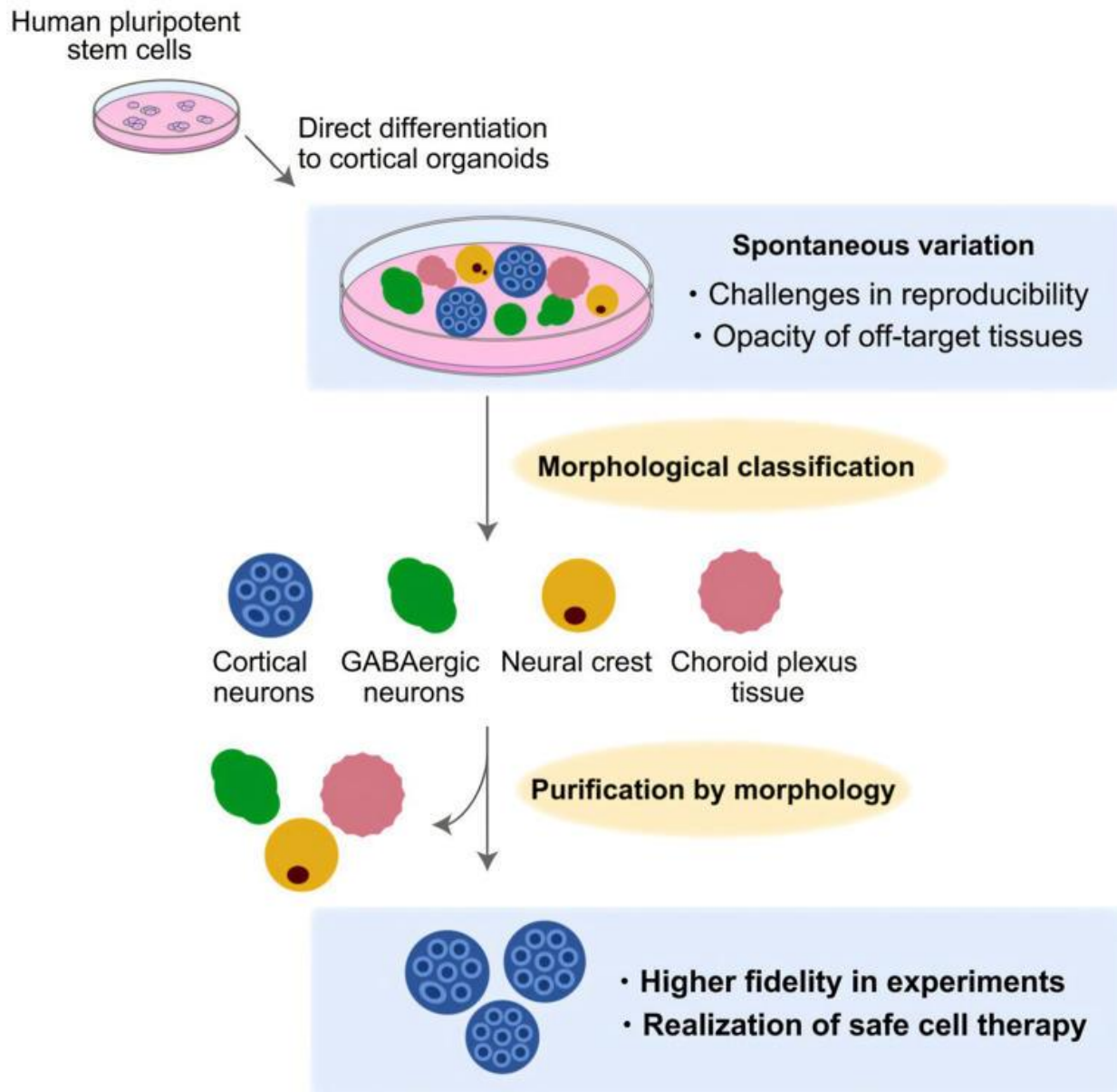
They compared these to measurements taken at the start of the trial, and found that people put on a diet had a 15 percent decrease in signs of tumor aggression. So the diet had actually slowed the prostate cancer's

Still, the researchers said, more research is needed before this link can be confirmed. Generally speaking, dietitians and doctors recommend focusing on eating a balanced diet as opposed to cutting one kind of food out of your diet.

Future research on the topic could provide better information for the hundreds of thousands of American men diagnosed with the condition each year, reducing the chance that they have to undergo painful, costly treatments like surgery.

Dr Aronson said: 'This is an important step toward understanding how diet can potentially influence prostate cancer outcomes.'

Seeing is believing: Leveraging defining morphological features for accurate selection of brain organoids



Credit: Stem Cell Reports (2024). DOI: 10.1016/j.stemcr.2024.09.005

By combining morphological and single-cell level gene expression analyses, a team of researchers led by Professor Jun Takahashi in the Department of Clinical Application at Kyoto University has established a new non-destructive system to select high-quality brain organoids as a potential tissue source for cell replacement therapy to treat patients after stroke or traumatic brain injuries. The paper is [published](#) in *Stem Cell Reports*.

Organoids, or self-organizing miniature organs, represent a powerful new tool to study organogenesis or model diseases and are considered a means to generate cells and tissues for cell transplantation therapies.

However, due to the stochastic self-organizing nature of organoids, they are highly variable and often produce non-target cell types, even with advanced induction protocols. Hence, there is a great demand for new ways to evaluate organoids in a non-destructive manner to select the most appropriate ones for transplantation.

As an ongoing effort to leverage organoid technology to produce transplantable tissues to replace damaged cells in affected brain regions following stroke or traumatic injuries, the researchers sought to develop a morphology-based evaluation system to select cerebral cortical organoids with the desired cell types for possible transplantation.

From independent batches of cerebral cortical organoids, the research team classified the resulting organoids into seven types, each displaying defining morphological features, for gene expression profiling at the single-cell level by single-cell RNA sequencing (scRNA-seq). Altogether, nine groups of cerebral cortical organoids, including two groups with mixed morphological characteristics, were examined.

Through scRNA-seq analysis, the identity of individual cells from each organoid group was annotated based on marker gene expression. Various neuronal subtypes, including cortical and GABAergic neurons, and non-neuronal cells, such as fibroblasts and endothelial cells, were identified.

Based on this information, the research team gained insights into the cellular compositions of different organoid types. For example, whereas organoids with rosette-like concentric layered structures were comprised primarily of cortical neurons, those with low transparency and no clear internal structures predominantly contained GABAergic neurons.

All samples showed similar gene expression profiles, thus demonstrating remarkable reproducibility based on morphological features alone and the ability to pick desired cerebral cortical organoids correctly in a non-destructive manner.

Notably, non-target cell types were not detected in the selected organoids, thus giving confidence that only desired cell types would be transplanted.

Through this work, the research demonstrated the feasibility of using simple visual information to accurately select cerebral cortical organoids that could potentially be used as a cell source for cell replacement therapy. This simple classification method is readily adaptable and could dramatically enhance the efficacy and safety of transplants.

More information: Megumi Ikeda et al, Validation of non-destructive morphology-based selection of cerebral cortical organoids by paired morphological and single-cell RNA-seq analyses, *Stem Cell Reports* (2024). [DOI: 10.1016/j.stemcr.2024.09.005](https://doi.org/10.1016/j.stemcr.2024.09.005)

Provided by Kyoto University

Gut-brain connection: Proinflammatory bacteria linked to hippocampal changes in depression

(Photo credit: Adobe Stock)© PsyPost

A neuroimaging study of unmedicated patients with major depressive disorder (MDD) has uncovered a link between gut microbiota composition and changes in brain function. Specifically, the study found that individuals with higher levels of certain proinflammatory gut bacteria exhibited altered functional connectivity in the hippocampus, a key brain region implicated in memory and emotion. The research, published in [Translational Psychiatry](#), highlights the growing recognition of the gut-brain axis as a potential player in the pathology of depression.

The hippocampus is a small, seahorse-shaped structure located in the brain's temporal lobe. It plays a crucial role in memory formation, learning, and spatial navigation. It is part of the limbic system, which regulates emotions and connects

memories to emotional responses. The hippocampus helps convert short-term memories into long-term ones and is essential for recalling past experiences.

In depression, the hippocampus often exhibits structural and functional changes, such as reduced volume or impaired neurogenesis. Chronic stress and elevated cortisol levels, commonly associated with depression, can damage hippocampal neurons and hinder their growth, leading to memory difficulties and emotional dysregulation. A smaller or less active hippocampus may contribute to the persistence of negative thoughts and difficulty in regulating emotions—hallmarks of depression. Furthermore, reduced hippocampal function can impair the ability to learn and implement coping mechanisms for stress.

Study authors Shu Xiao and colleagues aimed to explore the links between alterations in functional connectivity in subregions of the hippocampus and gut microbiota composition in patients with major depressive disorder.

In recent decades, scientists have discovered a bidirectional communication pathway between the brain and gut microbiota—the community of trillions of microorganisms living in the gut. This pathway, termed the microbiota-gut-brain axis, has been shown to play important roles in various processes within the body, including psychological functioning. It is possible that gut microbiota composition might also play a role in major depressive disorder.

The researchers recruited 49 adults with MDD and 44 healthy individuals as controls. Participants were aged between 18 and 55 and were screened for other medical or psychiatric conditions to ensure homogeneity. None of the MDD participants were on medication at the time of the study. The researchers collected fecal samples to analyze gut microbiota composition and performed resting-state magnetic resonance imaging (MRI) scans to examine hippocampal functional connectivity—a measure of how different brain regions communicate during rest.

The researchers found significant differences in gut microbiota composition between the two groups. Participants with MDD exhibited reduced species richness, indicating a lower variety of gut bacteria. However, the diversity index, which measures not only the number of species but also their relative proportions, did not significantly differ.

Importantly, individuals with MDD had a higher abundance of proinflammatory bacteria, specifically those from the *Enterobacteriaceae* family, and a lower abundance of beneficial bacteria like *Prevotella*, which are involved in producing short-chain fatty acids (SCFAs) that support gut health and reduce inflammation.

In terms of brain function, there were no global differences in hippocampal functional connectivity between the MDD and healthy control groups. However, a closer analysis revealed altered connectivity patterns within specific hippocampal subregions. In individuals with MDD, there was increased functional connectivity between the left CA3 and right caudal hippocampus, which correlated with the relative abundance of *Enterobacteriaceae*. This suggests that the presence of proinflammatory gut bacteria may influence hippocampal connectivity, potentially via systemic inflammation or immune signaling pathways.

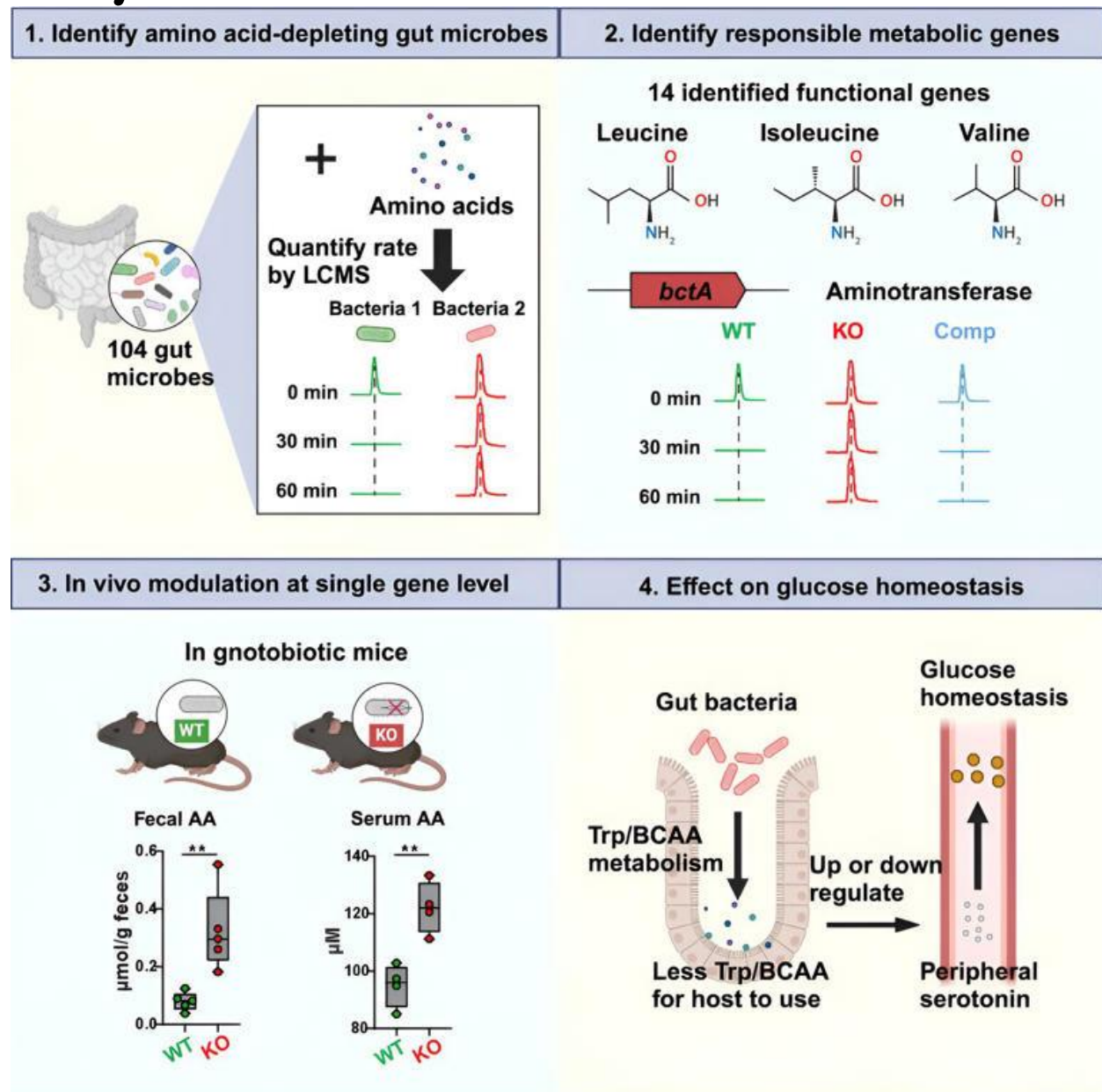
The findings support the hypothesis that the microbiota-gut-brain axis plays a role in the development of MDD. Gut dysbiosis (imbalance in gut bacteria) may contribute to hippocampal dysfunction through inflammatory pathways, disrupting processes critical for memory, learning, and emotional regulation. The study also noted that individuals with longer histories of MDD had significantly lower levels of *Prevotella*, highlighting a potential link between prolonged illness duration and gut microbiota changes.

Interestingly, the researchers combined data on hippocampal functional connectivity and gut microbiota composition to develop a machine-learning model that could distinguish MDD patients from healthy controls with high accuracy. This suggests that these biomarkers could eventually aid in diagnosing MDD or identifying individuals at risk.

The study sheds light on the links between brain function and gut microbiota composition. However, it should be noted that the study's design does not allow for any cause-and-effect conclusions to be drawn from the findings. Additionally, the number of study participants was relatively small, and all were recruited from a single hospital. Studies involving patients from other regions might not yield identical results.

The paper, "[Gut proinflammatory bacteria is associated with abnormal functional connectivity of hippocampus in unmedicated patients with major depressive disorder](#)", was authored by Shu Xiao, Zibin Yang, Hong Yan, Guanmao Chen, Shuming Zhong, Pan Chen, Hui Zhong, Hengwen Yang, Yanbin Jia, Zhinan Yin, Jiaying Gong, Li Huang, and Ying Wang.

Gut microbiota acts like an auxiliary liver, study finds



Microbes in the mammalian gut can significantly change their hosts' amino acid and glucose metabolism, acting almost like an extra liver, according to a new preclinical study by Weill Cornell Medicine investigators.

The [study](#), published in *Cell Host & Microbe*, adds to the growing list of ways in which the microbiome influences physiology, and could lead to new strategies to treat conditions such as inflammatory bowel disease and diabetes.

In recent years, scientists have found that the billions of microbes living on and in the human body profoundly influence our physiology. Senior author Dr. Chun-Jun Guo, an assistant professor of microbiology & immunology in medicine and a member of the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell Medicine, wanted to take a deeper look at how the essential microbes in the gut affect our access to the nutrients extracted from the food we've ingested.

"They 'eat' before us, taking first dibs on the nutrients from the food we consume, and leaving us with what remains after they satisfy their own nutritional needs," said Dr. Guo, who is also a member of the Friedman Center for Nutrition and Inflammation at Weill Cornell Medicine.

To better understand this process, first author Dr. Ting-Ting Li, a postdoctoral associate in the Guo lab, and collaborators, assessed how efficiently different bacteria that naturally inhabit our intestines, called human gut commensals, deplete amino acids, the building blocks of proteins.

Due to the poorly characterized metabolic functions of many gut bacteria, the team experimented with various settings to find the optimal conditions for their study. After screening more than 100 different human gut microbes, the investigators pinpointed several that are highly efficient at metabolizing various dietary amino acids. When these microbes colonized the gastrointestinal tracts of germ-free mice—mice that initially had no microbes—the levels of those amino acids dropped in the host's intestine and bloodstream.

The team then identified the specific bacterial metabolic genes that deplete amino acids. It was a long list.

"We found that in one single bacterium, there are over 20 different genes encoding a similar enzymatic function," Dr. Guo said. "And because we have improved our CRISPR-Cas9 gene deletion techniques for gut bacteria, we were able to perform a large gene deletion screen and identify the metabolic genes in the bacteria that were responsible for depleting amino acids."

The scientists took their findings from cultured cells into animals, giving germ-free mice genetically modified strains of bacteria, one at a time.

"We can now precisely manipulate individual genes for depleting amino acids in the gut," Dr. Guo said. "This allows us to assess the individual function of these genes and to see how they actually impacts host amino acid homeostasis."

That work produced a surprising result: By consuming a specific class of amino acids, gut microbes can alter their hosts' blood glucose homeostasis. Further analysis revealed that by changing amino acid availability, the microbes appear to affect the production of the neurotransmitter serotonin, which in turn changes glucose regulation.

"A lot of these metabolic functions can be done by the liver, but now we've found that there are functionally comparable enzymes encoded by the gut microbiota that can do the same or similar things," said Dr. Guo. "It's like there is a second liver operating in the gut."

The team is now designing new strategies to modulate the bacterial enzymes more precisely, and looking at how various combinations of bacteria affect the host's amino acid metabolism.

Tantalizingly, some of the same genes the current study highlights are also dysregulated in the gut microbiomes of patients with digestive and metabolic diseases. Drugs targeting specific microbial genes, or engineered strains of bacteria, could potentially provide new ways to treat such conditions, according to Dr. Guo.

"These metabolic genes might be potential biomarkers for diseases like type 2 diabetes or inflammatory bowel disease, and they are also potential treatment

targets," he added. "Our research demonstrates the possibility of precisely manipulating gut microbiota to regulate host metabolism and improve host metabolic functions."

More information: Ting-Ting Li et al, Microbiota metabolism of intestinal amino acids impacts host nutrient homeostasis and physiology, *Cell Host & Microbe* (2024). [DOI: 10.1016/j.chom.2024.04.004](https://doi.org/10.1016/j.chom.2024.04.004)

Provided by Weill Cornell Medical College

Groundbreaking new devices could restore lost brain functions

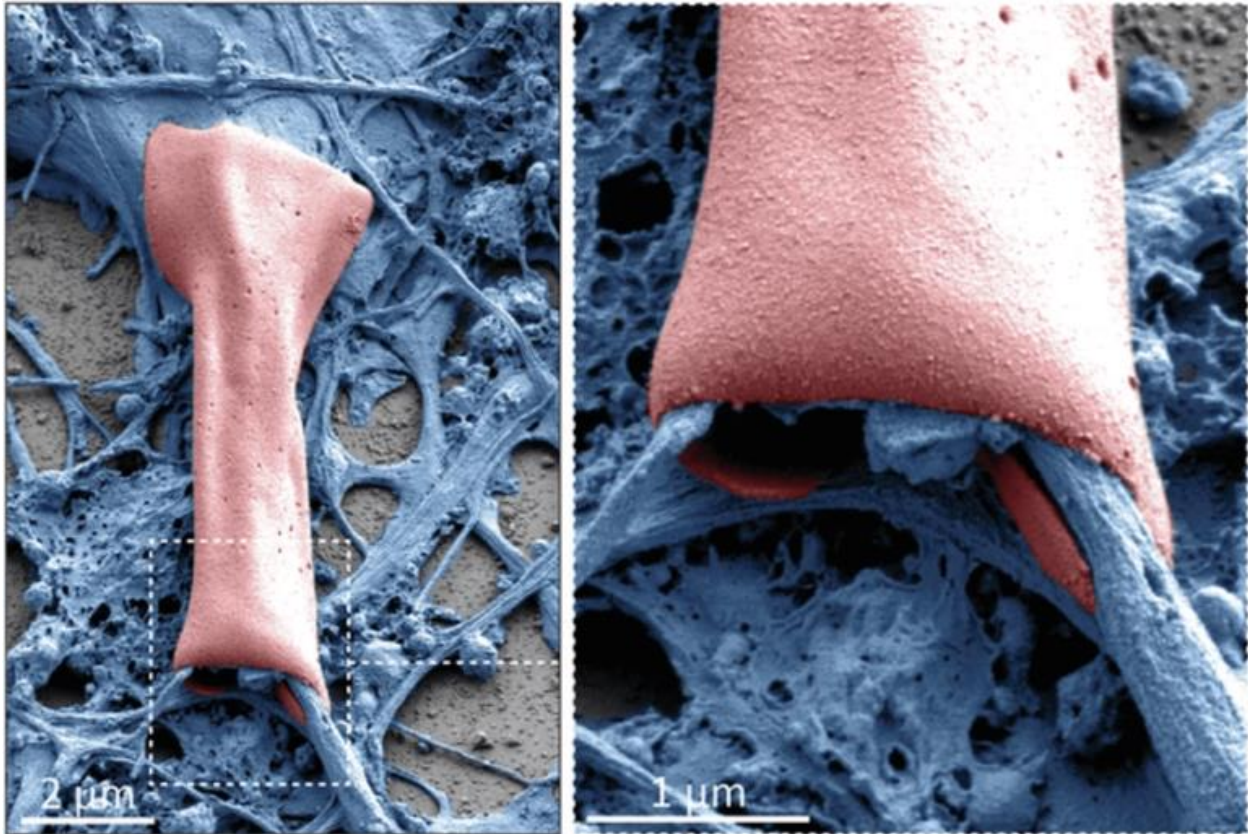
Recent advances from [MIT researchers](#) are paving the way for

unprecedented methods to monitor and potentially heal individual cells, with the focus now on neurons. Traditionally, cells have been seen as basic units of life, but they're remarkably complex.

In neurons, various activities occur within distinct subcellular compartments, such as axons, dendrites, and the cell body. Understanding and controlling these specialized regions is critical for probing cellular function and treating neurological diseases.

In a groundbreaking development, MIT scientists have created tiny, [battery-free devices](#) capable of interacting directly with neurons. These subcellular-sized devices, made from a soft polymer called azobenzene, are designed to wrap around cellular structures like axons and dendrites without damaging them.

By doing so, these devices allow researchers to measure and modulate a neuron's activity at a highly specific level, which could one day aid in treating diseases like multiple sclerosis (MS).



MIT researchers have developed tiny, wireless devices that wrap around neurons. (CREDIT: Nature Communications Chemistry)© The Brighter Side of News

The team envisions thousands of [these devices](#) being injected and wirelessly activated using light. This light-sensitive material transforms upon exposure, rolling into microtubes that can snugly encase the tiny, curved surfaces of neurons. "It is possible to very finely control the diameter of the rolling," explains Deblina Sarkar, senior author and head of MIT's Nano-Cybernetic Biotrek Lab, who led this research.

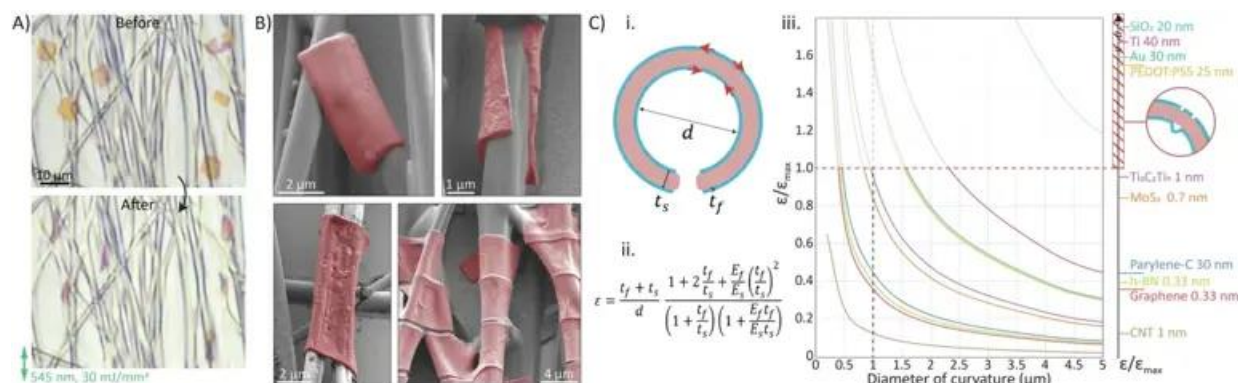
To achieve this, the researchers overcame several technical challenges, such as developing a scalable manufacturing process. Rather than a traditional semiconductor clean room, they utilized a novel technique where they deposited a drop of azobenzene onto a dissolvable layer.

By pressing a stamp onto the drop, they molded thousands of devices, each carefully shaped to [wrap around neurons](#)' various curves. This method allows them to bypass costly cleanroom environments and instead rely on simple etching and baking processes. The devices' flexibility is key, as they must conform to the complex shapes of brain cells without causing damage. This adaptability

has long been an unmet challenge, especially given that neurons and their processes are incredibly delicate.

The thin-film azobenzene sheets, which roll up into microtubes, make it possible for the devices to envelop axons and other [neuron components](#) gently. Sarkar emphasizes, "To have intimate interfaces with these cells, the devices must be soft and able to conform to these complex structures."

Another major application of this technology lies in treating neurodegenerative diseases, specifically those characterized by loss of myelin. Myelin is an insulating layer that wraps around axons, enabling efficient transmission of electrical impulses.

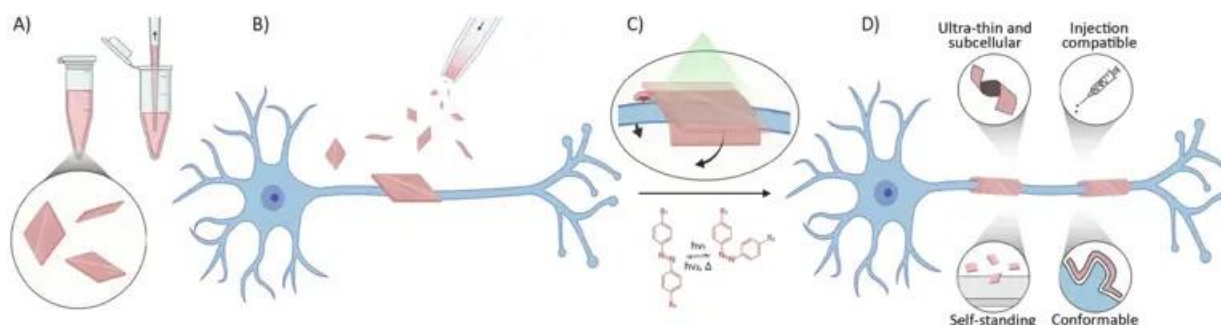


Cell-conformable platforms. Generalized freestanding thin-film microdevices of 5–100 μm^2 dispersed in physiological solution or cell medium at high concentrations. (CREDIT: Nature Communications Chemistry)© The Brighter Side of News

In conditions like multiple sclerosis, this insulation degrades, disrupting [communication between neurons](#). Since azobenzene acts as an insulator, these devices might serve as synthetic myelin, restoring lost functionality in damaged neurons.

The team demonstrated that integrating the azobenzene-based devices with optoelectrical materials could stimulate cells, and they showed that atomically thin materials can be added without compromising the device's structural integrity. This opens up possibilities for the devices to become [self-contained sensing tools](#) that deliver electrical, optical, or thermal signals to cells.

According to lead author Marta J. I. Airaghi Leccardi, the devices might eventually form circuits on a microscopic scale, capable of measuring or even modulating individual cells' functions. "This technology is possible," says Sarkar.

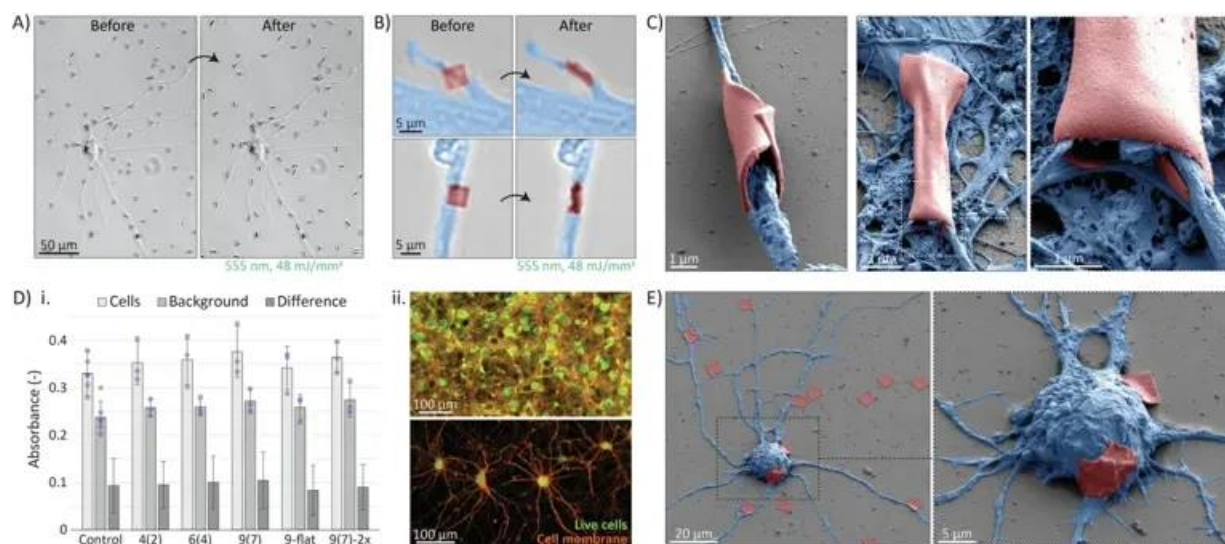


Cell-conformable platforms. Generalized freestanding thin-film microdevices of 5–100 μm^2 dispersed in physiological solution or cell medium at high concentrations. (CREDIT: Nature Communications Chemistry)© The Brighter Side of News

These devices offer a glimpse into a future where cellular-level monitoring could be used for more than research. The MIT team imagines them as tiny, minimally invasive tools that could one day modulate neurons' electrical activity, possibly aiding in brain disease treatments. By forming close connections with neurons, the devices require minimal energy to stimulate specific cellular regions.

The research team included Sarkar, Leccardi, MIT postdoc Benoît X. E. Desbiolles, MIT alum Anna Y. Haddad, and graduate students Bajju C. Joy and Chen Song. Their work appears in the journal [Nature Communications Chemistry](#).

Future directions for the research include customizing the device surfaces with molecules that target particular cell types. This could lead to devices that detect and treat distinct neuron types or other cell varieties in the body. For instance, functionalizing the devices with specific molecules might enable them to reach and wrap precisely around axons or synapses of interest.



Wrapping of neuronal processes in vitro. Colored SEM images of neurons (blue) with the pDR1M wrapped structures (red). (CREDIT: Nature Communications Chemistry)© The Brighter Side of News

The potential impact of this technology has attracted praise from experts like Flavia Vitale, an associate professor at the University of Pennsylvania. She says, "This work is an exciting step toward new symbiotic neural interfaces acting at the level of the individual axons and synapses."

She believes that, integrated with nanoscale materials, these devices could one day serve as versatile platforms for delivering various types of [signals to neurons](#) in a minimally invasive manner. Although early tests indicate cytocompatibility, extensive testing remains necessary to confirm safety for in-vivo applications.

The technology also has promising applications beyond the nervous system, potentially providing insight into the workings of many other cell types.

Supported by the [Swiss National Science Foundation](#) and the [U.S. National Institutes of Health Brain Initiative](#), this research may one day transform how scientists interface with living cells, fostering medical and technological breakthroughs.



MALE VIRILITY AND PERFORMANCE SUPPLEMENTS

Top 8 Best Tribulus Terrestris Supplements in 2024

[Contributor](#)

December 2, 2024



Tribulus terrestris, a plant long employed in traditional medicine, boasts benefits such as enhancing libido, promoting fertility, and facilitating overall wellness. In recent times, it has often been incorporated into dietary supplements intended for athletes and bodybuilders. The common belief is that Tribulus terrestris-infused supplements can boost athletic abilities by increasing testosterone levels, thereby augmenting muscle robustness and endurance.

When looking for the best tribulus terrestris supplement, it is important to consider the quality and purity of the product. Many supplements on the market contain low-quality ingredients or are contaminated with harmful

substances. It is also essential to choose a supplement that contains an appropriate dosage of tribulus terrestris extract, as taking too little may not provide any benefits, while taking too much may cause adverse effects.

After researching and testing various tribulus terrestris supplements, we have identified the top products that deliver the most significant benefits while maintaining high quality and safety standards. In this article, we will provide an in-depth review of the best tribulus terrestris supplements on the market, highlighting their key features, benefits, and potential drawbacks.

Best Tribulus Terrestris Supplements

We have researched and tested various tribulus terrestris supplements to bring you the best products available on Amazon. Tribulus terrestris is a popular natural supplement that is believed to boost testosterone levels, enhance athletic performance, and improve overall health. Our list includes products that are high-quality, effective, and affordable. Whether you're an athlete looking to improve your performance or someone looking to support your overall health, our list has something for everyone.

1. Double Wood Supplements Tribulus Terrestris Supplement

Our Pick



[Check Price on Amazon](#)

We highly recommend Double Wood Supplements Tribulus Terrestris Supplement for anyone looking for a natural way to boost their energy and stamina.

Pros

- Double Wood's Natural Tribulus fruit extract contains over 95% Saponins making it the strongest on the market.
- Tested in the USA for both safety and potency to ensure you are getting a product you can trust.
- Manufactured and tested for safety right here in the USA, Non-GMO, and Gluten Free.

Cons

- May not work for everyone.
- Some users may experience mild side effects such as stomach discomfort.

- May take a few weeks to see noticeable results.

After using this product ourselves, we can say that it definitely lives up to its claims. The high percentage of Saponins in Double Wood's Natural Tribulus fruit extract makes it much stronger and more effective than other Tribulus supplements on the market. We also appreciate that it is tested for both safety and potency in the USA, so we know we are getting a quality product.

One thing to keep in mind is that this supplement may not work for everyone. Some users may experience mild side effects such as stomach discomfort, although we did not experience any negative side effects ourselves. Additionally, it may take a few weeks of consistent use to see noticeable results.

Overall, we highly recommend Double Wood Supplements Tribulus Terrestris Supplement for anyone looking for a natural way to boost their energy and stamina.

2. Toniiq Ultra High Strength Tribulus Capsules



[Check Price on Amazon](#)

If you're looking for a high-quality tribulus terrestris supplement, Toniiq Ultra High Strength Tribulus Capsules are worth considering.

Pros

- Toniiq Tribulus is a super-concentrated extract with an unprecedented 95% saponins, making it one of the highest strength tribulus supplements available.
- Each serving of our 1300 mg tribulus provides you with a whopping 1,235 mg of saponins, giving you more value for your money.
- Toniiq products are produced in a GMP-certified and NSF-approved state-of-the-art manufacturing facility right here in the USA, ensuring quality and purity.

Cons

- Some users may find the capsules difficult to swallow.
- It may take a few weeks of consistent use to see noticeable results.
- The price point may be higher than other tribulus supplements on the market.

We've been using Toniiq Ultra High Strength Tribulus Capsules for a few weeks now, and we're impressed with the results so far. We've noticed an increase in energy and stamina, as well as improved mood and overall well-being.

One of the things we appreciate about Toniiq Tribulus is its high concentration of saponins. With 95% saponins, this supplement is much more potent than other tribulus supplements on the market. Plus, each serving provides a whopping 1,235 mg of saponins, giving you more value for your money.

We also appreciate the fact that Toniiq products are made in the USA in a GMP-certified and NSF-approved facility. This ensures that the product is of high quality and purity.

While we've had a positive experience with Toniiq Ultra High Strength Tribulus Capsules, we do acknowledge that the capsules may be difficult to swallow for some users. Additionally, it may take a few weeks of consistent use to see noticeable results. Lastly, the price point may be higher than other tribulus supplements on the market.

Overall, we believe that Toniiq Ultra High Strength Tribulus Capsules are a high-quality option for those looking to incorporate tribulus terrestris into their supplement regimen.

3. Zolotus Tribulus Terrestris Supplement



[Check Price on Amazon](#)

We highly recommend the Zolotus Tribulus Terrestris Supplement for its all-natural ingredients and high potency.

Pros

- The maximum extract available on the market with 20:1 extract ratio
- 9050mg per capsule with 5 months supply, one capsule per day is enough

- 7 in 1 formula with powerful ingredients like Panax Ginseng, Ashwagandha, Maca, Saw Palmetto, Shilajit, and Black Pepper

Cons

- May not work for everyone
- Some users may experience mild side effects like stomach upset or headache
- Not suitable for pregnant women or children under 18 years old

This supplement is made with all-natural, vegan, non-GMO, and gluten-free ingredients, making it safe and healthy for everyone. The high-quality formula is third-party tested and formulated in the USA in a GMP certified facility to ensure authentic and sustainable manufacturing.

The Zolotus Tribulus Terrestris Supplement is designed to boost energy, stamina, and performance for both men and women. It is an excellent choice for athletes, bodybuilders, and fitness enthusiasts who want to improve their physical and mental performance naturally.

In conclusion, if you want to improve your energy, stamina, and performance naturally, the Zolotus Tribulus Terrestris Supplement is an excellent choice. It is made with high-quality, all-natural ingredients, and has a potent formula that delivers results.

4. Natgrown Tribulus Terrestris Supplement



[Check Price on Amazon](#)

We highly recommend the Natgrown Tribulus Terrestris supplement for anyone looking to boost their energy and performance.

Pros

- Provides a pure and potent dose of Tribulus Terrestris extract standardized to 95% saponins, with 2X more saponins content than other best-selling brands.
- Ideal for both men and women, making it a versatile supplement for athletes, weekend warriors, and anyone looking to stay physically active.
- Made in the USA with Tribulus Terrestris extract and does not contain gluten, milk, soy, tree nuts, peanuts, or wheat.

Cons

- May not work for everyone, as individual results may vary.
- Some users may experience mild side effects such as stomach upset or headache.
- Requires taking two capsules once a day with a full glass of water, which may be inconvenient for some users.

We have personally tried the Natgrown Tribulus Terrestris supplement and have experienced a noticeable increase in energy and stamina during our workouts. The adaptogenic herb has helped us push through our plateaus and achieve peak performance.

The suggested use of taking two capsules once a day with a full glass of water was easy to follow, and we did not experience any adverse side effects.

Overall, we highly recommend the Natgrown Tribulus Terrestris supplement for anyone looking to enhance their physical performance and energy levels.

5. SOTALIX SUPPLEMENT Tribulus Terrestris Supplement



[Check Price on Amazon](#)

We highly recommend SOTALIX SUPPLEMENT Tribulus Terrestris Supplement for anyone looking to build muscle, increase stamina, and support their immune system.

Pros

- With 9150mg of concentrated herbal powder, this supplement is packed with maximum performance for natural muscle building and increased stamina.
- The 6-in-1 unique combination of premium ingredients including Tongkat Ali, Maca Root, and Panax Ginseng work together to support muscle growth and enhance your workout performance.
- Tested by 3rd-party labs, this 100% natural extract is completely free of harmful chemicals and perfect for those following a vegetarian diet.

Cons

- Some users may experience stomach discomfort after taking the supplement.
- The price point may be higher than other tribulus terrestris supplements on the market.
- It may take some time to see noticeable results, so patience is required.

We have personally used this supplement and have seen positive changes in our body, from increased strength and durability to overall improved health. The premium ingredients are carefully selected and processed in compliance with strict standards to screen unnecessary impurities, bringing high quality products.

The unique combination of Tribulus Terrestris, Horny Goat Weed, and Ashwagandha help to increase energy levels and promote intensity. We also appreciate that the supplement is created in a GMP-certified facility and comes with a satisfaction guarantee.

Overall, we highly recommend SOTALIX SUPPLEMENT Tribulus Terrestris Supplement for anyone looking to naturally enhance their workout performance and support their overall health.

6. NatureBell Tribulus Terrestris Supplement



[Check Price on Amazon](#)

We highly recommend purchasing the NatureBell Tribulus Terrestris Supplement for its natural herbal support for both men's and women's health.

Pros

- The high concentration of tribulus terrestris and tongkat ali extract provides 2 in 1 support for performance, stamina, peak energy, muscle strength, and immune health.
- Each serving is standardized to 95% active saponins, which are one of the main active ingredients from tribulus and provide majority of the key bioactive nutrients.
- The product is non-GMO, non-irradiated, and contains pure ingredients free of soy, dairy, gluten, preservatives, wheat, and fish.

Cons

- The product may take some time to see noticeable results.
- Some customers may experience mild side effects such as stomach discomfort or headaches.
- The serving size of two capsules may be inconvenient for some customers.

We have personally used the NatureBell Tribulus Terrestris Supplement and have noticed an increase in our energy levels and overall well-being. The product is easy to swallow and has no aftertaste. We appreciate that the product is 3rd party lab tested for safety and potency.

Regular use of this supplement may help support men's and women's health, performance, stamina, peak energy, muscle strength, and immune health over time. We highly recommend giving the NatureBell Tribulus Terrestris Supplement a try.

Note: Always consult with a healthcare professional before starting any new supplement regimen.

7. Zolotus Tribulus Terrestris Capsules



[Check Price on Amazon](#)

We highly recommend Zolotus Tribulus Terrestris Capsules for anyone looking for a natural energy and stamina supplement.

Pros

- Zolotus Tribulus Terrestris Capsules contains a 13-in-1 special formula with pure ingredients, including Horny Goat Weed, Panax Ginseng, Ashwagandha, Maca, Tongkat Ali, and more.
- Zolotus Tribulus Terrestris Capsules are all natural, vegan, and non-GMO.
- Zolotus Tribulus Terrestris Capsules are third-party tested and formulated in the USA in a GMP certified facility to ensure its authentic and sustainable manufacturing process.

Cons

- Zolotus Tribulus Terrestris Capsules may not work for everyone.
- Zolotus Tribulus Terrestris Capsules may cause some mild side effects like stomach upset, headache, and dizziness.
- Zolotus Tribulus Terrestris Capsules may not be suitable for pregnant or nursing women.

We have been using Zolotus Tribulus Terrestris Capsules for a few weeks now, and we have noticed a significant improvement in our energy levels and overall well-being. The 13-in-1 special formula is impressive, and we appreciate that the product is all natural and vegan.

The recommended dosage is two capsules daily, and we found that taking them in the morning provided us with sustained energy throughout the day. The 120 pills supply for 2 months is also a great value.

We also appreciate that Zolotus Tribulus Terrestris Capsules are third-party tested and formulated in the USA in a GMP certified facility. It gives us confidence in the product's authenticity and sustainable manufacturing process.

Overall, Zolotus Tribulus Terrestris Capsules are an excellent choice for anyone looking for a natural energy and stamina supplement.

8. Herbal Nutrition Tribulus Terrestris



[Check Price on Amazon](#)

If you're looking for a natural way to improve your athletic performance, then the Herbal Nutrition Tribulus Terrestris supplement might be a good option for you.

Pros

- This Tribulus Terrestris supplement is made with a proprietary formula of the finest Bulgarian Tribulus, providing 1500mg at 45% saponins extract per serving, and a new bioavailability factor which provides better uptake than competing products. That means this helps maximize testosterone levels more quickly and for longer duration.
- Promotes Testosterone Production to Help Increased Lean Muscle Growth, Stamina, Muscle Repair and Recovery. Tribulus contains a Saponin called Protodioscin, a precursor to testosterone which naturally increases testosterone production. Tribulus also provides cardiovascular benefits, helping to increase blood flow and NO levels, all promoting muscle growth, increased strength and enhanced athletic performance. Tribulus is widely used by professional bodybuilders and athletes.
- Premium Quality and Manufactured in the USA! Our Tribulus is manufactured in the U.S. by a GMP certified manufacturer. All our products are third party tested to ensure their quality, and we guarantee your satisfaction.

Cons

- Some users may experience mild side effects such as upset stomach or headache.
- The effects of the supplement may vary from person to person, so it may not work for everyone.
- The price point may be higher than some other Tribulus Terrestris supplements on the market.

Overall, we found the Herbal Nutrition Tribulus Terrestris supplement to be a good option for those looking to improve their athletic performance. The proprietary formula and bioavailability factor make it stand out from other similar supplements on the market. However, users should be aware of potential side effects and the fact that results may vary. If you're willing to invest in a high-quality supplement, this may be worth considering.

Buying Guide

When looking for the best tribulus terrestris supplement, there are a few key factors to consider. Here are some things to keep in mind:

Ingredients

The first thing to look for in a tribulus terrestris supplement is the list of ingredients. Make sure that the product contains pure tribulus terrestris extract and does not have any unnecessary fillers or additives. Look for a supplement that contains at least 45% saponins, which are the active compounds that provide the benefits of tribulus terrestris.

Dosage

The dosage of tribulus terrestris extract in a supplement is also important. Look for a product that provides a dosage of at least 750-1000mg per serving. This will ensure that you are getting a sufficient amount of the active compounds to experience the benefits of tribulus terrestris.

Quality

The quality of the supplement is another important factor to consider. Look for a product that is made by a reputable manufacturer and is manufactured in a facility that follows good manufacturing practices (GMP). This will ensure that the product is of high quality and is safe to use.

Price

While price should not be the only factor in your decision, it is important to consider. Look for a product that provides good value for money and is not overpriced. Compare the prices of different brands and products before making a decision.

Customer Reviews

Finally, it is important to read customer reviews before purchasing a tribulus terrestris supplement. Look for a product that has positive reviews and has

been shown to be effective for other users. This will give you an idea of what to expect from the product and can help you make an informed decision

Frequently Asked Questions

What is the recommended daily dosage for tribulus terrestris supplements?

The recommended daily dosage for tribulus terrestris supplements varies depending on the specific product and its concentration. However, generally, a dosage of 500-1500mg per day is considered safe and effective.

What are the benefits of taking tribulus terrestris supplements?

Tribulus terrestris supplements are commonly used to support testosterone levels, improve sexual function, enhance athletic performance, and increase muscle mass. Additionally, some studies suggest that tribulus terrestris may have antioxidant and anti-inflammatory properties.

Which form of tribulus terrestris supplement is most effective?

There are various forms of tribulus terrestris supplements available, including capsules, tablets, and powders. However, there is no conclusive evidence suggesting that one form is more effective than the others. It is recommended to choose a reputable brand with a high concentration of active ingredients.

Are there any potential side effects of taking tribulus terrestris supplements?

Tribulus terrestris supplements are generally considered safe when taken in recommended dosages. However, some individuals may experience side

effects such as stomach upset, diarrhea, or headaches. It is important to speak with a healthcare professional before taking any new supplement.

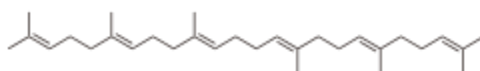
Can tribulus terrestris supplements improve athletic performance?

Tribulus terrestris supplements are often marketed as a natural way to enhance athletic performance by increasing testosterone levels and improving muscle mass. While some studies suggest that tribulus terrestris may have a positive effect on athletic performance, the evidence is not conclusive.

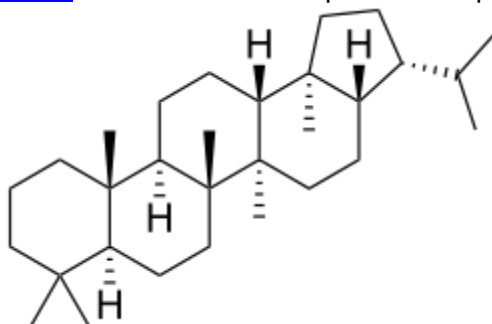
How long does it take to see results from taking tribulus terrestris supplements?

The time it takes to see results from taking tribulus terrestris supplements can vary depending on the individual and the specific product. Some individuals may notice an improvement in sexual function or athletic performance within a few weeks, while others may take longer to see results. It is important to follow the recommended dosage and speak with a health

Triterpene



[Squalene](#): One of the most important triterpenes



[Hopane](#): An example of a pentacyclic triterpene

Triterpenes are a class of [terpenes](#) composed of six [isoprene](#) units with the molecular formula $C_{30}H_{48}$; they may also be thought of as consisting of three [terpene](#) units. Animals, plants and fungi all produce triterpenes, including [squalene](#), the precursor to all [steroids](#).^{[1][2]}

Structures

[\[edit\]](#)

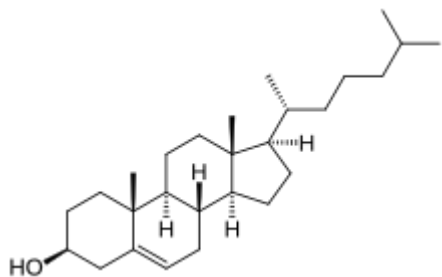
Triterpenes exist in a great variety of structures. Nearly 200 different skeletons have been identified.^[3] These skeletons may be broadly divided according to the number of rings present. In general pentacyclic structures (5 rings) tend to dominate.

Number of rings	Examples
0	Squalene
1	Achilleol A ^[4]
2	Polypodatetraene
3	Malabaricane
4	Lanostane , Cucurbitacin
5	Hopane , Oleanane , Ursolic acid
6	Chamaecydin

[Squalene](#) is biosynthesized through the head-to-head condensation of two [farnesyl pyrophosphate](#) units. This coupling converts a pair of C15 components into a C30 product. Squalene serves as precursor for the formation of many triterpenoids, including bacterial [hopanoids](#) and eukaryotic [sterols](#).

Triterpenoids

[\[edit\]](#)



Cholesterol: one of the simplest but most important triterpenoids

By definition triterpenoids are triterpenes that possess [heteroatoms](#), usually oxygen. The terms *triterpene* and *triterpenoid* often are used interchangeably.

Triterpenoids possess a rich chemistry and pharmacology (e.g. [cholesterol](#)) with several pentacyclic motifs. [Lupane](#), [oleanane](#) and [ursane](#) show particular promise as anti-cancer agents.^{[5][6]}

Steroids

Steroids feature a [cucurbitane](#) core, although in practice they are biosynthesised from either [lanosterol](#) (animals and fungi) or [cycloartenol](#) (plants) via the cyclization of [squalene](#). Steroids have two principal biological functions, being either key components of cell membranes or signaling molecules that activate [steroid hormone receptors](#). Important sub-classes include [sterols](#) and [cucurbitacins](#).

Triterpenoid saponins

[Triterpenoid saponins](#) are triterpenes which belong to the [saponin](#) group of compounds, making them triterpenoid [glycosides](#). They are produced by plants as part of their self-defense mechanism^[7] with important sub-classes including [ginsenosides](#)^[8] and [eleutherosides](#).

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- [Triterpenes](#)
- This page was last edited on 30 April 2023, at 14:51 (UTC).

Effects of triterpenes on the immune system

[José-Luis Ríos](#)¹

Affiliations Expand

- PMID: 20079412
- DOI: [10.1016/j.jep.2009.12.045](https://doi.org/10.1016/j.jep.2009.12.045)

Abstract

Ethnopharmacological relevance: Triterpenes, which comprise a broad chemical group of active principles, are implicated in the mechanisms of action and pharmacological effects of many medicinal plants used in folk medicine against diseases in which the immune system is implicated. They have been described as anti-inflammatory, antiviral, antimicrobial, and antitumoral agents, as well as being immunomodulator compounds. Several of them are implicated in the resolution of immune diseases, although their effects have not always been clearly correlated.

Aim of the review: The aim of this review is to compile relevant data on the mechanisms of action of triterpenes isolated from active ethnomedicinal plants and their role in the resolution of diseases in which the immune system is implicated to examine the mechanism by which they are useful as ethnopharmacological medicines.

Methods: The selection of papers was made using the most relevant databases for the biomedical sciences on the basis of their ethnopharmacological use. We principally chose those studies that examined the resolution of allergic responses in vivo and those that studied the effects of the more relevant mediators implicated in the immune response in vitro.

Results: The number of compounds actually studied is limited compared with the high number of principles that have been isolated and identified. Many studies focus on specific pathologies such cancer or inflammation, but in many cases they are clearly correlated with the immune response. Lanostanes, cucurbitanes, and oleananes are probably the most interesting groups; however, other compounds are also of potential importance.

Conclusions: Studies of specific mechanisms against mediators or transcription factors could be the objective for future research on ethnomedicinal plants used to combat immune diseases since the results obtained with cucurbitacins or derivatives of oleanolic acid support the use of different medicinal plants, thereby opening up a new frontier for future studies.

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Triterpenes and Their Essential Health Benefits

Updated: Feb 14, 2022

Although mushrooms have been used since the beginning of time as medical treatments, they only recently are being widely recognized for their benefits. It's no secret that regularly taking mushroom extracts, Reishi mushroom for example, can have a positive impact on our mental and physical health.

In fact, as stated by [WebMD](#), "the Reishi mushroom has been used to help enhance the immune system, reduce stress, improve sleep, and lessen fatigue. People also take Reishi mushrooms for health conditions such as high blood pressure and high cholesterol."

You see, Reishi mushrooms contain important compounds called Triterpenes, also known as Triterpenoids. It is believed that this component is what gives Reishi mushrooms the added health benefits they are known for.

We've done the research, so you don't have to! Here is a rundown of what Triterpenes are as well as their proven health benefits.



What are Triterpenes?

In short, Triterpenes are chemical compounds known for carrying a plethora of mental and physical health benefits. They are primarily found in plants and are especially prominent in various species of mushrooms. These chemical compounds are mostly found on the outside of plants, including bark, fruit peels, and even stems.

In a student published study on [Science Direct](#), it is stated that "Pharmacological screening of lupenone [a type of Triterpene] revealed various pharmacological activities including anti-inflammatory, anti-virus, anti-diabetes, anti-cancer, improving [Chagas disease](#) without major toxicity." These are the listed benefits for just one type of Triterpene!

Impressively, "Reishi is the only known source of a group of triterpenes" ([USPharmacist](#)).

This makes this particular mushroom a powerhouse when it comes to health benefits! Scientists have discovered ways to harness the power of Reishi by placing it in capsule forms for easy consumption.

Experience the benefits offered by the Reishi mushroom! You can start by checking out these [Reishi Extract Capsules](#) through Zenspora.

Anti-Inflammatory Benefits

When we think about inflammation, we often think about swollen joints or even an infected wound becoming enlarged. As it turns out, inflammation in the body can present itself in many ways. Inflammation in the stomach can cause nausea and even vomiting, while an injured knee can become swollen and sore.

Conditions such as Arthritis and even Lupus, although they are two very different ailments, can create great amounts of inflammation throughout the body. Triterpenes, found within Reishi, are known for reducing various types of inflammation throughout the body.

Anti-Virus Benefits

We all know what a virus is. They're those submicroscopic lifeforms that sneak into our systems, infiltrate our cells, and make us sick. In cases of a cold, you may only find yourself sick for three days to a week. However, more intense viruses can leave you bedridden or worse.

Viruses such as the Flu (Influenza), common cold, and many others in the news today are known for their nasty side effects. Triterpenes can boost your immune system and set you up for success if you ever contract one of these distasteful viruses.

Anti-Diabetes Benefits

Some of the leading causes of type [#2](#) diabetes include leading an inactive lifestyle and being overweight. As you probably already know, type [#1](#) diabetes is a term reserved for those who inherited the diabetic condition from one or both parents.

At this point, you may be wondering what Triterpenes have to do with diabetes. Well, as reported by a study published on [NCBI](#), "Many experiments have shown that these compounds have several antidiabetic mechanisms. They can inhibit enzymes involved in glucose metabolism, prevent the development of insulin resistance and normalize plasma glucose and insulin levels."

Preventing the body from developing insulin resistance is highly effective in reducing the chances of the person developing diabetes. Although it isn't an overall fix for the condition, it certainly helps as a preventative!

Anti-Cancer Benefits

"Cancer is among the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide" (National Cancer Institute). It is well known that a diagnosis can often feel like a death sentence depending on the phase and type of cancer.

Triterpenes are known for being anti-cancer. However, like their anti-diabetes benefits, they are nowhere near being an overall cure. Instead, they can be taken regularly as an extra measure to try and prevent cancer.

A [Pubmed](#) study discusses the anti-cancer components of triterpenes. In short, this study discusses the triterpenes' ability to regulate "cancer-related signaling pathways" and

processes.” Furthermore, it is stated that triterpenes contribute to the prevention of “cell death, which are uncontrolled in malignant tumors.”

Autoimmune Benefits

“Triterpenes also affected the humoral response causing auto-antibody production inhibition” ([NCBI](#)). That is, Triterpenes have a positive impact on the body’s production of autoantibodies that help us fight off autoimmune disorder side effects.

Mushrooms such as Reishi promote a healthy immune system. By taking this triterpenoid-dense mushroom supplement each day, you can up your chances of fighting off unwanted ailments. In fact, many people testify that taking a mushroom extract is one of the reasons they have been able to avoid seasonal illnesses.

Concluding Thoughts

Although Triterpenes can bring undeniable benefits to the body, they are far from being considered a cure for major diseases and conditions. In many ways, the Triterpenes found in Reishi can prevent ailments and provide overall benefits. These positives can, according to many, significantly improve quality of life.

Mushrooms have been used for thousands of years for their medicinal qualities. From food to medicines, even our ancestors recognized the special benefits of mushrooms and utilized them to their fullest potential.

Even after so many millennia of being consumed, mushrooms still pose some great mysteries that have us stumped. Today, scientists are working diligently to uncover further revelations about how mushrooms, including the rare Reishi, can benefit humankind.

For more information about the benefits of Triterpenes and the many health perks of consuming Reishi, we invite you to follow the [Zenspora Blog](#). Here, we are dedicated to keeping you updated on anything and everything that has to do with the benefits of

What are triterpenes, why are they important to my health and where do I get them?

Triterpenes are a class of compounds found in many plants, including mushrooms, that have a wide range of potential health benefits. They are known for their [anti-inflammatory](#), anti-cancer, and [immune-enhancing](#) properties.

One of the most studied triterpenes is [ganoderic acid](#), which is found in the reishi mushroom. Ganoderic acid has anti-inflammatory and immune-enhancing properties, making it of interest for improving overall health and wellness. It may also improve heart health by reducing blood pressure, cholesterol levels, and inflammation.

[Cordycepin](#) is another triterpene and is found in the cordyceps mushroom. Cordycepin has anti-inflammatory and anti-cancer properties, as well as the ability to improve athletic performance. It may also improve lung function and protect against kidney damage caused by diabetes.

The triterpene found in chaga mushroom is [betulinic acid](#), which has anti-inflammatory, anti-cancer and anti-oxidant properties.

Triterpenes found in turkey tail mushrooms is [polysaccharide-K](#), which is found to have anti-cancer properties and enhance immunity.

Triterpenes are found in various fruits, vegetables, and medicinal plants and mushrooms including:

Grapes: Triterpene oleanolic acid and ursolic acid have anti-inflammatory and anti-cancer effects.

Olive oil: Is rich in triterpene oleuropein, which has anti-inflammatory, antiviral, and anti-cancer effects.

Aloe vera: Contains triterpenes aloin, which has anti-inflammatory and anti-cancer effects.

Pine bark: Contains triterpene pycnogenol, which has anti-inflammatory, antioxidant, and anti-cancer effects.

These are just a few examples of plants that contain triterpenes.

Triterpenes are thought to exert their health benefits by a variety of molecular mechanisms, including:

Anti-inflammatory Effects: Triterpenes have been shown to inhibit the production and release of pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, which play a crucial role in the development of chronic inflammation. By blocking the action of these cytokines, triterpenes can help to reduce the severity of inflammatory responses and protect against cellular damage.

Anti-oxidant Effects: Triterpenes scavenge free radicals, which are highly reactive molecules that can cause cellular damage and contribute to the development of various diseases. By neutralizing free radicals, triterpenes can help to protect against oxidative stress and reduce the risk of various health conditions, such as cardiovascular disease and neurodegenerative disorders.

Immune System Modulation: Triterpenes enhance and regulate the immune system, including the activation and proliferation of immune cells, such as T cells and natural killer cells. By boosting the immune system, triterpenes may help to improve resistance to infections and reduce the risk of various diseases.

Anti-viral Effects: Triterpenes have antiviral effects, including the inhibition of viral replication and the activation of the immune system. By blocking the replication of viruses, triterpenes may help to prevent the spread of infections and reduce the risk of disease.

While triterpenes are commonly associated with medicinal mushrooms, they are also found in a variety of other plant-based sources, such as ginseng.

If you are looking to incorporate some of these benefits into your diet, try our [Level Up Bar Chocolate + Hazelnut](#) containing Reishi, chaga, cordyceps and Turkey Tail mushrooms.

Terpenoids

A. Ludwiczuk, ... M.I. Georgiev, in [Pharmacognosy](#), 2017

11.2.7 Triterpenoids

Triterpenoids are compounds with a carbon skeleton based on six isoprene units which are derived biosynthetically from the acyclic C₃₀ hydrocarbon, [squalene](#). They have relatively complex cyclic structures, most being either alcohols, aldehydes or [carboxylic acids](#) [16].

Sterols are [triterpenes](#) which are based on the [cyclopentane](#) perhydrophenanthrene ring system. [Plant sterols](#) called “phytosterols,” e.g., [sitosterol](#), [stigmasterol](#), and [campesterol](#) are widespread in higher plants. A less common compound, α-spinasterol (isomer of stigmasterol) was found in spinach, alfalfa, and senega root. Others occur mainly in lower plants, e.g., algae and [liverworts](#) [17]. The examples of most important triterpenes are shown in Table 11.9.

Table 11.9. The Chemical Structures, Resources, and Habitats of Triterpenoids and Sterols

Representatives

Name of Compounds	Structure	Resource	Habitat
Squalene		Liver oil of shark (e.g., gray reef shark, <i>Carcharhinus amblyrhynchos</i>). Olive oil from the fruit of <i>Olea europaea</i> L., Oleaceae	Africa, the Mediterranean Basin from Portugal to the Levant, the Arabian Peninsula, and southern Asia as far east as China, as well as the Canary Islands, Mauritius and Reunion
α-Amyrin		Resins of <i>Bursera</i> and <i>Protium</i> species (Burseraceae)	Native (for many species endemic) to the Americas, from the southern United States south through to northern Argentina Native to the Neotropics, Madagascar, New Guinea, and southern Asia from Pakistan east to Vietnam

Name of Compounds	Structure	Resource	Habitat
		<i>Taraxacum officinale</i> F. H. Wigg., Asteraceae	Temperate regions of the world
β-Amyrin		Lotus (<i>Nelumbo nucifera</i> Gaertn., Nelumbonaceae)	Native to Tropical Asia and Queensland, Australia
		Cuachalalate (<i>Amphipterygium adstringens</i> (Schltdl.) Standl., Anacardiaceae)	Central and southern Mexico
Ursolic acid		Holy basil (<i>Ocimum sanctum</i> L., Lamiaceae)	Native to Indian subcontinent
		Bilberry (<i>Vaccinium myrtillus</i> L., Ericaceae)	Native to Europe, northern Asia, Greenland, western Canada, and the western United States
		Rosemary (<i>Rosmarinus officinalis</i> L., Lamiaceae)	Native to Mediterranean region
Oleanolic acid		Olive leaves (<i>Olea europaea</i> L., Oleaceae)	See above
		Pot marigold (<i>Calendula officinalis</i> L., Asteraceae)	Native to southern Europe
Betulinic acid		White birch (<i>Betula pubescens</i> Ehrh., Betulaceae)	Native and abundant throughout northern Europe, Iceland, northern Asia, and Greenland
Cucurbitacin B		Various species from Cucurbitaceae family	Native to temperate and tropical areas
Sitosterol		Common nettle (<i>Urtica dioica</i> L., Urticaceae)	Native to Europe, Asia, northern Africa, and North America
		<i>Nigella sativa</i> L., Ranunculaceae	Native to south and southwest Asia
Stigmasterol		Calabar bean (<i>Physostigma venenosum</i> Balf., Fabaceae)	Native to tropical Africa
		Rape seeds (<i>Brassica napus</i> L. Brassicaceae)	Wild forms occur in Sweden, the Netherlands, and Britain
Campesterol		Banana (<i>Musa</i> species e.g., <i>Musa acuminata</i> Colla., Musaceae)	Native to tropical Indomalaya and Australia
α-Spinasterol		Spinach (<i>Spinacia oleracea</i> L., Amaranthaceae)	Native to central and southwestern Asia

Classification, biosynthesis, and biological functions of triterpene esters in plants

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Abstract

Triterpene esters comprise a class of secondary metabolites that are synthesized by decorating triterpene skeletons with a series of oxidation, glycosylation, and acylation modifications. Many triterpene esters with important bioactivities have been isolated and identified, including those with applications in the pesticide, pharmaceutical, and cosmetic industries. They also play essential roles in plant defense against pests, diseases, physical damage (as part of the cuticle), and regulation of root microorganisms. However, there has been no recent summary of the biosynthetic pathways and biological functions of plant triterpene esters. Here, we classify triterpene esters into five categories based on their skeletons and find that C-3 oxidation may have a significant effect on triterpenoid acylation. Fatty acid and aromatic moieties are common ligands present in triterpene esters. We further analyze triterpene ester synthesis-related acyltransferases (TEsACTs) in the triterpene biosynthetic pathway. Using an evolutionary classification of BAHD acyltransferases (BAHD-ATs) and serine carboxypeptidase-like acyltransferases (SCPL-ATs) in *Arabidopsis thaliana* and *Oryza sativa*, we classify 18 TEsACTs with identified functions from 11 species. All the triterpene-skeleton-related TEsACTs belong to BAHD-AT clades IIIa and I, and the only identified TEsACT from the SCPL-AT family belongs to the CP-I subfamily. This comprehensive review of the biosynthetic pathways and bioactivities of triterpene esters provides a foundation for further study of their bioactivities and applications in industry, agricultural production, and human health.

Key words

1. [triterpene esters](#)
2. [acyltransferases](#)
3. [classification](#)
4. [biosynthesis](#)
5. [biological functions](#)

Introduction

Plants produce various low-molecular-weight natural products that play essential roles in their adaptation to various environmental conditions. These natural products are frequently referred to as plant specialized metabolites, secondary metabolites, or natural products ([Hamberger and Bak, 2013](#)). Triterpenoids are among the largest

groups of plant secondary metabolites, with more than 20 000 different structures reported ([Thimmappa et al., 2014](#)). The majority of triterpenoids can be classified into three classes: free triterpenes, acylated forms, and glycosylated forms, which are commonly referred to as saponins ([Hamberger and Bak, 2013](#)). Many triterpenoids exhibit significant functions as anti-inflammatory and anticancer agents, establishing their clear commercial value ([Xu et al., 2004](#)). Nonetheless, the natural reservoir of triterpenes remains largely unexplored and contains vast untapped potential ([Thimmappa et al., 2014](#)).

The current model of triterpenoid biosynthesis involves the joining of six isoprene units to form squalene, a branched long-chain hydrocarbon ([Wang et al., 2011](#)). In prokaryotes, squalene undergoes direct cyclization into hopanoid triterpenoids. In eukaryotes, it is initially activated into 2,3-epoxysqualene, which is then cyclized by the oxidosqualene cyclases (OSCs) into many cyclical triterpene scaffolds ([Abe, 2007](#); [Wang et al., 2011](#); [Hamberger and Bak, 2013](#)). These triterpene scaffolds serve as substrates for further decorations by skeleton-modifying enzymes such as cytochrome P450s (CYPs), glycosyltransferases, and acyltransferases, leading to the production of a diverse array of structurally unique molecules ([Thimmappa et al., 2014](#); [Huang et al., 2019](#)).

Triterpenoids have garnered considerable attention from the scientific community, including researchers in the fields of plant science, pharmacy, and chemistry. Significant progress has been made in characterizing the genes, enzymes, and pathways involved in their biosynthesis. Triterpene esters are triterpenoids that serve as the major components of plant epidermal wax and as signaling molecules in the regulation of plant growth and development ([Campbell and Peerbaye, 1992](#); [Dinda et al., 2010](#); [Haralampidis et al., 2002](#); [Lu et al., 2018](#); [Rahimi et al., 2019](#); [Wang et al., 2021a](#); [2021b](#)). Here, we classify the triterpene esters on the basis of their skeletons and acyl donors, describe their biosynthetic pathways, and summarize their biological functions.

Classification and structural characteristics

In recent years, tremendous progress has been made in the discovery of triterpenoids ([Xu et al., 2004](#); [Valitova et al., 2016](#)) and the classification of triterpenoid skeletons ([Abe, 2007](#); [Haralampidis et al., 2002](#); [Thimmappa et al., 2014](#); [Wang et al., 2021a](#); [2021b](#)). Differences in the structures of triterpene esters reflect differences in their triterpenoid skeletons, which are modified by oxidation or glycosylation and acylation ([Thimmappa et al., 2014](#)).

Classification of triterpene esters

In accordance with the number of rings in their skeletons, triterpenes can be classified as mono-, bi-, tri-, tetra-, and pentacyclic ([Wang et al., 2021a](#); [2021b](#)). Triterpenoids with 1–3 rings are less common than tetra- and pentacyclic triterpenes. Tetracyclic triterpenes include cycloartane-, lanostane-, cucurbitane-, dammarane-, ephane-, and tirucallane-type skeleton structures, whereas pentacyclic triterpenes have lupane-,

hopane-, oleanane-, taraxaterane-, ursane-, friedelane-, and ceanothane-type skeletons ([Suksamrarn et al., 2006](#); [Kang et al., 2017](#); [Wang et al., 2021a](#); [2021b](#)).

Monocyclic-type triterpene esters. Monocyclic-type triterpene esters are commonly found in the roots of plants from the Iridaceae family (e.g., monocyclic triterpene esters in *Iris germanica* and *Belamcanda chinensis*). The acylation of monocyclic triterpenes typically occurs at the C-3 and C-16 hydroxyl groups, with long-chain fatty acids and acetic acid as donors, respectively ([Ito et al., 1995](#); [Ritzdorf et al., 1999](#); [Bonfils et al., 2001](#); [Orhan et al., 2002](#); [Gu et al., 2016](#); [Amin et al., 2021](#)) ([Figure 1](#)). In addition, camelliol C ([Table 1](#)), a monocyclic triterpene acylated at C-3, has been detected in the oil of *Camellia sasanqua* ([Akihisa et al., 1999](#)).

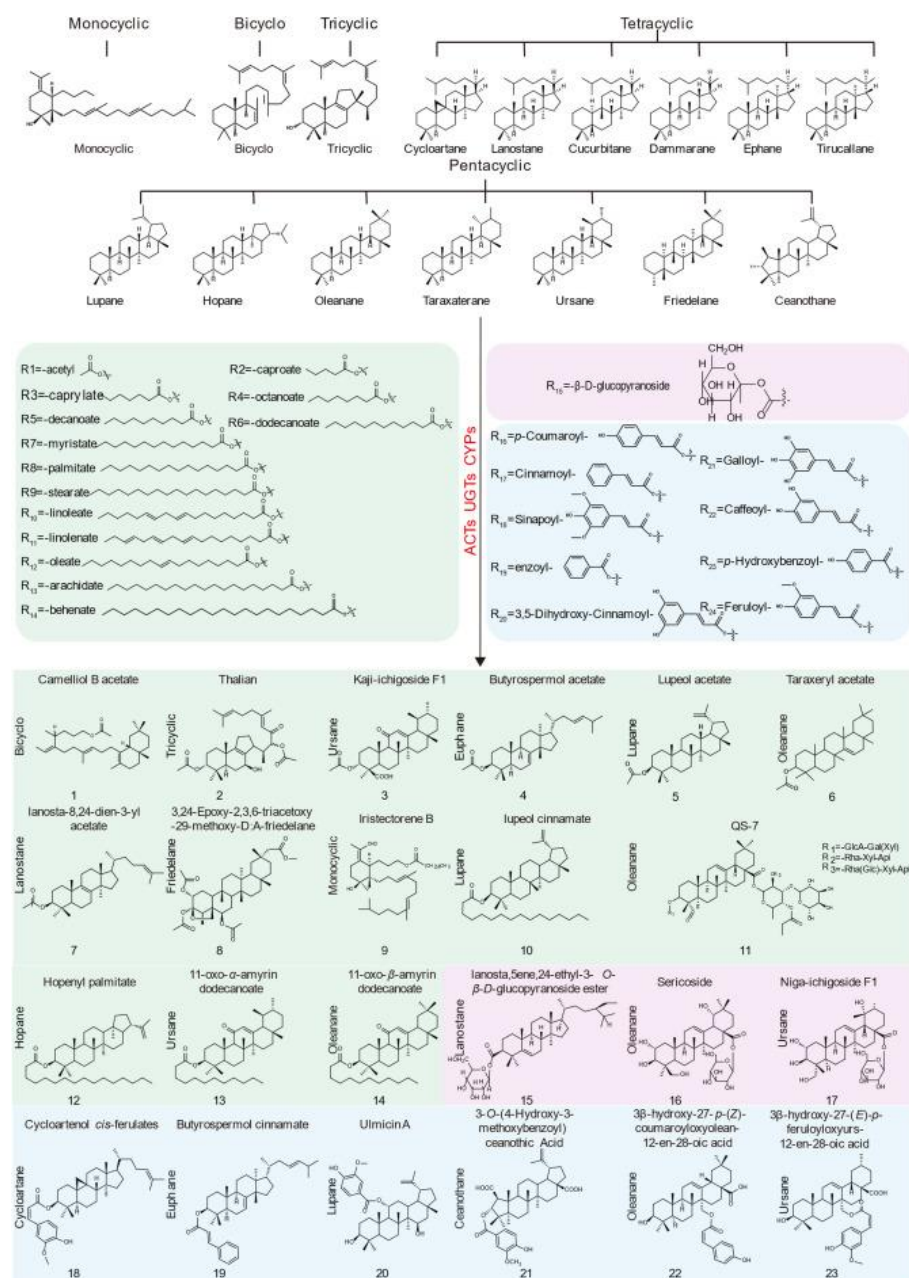


Figure 1 The diverse structures of triterpene esters.

[Show full captionFigure viewer](#)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Monocyclic	16-O-acetyl-isoiridogermanal; iristectorone K; 3-O-decanoyl-16-O-acetyl-isoiridogermanal; 3-O-tetradecanoyl-16-O-acetyl-isoiridogermanal	fatty acid	<i>Iris germanica</i>	C-16 C-3 C-3/C-16	(Bonfils et al., 2001; Ito et al., 1995; Miyake and Yoshida, 1997; Orhan et al., 2002; Gu et al., 2016; Amin et al., 2021)
Monocyclic	camelliol C acetate	fatty acid	<i>Camellia sasanqua</i>	C-3	(Akihisa et al., 1999)
Bicyclic	spirotriene ester; belamcandal	fatty acid	<i>Belinda chinensis</i> <i>I. germanica</i>	C-28/C-3 C-28	(Abe et al., 1991; Gu et al., 2016; Miyake et al., 1997)
Bicyclic	28-acetoxyspiroiridal; 29-acetoxyspiroiridal	fatty acid	<i>I. germanica</i>	C-28/C-29	(Bonfils et al., 1998, 2001; Ritzdorf et al., 1999; Fang et al., 2007; Amin et al., 2021)
Bicyclic	camelliol B acetate	fatty acid	<i>C. sasanqua</i>	C-3	(Akihisa et al., 1999)
Bicyclic	lamesticum A; lansic acid 3-ethyl ester	fatty acid	<i>Lancium domesticum</i>	C-3	(Dong et al., 2011; Matsumoto et al., 2018; Nishizawa et al., 1983)
Bicyclic	poaceatapelol palmitic acid ester; oleic acid ester; stearic acid ester	fatty acid	<i>Oryza sativa</i>	C-3	(Xue et al., 2018)
Onoceranoid	lamesticum B; lamesticum E; ethyl lansiolate; methyl lansiolate	fatty acid	<i>L. domesticum</i>	C-21/C-23	(Dong et al., 2011; Matsumoto et al., 2018; Nishizawa et al., 1983)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Tricyclic	camelliol A acetate	fatty acid	<i>L. domesticum</i>	C-3	(Akihisa et al., 1999 ; Xue et al., 2018)
Tricyclic	(-)-3 β ,7 β -dihydroxy-16-keto-thalian-15-yl acetate	fatty acid	<i>C. sasanqua</i>	C-15	(Huang et al., 2019 ; Liu et al., 2020)
Tricyclic	thalian; arabidin; thalianyl pamitate; thalianyl myristate; thalianyl laurate; arabidiyl pamitate; arabidiyl myristate; arabidiyl laurate	fatty acid	<i>Arabidopsis thaliana</i>	C-3/C-15	(Huang et al., 2019)
Euphane	euphol 3	fatty acid	<i>Arabidopsis lyrata</i>	C-3	(Liu et al., 2020)
Euphane	butyrospermol acetate; butyrospermol cinnamate	fatty acid	<i>A. thaliana</i>	C-3	(Di Vincenzo et al., 2005 ; Akihisa et al., 2010 , 2011)
Lanostane	methyl 25-hydroxy-3-epidehydrotumulosate; methyl dehydroeburiconate	fatty acid	<i>Poria cocos</i>	C-21	(Kikuchi et al., 2011)
Lanostane	lanosta-8,24-dien-3-yl acetate	fatty acid	<i>Dorstenia arifolia</i>	C-3	(Fingolo et al., 2013)
Lanostane	dimethyl poricoate A; dimethyl poricoate C; dimethyl poricoate G; dimethyl poricoate H	fatty acid	<i>P. cocos</i>	C-3/C-21	(Kikuchi et al., 2011)
Lanostane	leplaeric acid B; dimethyl ester	fatty acid	<i>Leplaea mayombensis</i>	C-3	(Sidjui et al., 2017)
Lanostane	lanosta,5ene,24-ethyl-3- β -D-O- β -D-glucopyranoside ester	glucopyranoside	<i>Alstonia scholaris</i>	C-3	(Sultana et al., 2020)
Cucurbitane	CuB; CuE; CuC; 16-O-acetyl CuB; 16-O-acetyl CuE; 16-O-acetyl CuC; 16-O-acetyl CuI;	fatty acid	<i>Citrullus lanatus</i>	C-25/C-16	(Shang et al., 2014 ; Zhou et al., 2016 ; Kim et al.,

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
	16-O-acetyl CuD; 16-O-acetyl CuI-Glu; 16-O-acetyl CuE-Glu; CuE-Glu				(2020; Zhong et al., 2022)
Cycloartane	cycloartenol palmitate	fatty acid	<i>A. thaliana</i>	C-23	(Chen et al., 2007)
Cycloartane	codonopilate A; codonopilate B; codonopilate C	fatty acid	<i>Codonopsis pilosula</i>	C-3	(Wakana et al., 2011; Xie et al., 2017)
Cycloartane	24-methylenecyclortanyl linolate	fatty acid	<i>C. pilosula</i>	C-3	(Goro et al., 1991; Wakana et al., 2011)
Cycloartane	anopaniester	fatty acid	<i>Anodendron paniculatum</i>	C-3	(Viet Ho et al., 2018)
Cycloartane	β -sitosteryl linoleate; β -sitosteryl linolenate; β -sitosteryl palmitate; campesteryl linoleate; campesteryl linolenate; stigmasteryl linoleate	fatty acid	<i>Malus pumila</i> Mill.	C-3	(Poirier et al., 2018)
	24-methylenecycloartanol <i>cis</i> -ferulates; 24-methylenecycloartanol <i>trans</i> -ferulates; cycloartenol <i>cis</i> -ferulates; cycloartenol <i>cis</i> -ferulates;				
Cycloartane	cycloartenol <i>trans</i> -ferulates; 24-methylcholesterol <i>cis</i> -ferulates; 24-methylcholesterol <i>trans</i> -ferulates; 24-methylenecholesterol <i>cis</i> -ferulates; 24-methylenecholesterol <i>trans</i> -ferulates; stigmastanol <i>cis</i> -	aromatic	rice bran	C-3	(Akihisa et al., 2000; Fang et al., 2003)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
	ferulate; stigmastanol <i>trans</i> -ferulates; sitosterol <i>cis</i> -ferulates; sitosterol <i>trans</i> -ferulates; cycloeucalenol <i>cis</i> -ferulates; citrostadienol <i>cis</i> -ferulates; cycloeucalenol <i>trans</i> -ferulates; gramisterol <i>trans</i> -ferulates; citrostadienol <i>trans</i> -ferulates;				
Lupane	lupeol acetate	fatty acid	<i>A. scholaris</i> <i>Brachylaena ramiflora</i> <i>Dorstenia arifolia</i> <i>Vitellaria paradoxa</i>	C-3	(Chaturvedula, Chaturvedula et al., 2002 ; Sultana et al., 2020)
Lupane	lupeol-3-linoleate; lupeol-3-palmitate	fatty acid	<i>Alstonia boonei</i> De Wild	C-3	(Hodges et al., 2003)
Lupane	lupeol linoleate		<i>Crataeva nurvala</i>	C-3	(Sudharsan et al., 2005)
Lupane	globrauneine A; globrauneine B; globrauneine C; globrauneine D; globrauneine E; globrauneine F	fatty acid	<i>Globimetula braunii</i>	C-3	(Muhammad et al., 2020)
Lupane	(3 β)-lup-20(29)-en-3-yl stearate	fatty acid	<i>Maytenus salicifolia</i>	C-3	(De Miranda et al., 2007)
Lupane	lup-20(29)-en-3,28-diol 28- <i>O</i> -vinylacetate	fatty acid	/	C-28	(Krainova et al., 2016)
Lupane	lup-20(29)-en-3,28-diol 28- <i>O</i> -vinylbenzoate	aromatic	/	C-28	(Krainova et al., 2016)
Lupane	ulmicin A; ulmicin B	aromatic	<i>Ulmus davidiana</i> var. <i>japonica</i>	C-11	(Lee and Kim, 2001a)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Lupane	ulmicin C; ulmicin D; ulmicin E	aromatic	<i>U. davidiana</i> var. <i>jaпонica</i>	C-11/C-15	(Lee and Kim, 2001a)
Lupane	betulinaldehyde-3 β -yl-caffeate; betulin-3 β -yl-caffeate	aromatic	<i>Celastrus stephanotifolius</i>	C-3	(Chen et al., 1999)
Lupane	3- <i>O</i> -(<i>E</i>)- <i>p</i> -coumaroyl-23-hydroxy-3- <i>epi</i> -betulin; 3- <i>O</i> -(<i>Z</i>)- <i>p</i> -coumaroyl-23-hydroxy-3- <i>epi</i> -betulin; 3- <i>O</i> -(<i>E</i>)- <i>p</i> -coumaroyl-23-hydroxybetulin; 23- <i>O</i> -(<i>E</i>)- <i>p</i> -coumaroyl-23-hydroxybetulin; 23- <i>O</i> -(<i>Z</i>)- <i>p</i> -coumaroyl-23-hydroxybetulin	aromatic	<i>Buxus cochinchinensis</i>	C-3	(Pan et al., 2015)
Lupane	27- <i>O</i> - <i>E</i> -caffeoylcylicodiscic acid	aromatic	<i>Alnus viridis</i>	C-27	(Novakovic et al., 2017)
Lupane	betulinic acid-3 β -yl-caffeate	aromatic	<i>Oenothera biennis</i> <i>C. stephanotifolius</i>	C-3	(Chen et al., 1999 ; Hamburger et al., 2002 ; Knorr and Hamburger, 2004 ; Zaugg et al., 2006)
Lupane	7 β -(4-hydroxybenzoyloxy)-betulinic acid; 7 β -(4-hydroxy-3'-methoxybenzoyloxy)-betulinic acid	aromatic	<i>Zizyphus joazeiro</i>	C-7	(Schuhly et al., 1999)
Lupane	27- <i>O</i> - <i>p</i> -hydroxybenzoylbetulinic acid; 27- <i>O</i> -protocatechuoylbetulinic acid; 27- <i>O</i> -syringoylbetulinic acid; 27- <i>O</i> -vanilloylbetulinic acid	aromatic	<i>Hovenia dulcis</i>	C-27	(Kang et al., 2017)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Lupane	3- <i>O-trans-p</i> -coumaroylalphitolic acid; 3- <i>O-cis-p</i> -coumaroylalphitolic acid	aromatic	<i>H. dulcis</i>	C-3	(Kang et al., 2017 ; Schuhly et al., 1999 ; Yagi et al., 1978)
Lupane	2- <i>O-E</i> -caffeoyl-3- <i>O-E-p</i> -coumaroyl-27-hydroxymethylalphitolic acid; 2- <i>O-E</i> -caffeoyl-3- <i>O-Z-p</i> -coumaroyl-27-hydroxymethylalphitolic acid	aromatic	<i>A. viridis</i>	C-2/C-3	(Novakovic et al., 2017)
Lupane	2- <i>O-E</i> -caffeoyl-27-hydroxymethylalphitolic acid; 27-hydroxybetunolic acid; 2- <i>O-E</i> -caffeoylalphitolic acid	aromatic	<i>A. viridis</i>	C-2	(Novakovic et al., 2017)
Oleanane	avenacin A-1; avenacin A-2; avenacin B-1; avenacin B-2	fatty acid	<i>Avena strigosa</i>	C-21	(Mugford et al., 2009)
Oleanane	(3 β)-olean-18-en-3-yl stearate	fatty acid	<i>M. salicifolia</i>	C-3	(De Miranda et al., 2007)
Oleanane	oleana-9(11),12-dien-3-yl acetate; oleana-9(11),12-dien-3-yl decanoate; 12,13-epoxyolean-3-yl acetate; 12,13-epoxyolean-9(11)en-3-yl acetate	fatty acid	<i>D. arifolia</i>	C-3	(Fingolo et al., 2013)
Oleanane	22-hydroxy-29-methoxy-3-tetradecanoate-olean-12-ene	fatty acid	<i>Maytenus cuzcoina</i>	C-3/C-29	(Reyes et al., 2017)
Oleanane	alstoprenylol	fatty acid	<i>A. scholaris</i>	C-28	(Sultana et al., 2020)
Oleanane	11-oxo- β -amyrin acetate; 11-oxo- β -amyrin decanoate; 11-	fatty acid	<i>D. arifolia</i>	C-3	(Fingolo et al., 2013)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
	oxo- β -amyirin dodecanoate; 11-oxo- β -amyirin octanoate				
Oleanane	acerotin; acerocin	fatty acid	<i>Acer negundo</i> L.	C-21/C-22	(Kupchan et al., 1971)
Oleanane	3-O-acetyl- α -BA (A α BA)	fatty acid	<i>Boswellia serrata</i>	C-3	(Syrovets et al., 2000)
Oleanane	β -amyirin acetate; β -amyirin caproate; β -amyirin caprylate; β -amyirin cinnamate; β -amyirin decanoate; β -amyirin dodecanoate; β -amyirin hexadecanoate; β -amyirin octanoate; β -amyirin palmitate; β -amyirin tetradecanoate	fatty acid	<i>Manilkara subsericea</i> <i>V. paradoxa</i> <i>D. arifolia</i> <i>B. ramiflora</i>	C-3	(Chaturvedula et al., 2002 ; Di Vincenzo et al., 2005 ; Akihisa et al., 2010, 2011 ; Fernandes et al., 2013 ; Fingolo et al., 2013)
Oleanane	taraxeryl acetate	fatty acid	<i>Ficus ovata</i> <i>C. pilosula</i> <i>Echinops taeckholmiana</i> <i>Atractylodes macrocephala</i> <i>Artemisia roxburghiana</i> <i>Alnus hirsuta</i> <i>Koelpinia linearis</i> <i>D. arifolia</i>	C-3	(Jin et al., 2007 ; Koul et al., 2000 ; Kue et al., 2009 ; Fingolo et al., 2013 ; Rehman et al., 2013 ; Shah et al., 2016 ; Li et al., 2017 ; Xie et al., 2017 ; Hamdan et al., 2021)
Oleanane	7 α -hydroxymultiflor-8-ene-3 α ,29-diol 3-acetate-29-benzoate; multiflora-7,9(11)-diene-3 α ,29-diol 3,29-dibenzoate	fatty acid	<i>Cucurbita maxima</i>	C-3/C-29	(Kikuchi et al., 2014)
Oleanane	7 α -methoxymultiflor-8-ene-3 α ,29-diol 3,29-	fatty acid	<i>C. maxima</i>	C-3/C-7/C-29	(Kikuchi et al., 2014)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Oleanane	dibenzoate; 7 β -methoxymultiflor-8-ene-3 α ,29-diol 3,29-dibenzoate (3 α ,7 β)-3,7,29-trihydroxymultiflor-8-ene-3,29-diyl dibenzoate; (3 α)-3,29-dihydroxy-7-oxomultiflor-8-ene-3,29-diyl dibenzoate	fatty acid	<i>Trichosanthes kirilowii</i>	C-3/C-29	(Tao et al., 2005)
Oleanane	olean-28-aL-3 β -yl caffeate	aromatic	<i>C. stephanotifolius</i>	C-3	(Chen et al., 1999)
Oleanane	2-O-E-caffeoyl-3-epimaslinic acid	aromatic	<i>A. viridis</i>	C-2	(Novakovic et al., 2017)
Oleanane	3-acetoxy-27-trans-caffeoyloxyolean-12-en-28-oic acid methyl ester	aromatic	<i>Peganum nigellastrum</i>	C-3/C-27/C-28	(Ma et al., 2007)
Oleanane	3 β -trans-(3,4-dihydroxycinnamoyloxy)olean-12-en-28-oic acid; 3 β -trans-(3,4-dihydroxycinnamoyloxy)olean-18-en-28-oic acid	aromatic	<i>O. biennis</i>	C-3	(Hamburger et al., 2002 ; Knorr and Hamburger, 2004 ; Zaugg et al., 2006)
Oleanane	23-galloylarjunolic acid	aromatic	<i>Terminalia macroptera</i>	C-23	(Jürgen et al., 1998)
Oleanane	3,24-(S)-hexahydroxydiphenoyl-2 α ,3 β ,23,24-tetrahydroxyolean-12-en-28-oic acid	aromatic	<i>Castanopsis fissa</i>	C-3/C-4	(Huang et al., 2011)
Oleanane	3 β -hydroxy-27-p-(Z)-coumaroyloxyolean-12-en-28-oic acid; 3 β -hydroxy-27-(E)-feruloyloxyolean-12-en-28-oic acid; 3 β -hydroxy-27-(Z)-	aromatic	<i>Keetia leucantha</i>	C-27	(Lee et al., 2000 ; Bero et al., 2013 ; Beaufay et al., 2017 , 2019)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Oleanane	feruloyloxyolean-12-en-28-oic acid; uncarinic acid E germanicol caffeoyl ester; germanicol <i>trans</i> -coumaroyl ester; germanicol <i>cis</i> -coumaroyl ester	aromatic	<i>Barringtonia asiatica</i>	C-3	(Ragasa et al., 2011)
Oleanane	3,24-di-O-galloyl-2,3-23,24-tetrahydroxyolean-12-en-28-oic acid	aromatic	<i>Castanopsis cuspidata</i>	C-3/C-24	(Ogata et al., 2016)
Oleanane	castanopsinin E	aromatic/ β -D-glucopyranoside	<i>C. fissa</i>	C-3/C-4/C-28	(Huang et al., 2011)
Oleanane	2 α ,3 α ,19 α ,24-tetrahydroxyolea-12-en-28-oic acid β -D-glucopyranosyl ester; sericoside	β -D-glucopyranosyl	<i>Callicarpa japonica</i>	C-28	(Ono et al., 2009)
Oleanane	28-O- <i>p</i> -D-glucopyranosyl ester	β -D-glucopyranoside	<i>T. macroptera</i>	C-23/C-28	(Jürgen et al., 1998)
Ursane	ursolic acid-3-arachidate; ursolic acid-3-behenate; ursolic acid-3-heneicosylate; ursolic acid-3-linoleate; ursolic acid-3-linolenate; ursolic acid-3-oleate; ursolic acid-3-stearate; uvaol linoleate; uvaol linolenate; uvaol oleate; uvaol stearate	fatty acid	<i>M. pumila</i> Mill.	C-3	(Poirier et al., 2018)
Ursane	ursa-9(11),12-dien-3-yl acetate; ursa-9(11),12-dien-3-yl decanoate	fatty acid	<i>D. arifolia</i>	C-3	(Fingolo et al., 2013)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Ursane	acetyl-11-keto-amyrin; 3-O-acetyl- β -BA (A β BA); acetyl-11-keto- β -boswellic acid (AKBA)	fatty acid	<i>B. serrata</i>	C-3	(Sailer et al., 1996 ; Syrovets et al., 2000 ; Lu et al., 2008)
Ursane	3 β ,6 β ,19 α -trihydroxy-urs-12-en-24, 28-dioic acid 24-methyl ester	fatty acid	<i>Mitragyna diversifolia</i>	C-24	(Kang and Hao, 2006 ; Cao et al., 2014)
Ursane	(3 β)-urs-12-en-3-yl stearate	fatty acid	<i>M. salicifolia</i>	C-3	(De Miranda et al., 2007)
Ursane	α -amyrin acetate; α -amyrin caproate; α -amyrin linolenate; α -amyrin myristate; α -amyrin stearate; α -amyrin palmitate; α -amyrin decanoate; α -amyrin dodecanoate; α -amyrin hexadecanoate; α -amyrin octanoate; α -amyrin tetradecanoate; 11-oxo- α -amyrin acetate; 11-oxo- α -amyrin decanoate; 11-oxo- α -amyrin dodecanoate; 11-oxo- α -amyrin octanoate	fatty acid	<i>A. scholaris</i> <i>A. boonei</i> <i>D. arifolia</i> <i>B. ramiflora</i> <i>M. subsericea</i> <i>V. paradoxa</i>	C-3	(Chaturvedula et al., 2002 ; Fingolo et al., 2013 ; Okoye et al., 2014 ; Sultana et al., 2020 ; Fernandes et al., 2013 ; Akihisa et al., 2010, 2011 ; Di Vincenzo et al., 2005 ; Fingolo et al., 2013, 2013 ; Poirier et al., 2018)
Ursane	2 α ,3 β ,23-trihydroxy-urs-12,18-dien-28-oic acid methyl ester; 2 α ,3 β ,23-trihydroxy-urs-12,19-dien-28-oic acid methyl ester	fatty acid	<i>Rubus allegheniensis</i>	C-28	(Ono et al., 2003)
Ursane	α -amyrin cinnamate	aromatic	<i>V. paradoxa</i>	C-3	(Di Vincenzo et al., 2005 ; Akihisa et al., 2010, 2011)
Ursane	3 β -hydroxy-27- <i>p</i> -(<i>E</i>)-coumaroyloxyurs-12-	aromatic	<i>Uncaria rhynchophylla</i>	C-27	(Lee et al., 2000)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Ursane	en-28-oic acid; 3 β -hydroxy-27- <i>p</i> -(<i>Z</i>)-coumaroyloxyurs-12-en-28-oic acid 3 β -hydroxy-27-(<i>E</i>)-feruloyloxyurs-12-en-28-oic acid; 3 β -hydroxy-27-(<i>Z</i>)-feruloyloxyurs-12-en-28-oic acid	aromatic	<i>K. leucantha</i>	C-27	(Bero et al., 2013 ; Beaufay et al., 2017 , 2019)
Ursane	uncarinic acid C; uncarinic acid D	aromatic	<i>U. rhynchophylla</i>	C-27	(Lee et al., 1999 , 2000 ; Umeyama et al., 2010)
Ursane	kaji-ichigoside F1	β -D-glucopyranoside	<i>C. japonica</i>	C-28	(Ono et al., 2009)
Ursane	2 α ,3 α ,19 α ,24-tetrahydroxyurs-12-en-28-oic acid β -D-glucopyran ester	β -D-glucopyranoside	<i>C. japonica</i>	C-28	(Ono et al., 2009)
Ursane	niga-ichigoside F1	β -D-glucopyranoside	<i>R. allegheniensis</i>	C-28	(Ono et al., 2003 ; Tonin et al., 2016 ; Xia et al., 2018)
Ursane	3,24-di- <i>O</i> -galloyl-2 α ,3 β -23,24-tetrahydroxyurs-12-en-28-oic acid; 4-epi-niga-ichigoside F1	β -D-glucopyranoside	<i>C. cuspidata</i>	C-3 C-24	(Ogata et al., 2016)
Ursane	rubusside A	β -D-glucopyranoside	<i>R. allegheniensis</i>	C-28	(Ono et al., 2003)
Ursane	nighascholarene	β -D-glucopyranoside	<i>A. scholaris</i>	C-28	(Sultana et al., 2020)
Hopane type	hopenyl palmitate	fatty acid	<i>B. ramiflora</i>	C-3	(Chaturvedula et al., 2002)
Friedelane type	3 β ,24 β -epoxy-29-methoxy-2 α ,3 α ,6 α -	fatty acid	<i>M. cuzcoina</i>	C-29	(Reyes et al., 2017)

Triterpenoid skeleton	Compounds	Acyl donor	Species	Reaction position	Ref.
Friedelane type	trihydroxy- <i>D:A</i> -friedelane				
	3,24-epoxy-2,3,6-triacetoxy-29-methoxy- <i>D:A</i> -friedelane	fatty acid	<i>M. cuzcoina</i>	C-2/C-3/C-6/C-29	(Reyes et al., 2017)
Ceanothane type	27- <i>O</i> -protocatechuoyl-3-dehydroxyisoceanothanoic acid; 27- <i>O</i> -protocatechuoyl-3-dehydroxycolubrinic acid; 27- <i>O</i> -protocatechuoyl-3-dehydroxyepicolubrinic acid	aromatic	<i>H. dulcis</i>	C-27	(Kang et al., 2017)
	3- <i>O</i> -(4-hydroxy-3-methoxybenzoyl)ceanothanic acid	aromatic	<i>Ziziphus cambodiana</i>	C-3	(Suksamrarn et al., 2006)

Table 1

Classification of triterpenoid skeleton-modified triterpene esters.

- [Open table in a new tab](#)

Bicyclic-type triterpene esters

Lansium domesticum, a fruit-bearing tree commonly found in southeastern Asia, is rich in onoceranoid-type bicyclic triterpene esters ([Matsumoto et al., 2018](#); [Nishizawa et al., 1983](#)). In the fruits, seeds, and bark of *L. domesticum*, the C-3 carboxyls of onoceranoid-type triterpenes react with hydroxyl donors, which are mostly alcohols with one or two carbon atoms, to form triterpene esters ([Table 1](#)) ([Dong et al., 2011](#); [Matsumoto et al., 2018, 2019](#)). The incompletely cyclized bicyclic triterpene, camelliol B, found in *C. sasanqua* oil, can be acylated at C-3 to form Camelliol B acetate (compounds **1** in [Figure 1](#)) ([Akihisa et al., 1999](#)) ([Table 1](#)). In addition, certain bicyclic triterpenoids present in *Oryza sativa* can also be acylated at C-3 by various long-chain fatty acids ([Table 1](#)) ([Xue et al., 2018](#)). In Iridaceae, bicyclic triterpenoid acylation frequently occurs at C-3 or C-28 ([Abe et al., 1991](#); [Gu et al., 2016](#); [Ritzdorf et al., 1999](#)). However, in some spiro-bicyclic triterpenes of Iridaceae, acylation also occurs at C-29, as seen in Compound **1** ([Figure 1](#)) ([Bonfils et al., 1998, 2001](#); [Ritzdorf et al., 1999](#); [Fang et al., 2007](#); [Amin et al., 2021](#)).

Tricyclic-type triterpene esters

[Huang et al. \(2019\)](#) reported that tricyclic triterpene esters found in *A. thaliana* play a regulatory role in the colonization and development of rhizosphere microorganisms. These triterpenes are typically acylated on the C-3 hydroxyl, C-15, or both ([Table 1](#)) ([Huang et al., 2019](#); [Liu et al., 2020](#)). There are also some tricyclic triterpenes with long-chain fatty acids ([Sohrabi et al., 2017](#); [Huang et al., 2019](#)). In addition to tricyclic triterpene esters in *Brassicaceae*, incompletely cyclized tricyclic triterpene esters with monocyclic and bicyclic-type skeletons have been found in extracts of *C. sasanqua* oil ([Akihisa et al., 1999](#)).

Tetracyclic-type triterpene esters

Compared with monocyclic, bicyclic, and tricyclic triterpenes, tetracyclic and pentacyclic triterpenes exhibit greater complexity of skeleton types and esterification positions. Lanostane ([Kikuchi et al., 2011](#); [Sidjui et al., 2017](#); [Sultana et al., 2020](#)), euphane ([Di Vincenzo et al., 2005](#); [Akihisa et al., 2010, 2011](#); [Liu et al., 2020](#)), and cycloartane ([Di Vincenzo et al., 2005](#); [Akihisa et al., 2010, 2011](#); [Kikuchi et al., 2011](#); [Sidjui et al., 2017](#); [Liu et al., 2020](#); [Sultana et al., 2020](#)) are the major types of tetracyclic-type triterpene esters. These skeletons typically feature hydroxylation at C-3 and C-21, and they can react with various acyl donors to produce different types of triterpene esters ([Di Vincenzo et al., 2005](#); [Akihisa et al., 2010, 2011](#); [Kikuchi et al., 2011](#); [Sidjui et al., 2017](#); [Liu et al., 2020](#); [Sultana et al., 2020](#)). However, a distinct group of tetracyclic triterpenes referred to as nortriterpenoids is found primarily in *Schisandra chinensis* ([Shi et al., 2015](#); [Yang, 2019](#)) and *Melia azedarach* L. ([Fan et al., 2022](#)). Nortriterpenoids have been reviewed extensively elsewhere ([Shi et al., 2015](#); [Li et al., 2016](#); [Yang, 2019](#); [Fan et al., 2022](#); [Huo et al., 2022](#)) and are not discussed further here. In addition, another category of tetracyclic triterpenes with novel structures, the nor-cucurbitacin triterpenes ([Huo et al., 2022](#)), exhibit numerous biological functions and medicinal activities.

Pentacyclic-type triterpene esters

Pentacyclic triterpenes are widely distributed in nature and exhibit various skeleton types. The lupane ([Chen et al., 1999](#); [Lee and Kim, 2001](#); [Chaturvedula et al., 2002](#); [Hodges et al., 2003](#); [Knorr and Hamburger, 2004](#); [Sudharsan et al., 2005](#); [Zaugg et al., 2006](#); [de Miranda et al., 2007](#); [Akihisa et al., 2010](#); [Kang et al., 2017](#); [Novakovic et al., 2017](#); [Sultana et al., 2020](#)), oleanane ([Kupchan et al., 1971](#); [Chen et al., 1999](#); [Lee et al., 1999, 2000](#); [Syrovets et al., 2000](#); [Hamburger et al., 2002](#); [Knorr and Hamburger, 2004](#); [Zaugg et al., 2006](#); [de Miranda et al., 2007](#); [Csuk et al., 2012](#); [Bero et al., 2013](#); [Fernandes et al., 2013](#); [Fingolo et al., 2013](#); [Langer et al., 2016](#); [Ogata et al., 2016](#); [Beaufay et al., 2017, 2019](#); [Novakovic et al., 2017](#); [Reyes et al., 2017](#); [Xiang et al., 2019](#)), and ursane types ([Sailer et al., 1996](#); [Ono et al., 2003, 2009](#); [Lu et al., 2008](#); [Fingolo et al., 2013](#); [Cao et al., 2014](#); [Tonin et al., 2016](#)) account for over 95% of the known configurations of pentacyclic triterpene esters ([Table 1](#)). A few hopane-, friedelane-, and ceanothane-type triterpene esters also exist. Most of these pentacyclic triterpenes are hydroxylated at the C-3 position and then esterified with various donors to produce different types of triterpene esters. Apart from

the C-3 position, they can also form esters with different donors at C-2 ([Novakovic et al., 2017](#)), C-4 ([Huang et al., 2011](#); Marzouk and MS, 2013), C-6 ([Reyes et al., 2017](#)), C-7 ([Schuhly et al., 1999](#)), C-11 ([Lee and Kim, 2001a](#)), C-15 ([Lee and Kim, 2001a](#)), C-21 ([Kupchan et al., 1971](#); [Kupchan et al. 1970](#)), C-22 ([Kupchan et al., 1971](#); [Kupchan et al. 1970](#)), C-23 ([Pan et al., 2015](#)), C-24 ([Ogata et al., 2016](#)), C-27 ([Kang et al., 2017](#)), C-28 ([Kang et al., 2017](#)), and C-29 ([Tao et al., 2005](#)).

Characteristics of triterpene esters

Acylation of the skeleton

Triterpene esters are classified according to both their skeleton types and the esterified ligands on their backbones. On the basis of their acyl ligands, triterpene esters are grouped into fatty acid, glycosyl, and aromatic triterpene esters ([Xu et al., 2004](#)). Our analysis revealed that most acyl ligands on triterpene esters are fatty acids, comprising 141 positions in 236 compounds. Notably, more than half (56%) of these fatty acids are non-short-chain fatty acids ($C \geq 6$), which are always hydrophobic and found on plant surfaces ([Di Vincenzo et al., 2005](#); [Poirier et al., 2018](#); [Xue et al., 2018](#)). Approximately 40% of fatty acid triterpene esters are short-chain fatty acids ($C < 6$), and the remainder are both short-chain fatty acids and non-short-chain fatty acids or both short-chain fatty acids and aromatic groups ([Figure 2](#)). Multiple acylation sites frequently occur on the triterpene skeleton. We found that fatty acid donors can coexist on triterpenes ([Kupchan et al., 1971](#); [Shang et al., 2014](#); [Gu et al., 2016](#); [Zhou et al., 2016](#); [Huang et al., 2019](#); [Kim et al., 2020](#)). Although both glucosyl and non-short-chain fatty acid esters can coexist on the same triterpene skeleton, the occurrence of both is rare. The predominant site of acylation in triterpene esters is C-3, with 67% of triterpene esters acylated at this position. Approximately 85% of these triterpene esters had only one acylation, highlighting the significance of oxidation at C-3 in triterpene ester biosynthesis.

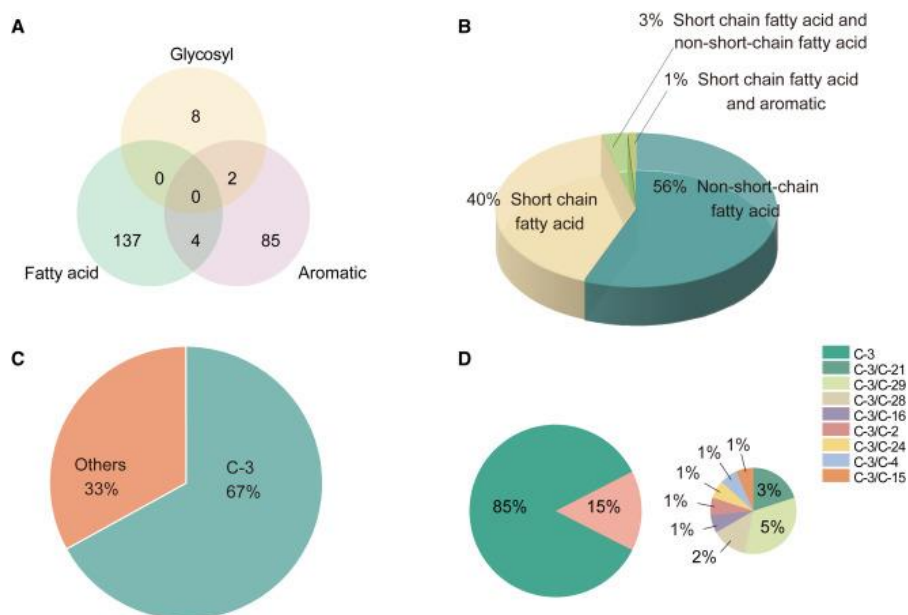


Figure 2 Different acyl donors and acylation sites of triterpene esters.

[Show full captionFigure viewer](#)

Acylation on triterpenoid saponins

In addition to acylation directly on the triterpenoid skeleton, acylation can also occur on the sugar donor of triterpenoid saponins. This group of triterpene esters is widely distributed in nature, and their diversity is attributed to the wide range of triterpenoid scaffolds and complex glycosylation structures ([Yao et al., 2020](#); [Wang et al., 2021a, 2021b](#)). The structural characteristics of this group of triterpenoid saponins are mainly due to the acylation that occurs on the glycosyl donor of saponin and the glycosylation that occurs on the triterpenoid backbone.

In nature, triterpenoid saponins are primarily used by plants to defend against various biotic and abiotic stresses ([Szakiel et al., 2011](#)). They also play an important role in human health, with reported anti-inflammatory, anticancer, and other activities ([Vincken et al., 2007](#); [Augustin et al., 2011](#)). Acylation at different sites plays a crucial role in determining the biological activities of triterpenoid saponins. Some acylation of triterpene saponins occurs on the glycoside donors after triterpene glycosylation ([Jozwiak et al., 2020](#); [Reed et al., 2023](#); [Wang et al., 2023](#); [Yuan et al., 2023](#)). For example *Quillaja saponaria* saponin 7 (QS-7), an acetylated saponin (on fucose C-4) from *Q. saponaria*, can be one of the saponin adjuvants in the Novovax NVX-CoV2373 COVID-19 vaccine. It is also a favored anticancer candidate that has shown negligible toxicity in mice ([Reed et al., 2023](#)). Another aspect involves acylation modifications of the triterpene skeleton of triterpenoid saponins ([Osborn et al., 2011](#); [Cárdenas et al., 2019](#); [Zhang et al., 2019](#); [Matsuda et al., 2023](#)). This portion likely represents advanced acylation followed by glycosylation or the simultaneous occurrence of both processes.

Biosynthetic pathways

Plants contain a variety of triterpene esters with complex biosynthetic pathways. The immediate precursor of triterpenes, 2,3-oxidosqualene, is cyclized by OSCs to form a variety of triterpene skeletons ([Xu et al., 2004](#); [Abe, 2007](#); [Racolta et al., 2012](#); [Thimmappa et al., 2014](#); [Ladhari and Chappell, 2019](#)). Subsequently, different modifying enzymes such as CYPs, UDP-glycosyltransferases (UGTs), and acyltransferases (ACTs) decorate these triterpene skeletons, converting them into triterpene esters. Most studies have focused on the early steps of the triterpene metabolic pathway catalyzed by OSCs and CYPs ([Hamberger and Bak, 2013](#); [Kim et al., 2020](#); [Ladhari and Chappell, 2019](#); [Mizutani, 2012](#); [Ohnishi et al., 2009](#); [Racolta et al., 2012](#)). Here, we will not review details of triterpene skeleton biosynthesis, as they have been reported extensively (e.g., [Xu et al., 2004](#); [Sawai and Saito, 2011](#); [Racolta et al., 2012](#); [Hamberger and Bak, 2013](#); [Thimmappa et al., 2014](#); [Valitova et al., 2016](#); [Ladhari and Chappell, 2019](#); [Rahimi et al., 2019](#)). Some UGTs involved in triterpenoid glycosylation have also been described ([Lu et al., 2018](#); [Rahimi et al., 2019](#)). However, the role of ACTs, which catalyze an important step in triterpene ester formation, has been largely overlooked in previous studies. Currently, triterpene

ester synthesis-related acyltransferases (TEsACTs) are known to belong to two acyltransferase families. The first is the BAHD acyltransferase (BAHD-AT) family, which includes benzylalcohol O-acetyltransferase (BEAT), anthocyanin O-hydroxycinnamoyltransferase (AHCT), anthranilate N-hydroxycinnamoyl-/benzoyltransferase (HCBT), and deacetylindoline 4-O-acetyltransferase (DAT). The second is the serine carboxypeptidase-like acyltransferase (SCPL-AT) family ([Bontpart et al., 2015](#); [D'Auria, 2006](#)). The BAHD-ATs are the most common acyltransferase superfamily in plants, and their primary substrate is Coenzyme A (CoA) ([D'Auria, 2006](#); [Moghe et al., 2023](#); [Wang et al., 2022](#)) ([Figure 3](#)). The acyl donor of SCPL-ATs generally originates from glucose esters ([Figure 3](#)), which are the products of UGTs. Because of the sequence homology of SCPL-ATs to serine carboxypeptidase (SCP), these enzymes are called SCP-like (SCPL); they belong to the α/β superfamily of macromolecules but lack the peptide hydrolysis activity of genuine SCPs ([Shirley and Chapple, 2003](#); [Milkowski and Strack, 2004](#); [Mugford et al., 2009](#); [Mugford and Milkowski, 2012](#)).

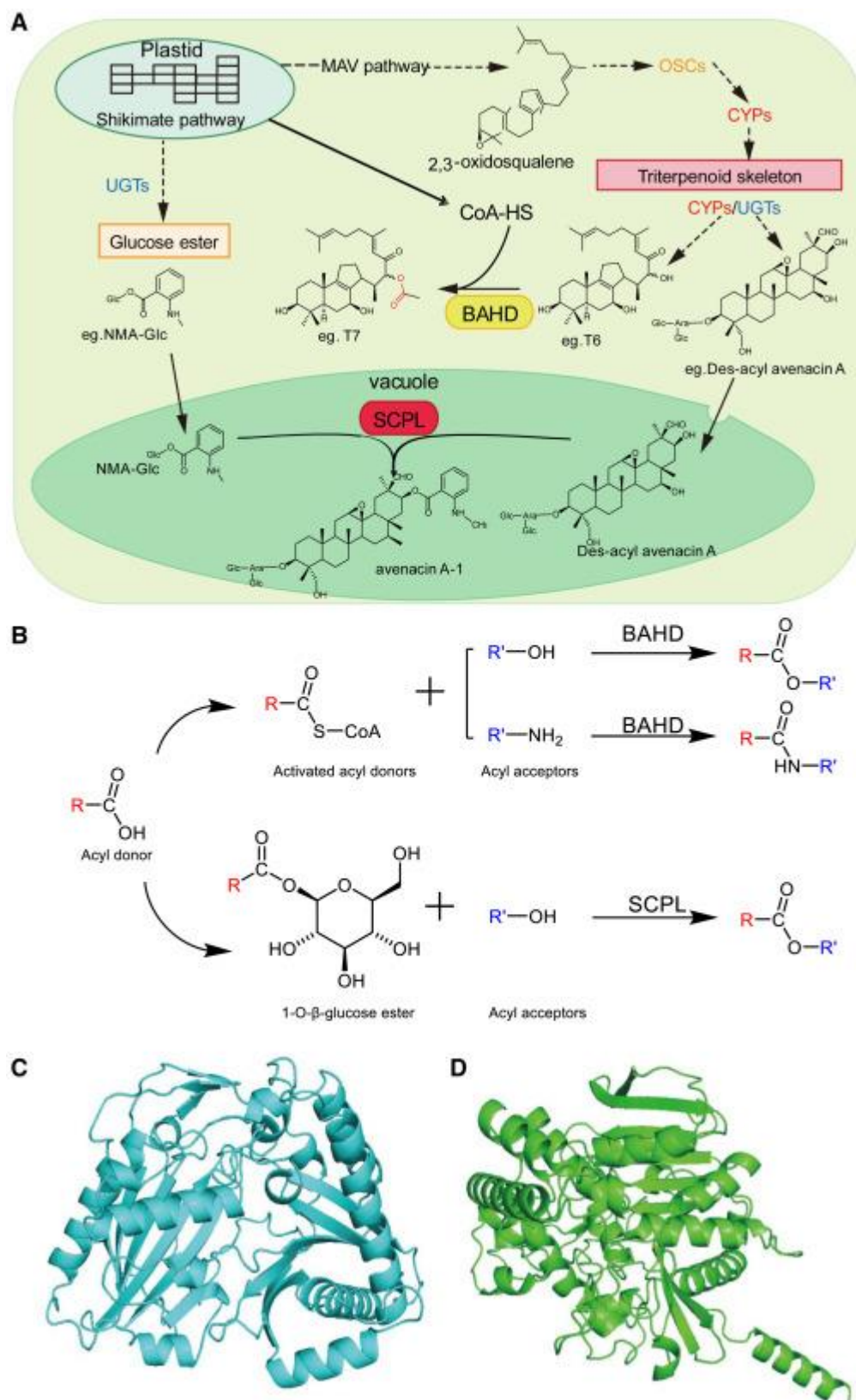


Figure 3 Acylation mechanisms and the structure of BAHD and SCPL acyltransferases.

[Show full caption](#)[Figure viewer](#)

BAHD-AT family

The BAHD superfamily contains a large number of enzymes. Previous reports have indicated that members of this family are mostly monomeric proteins with a cytoplasmic localization whose molecular weights range from 48 kD to 55 kD ([Bontpart et al., 2015](#); [D'Auria, 2006](#)). Sequence comparisons among enzymes within the BAHD superfamily have revealed a low similarity of 10%–30% and a high similarity of up to 90%. This family is primarily characterized by two conserved motifs, HXXXD and DFGWG ([Bontpart et al., 2015](#); [D'Auria, 2006](#); [Molina and Kosma, 2015](#)) ([Figure 3C](#)). The HXXXD domain is present in the active center of the enzymes and represents a shared structural feature between the BAHD superfamily and several other CoA-dependent acyl-coenzyme superfamilies; the DFGWG motif is located near the C terminus ([D'Auria, 2006](#); [Molina and Kosma, 2015](#)).

[D'Auria \(2006\)](#) constructed a phylogenetic tree of 46 functionally characterized BAHD-ATs, which were classified into five clades ([Wang and Luca, 2005](#)). In a subsequent study, [Tuominen et al. \(2011\)](#) further refined their classification by constructing a phylogenetic tree that divided the BAHD-ATs into eight main clades, providing a more comprehensive classification. In this study, we followed a similar approach and classified the BAHD acyltransferase superfamily members of *A. thaliana* and *O. sativa* on the basis of their phylogenetic relationships. We then performed a phylogenetic analysis that included acyltransferases associated with triterpene ester biosynthesis that have been identified and characterized to date in multiple species. Using the classification of BAHD-ATs from *A. thaliana* and *O. sativa*, we found that most BAHD-ATs associated with triterpene ester synthesis fell into clade IIIa, although three fell into clade I ([Figure 4](#)).

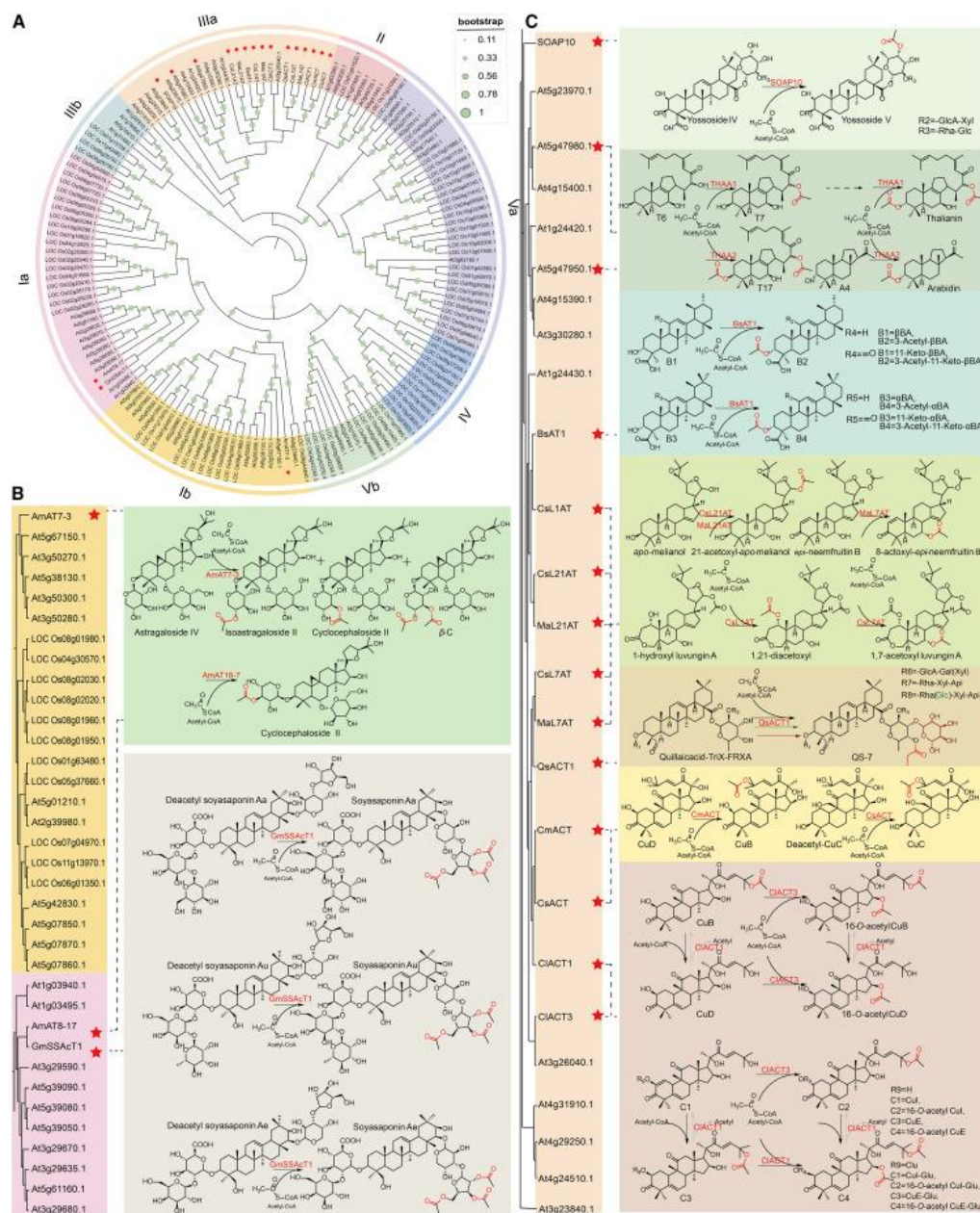


Figure 4 Biosynthetic pathways of triterpene esters involving BAHD acyltransferases.

[Show full captionFigure viewer](#)

Fourteen TESACTs in the BAHD family fell into clade IIIa, and most were acylated on their triterpene skeletons. Cucurbitacins (tetracyclic) are a highly studied class of triterpene esters, and BAHD-ATs have been identified from four Cucurbitaceae species. For instance, *Cucumis melo* acyltransferase (CmACT) and *Cucumis sativus* acetyltransferase (CsACT) catalyze acetylation at C-16. CmACT can catalyze the synthesis of cucurbitacin B (CuB) from cucurbitacin D (CuD) ([Zhou et al., 2016](#)), and Shang et al. found that conversion of deacetyl-CuB to CuB in cucumber was governed by CsACT, an enzyme associated with bitterness in this species ([Shang et al., 2014](#); [Zhou et al., 2016](#)) ([Figure 4B](#)). However, *Citrullus lanatus* acyltransferase 1

(CIACT1) not only catalyzes the CuD to CuB conversion but also catalyzes the deacylation of CuD, as well as conversions between 16-O-acetyl CuD and 16-O-acetyl CuB; cucurbitacin I (CuI), cucurbitacin I-2-O-glucoside (CuI-Glu) and cucurbitacin E (CuE), cucurbitacin E-2-O-glucoside (CuE-Glu); 16-O-acetyl CuI, 16-O-acetyl CuI-Glu and 16-O-acetyl CuE and 16-O-acetyl CuE-Glu ([Kim et al., 2020](#)). Another acyltransferase in *C. lanatus*, *C. lanatus* acyltransferase 3 (CIACT3), can acylate CuB, CuD, CuI, CuE, CuI-Glu, and CuE-Glu on C-25 ([Kim et al., 2020](#)). TEACTs in *A. thaliana* serve as a reference for identifying homologous genes in other plant species. Thalianol acyltransferase 1 (THAA1) is responsible for acylating hydroxylated thalianol, and THAA2 acylates the product of THAA1 to produce thalianin. THAA1 can also catalyze the acylation of arabidiol to generate arabidin ([Figure 4A](#) and [4C](#)) ([Sohrabi et al., 2017](#); [Huang et al., 2019](#)). Production of some triterpene esters is associated with plant injury responses. Upon injury, the bark of *Boswellia* trees can secrete a unique resin that contains triterpene esters ([Ammon, 2016](#); [Yamamoto et al., 2020](#); [Kumar et al., 2021](#)). [Kumar et al. \(2021\)](#) performed a tissue-specific transcriptome analysis of *Boswellia* and identified a wound-responsive BAHD acetyltransferase that could catalyze the C-3 acylation of α - and β -boswellic acid ([Figure 4](#)). Limonoids are a class of triterpenoids with complex structures and extensive activities, and analysis of their biosynthetic pathways has attracted extensive attention. Recently, [De La Pena et al. \(2023\)](#) clarified some of the biosynthetic pathways of limonoids, in which BAHD-ATs play a key role. *Meliaceae azedarach* 21 acyltransferase (MaL21AT)/*Citrus sinensis* 21 acyltransferase (CsL21AT), *C. sinensis* 1 acyltransferase (CsL1AT), *C. sinensis* 7 acyltransferase (CsL7AT), and *M. azedarach* 7 acyltransferase (MsL7AT) can catalyze the acylation of C-21, C-1, and C-7 triterpenes ([De La Pena et al., 2023](#)) ([Figure 4](#)). Other TEACTs in clade IIIa include SOAP10 (an acyltransferase in spinach) and *Q. saponaria* acyltransferase 1 (QsACT1), which can catalyze the acylation of triterpene saponin glycoside donors ([Jozwiak et al., 2020](#); [Reed et al., 2023](#)) ([Figure 4B](#) and [4C](#)). SOAP10 can acylate Yossoside IV to Yossoside V in spinach ([Jozwiak et al., 2020](#)). QS-7 (QS saponin 7, a soap-like compound in *Q. saponaria*) is a saponin with excellent therapeutic properties and low toxicity that is an important vaccine adjuvant. In the biosynthetic pathway of QS7, acylation (via QsACT1) occurs simultaneously with a two-step glycosylation (via QsUGT73B44 and QsUGT91AP1), and transient expression of QsACT1, QsUGT73B44, or QsUGT91AP1 individually in *Nicotiana benthamiana* did not result in production of any new products ([Reed et al., 2023](#)). This result provides guidance for future studies on TEACTs, suggesting that acylation reactions may need to be combined with other types of reactions to obtain the target product.

Besides those in clade IIIa, three other BAHD-ATs were placed into clade I. Interestingly, all of them acylate the glycoside donors of saponins ([Wang et al., 2023](#); [Yuan et al., 2023](#)). Type-A soyasaponins, which accumulate in soybean (*Glycine max*) seeds, are fully acetylated at the terminal sugar of their C22 sugar chain and are responsible for the bitter taste of soybean-derived foods ([Yuan et al., 2023](#)). Wang et al. identified soyasaponin acyltransferase 1 (GmSSAcT1), a BAHD-type acetyltransferase, that can catalyze three or four consecutive acetylations on type-A soyasaponins *in vitro* and *in planta* ([Yuan et al., 2023](#)) ([Figure 4B](#)). Closely related to GmSSAcT1, *Astragalus membranaceus* acyltransferase 8-17 (AmAT8-17) also fell into

clade Ia and can catalyze astragaloside IV at the C4'-OH position ([Wang et al., 2023](#)). Another TEsACT in *A. membranaceus*, AmAT7-3, can modify astragaloside IV to isoastragaloside II, cyclocephaloside II, and 3-O-3',4'-diacetyl- β -D-xylopyranosyl-6-O- β -D-glucopyranosyl-cycloastragenol, providing a new method for future modification of drug structure ([Wang et al., 2023](#)). Wang et al. also analyzed the crystal structure of AmAT7-3 ([Wang et al., 2023](#)), performed theoretical chemical calculations, and used site-specific mutation to modify AmAT7-3 function.

On the basis of their phylogenetic positions, we found that all the acyltransferases that modify the triterpenoid skeleton were clustered into clade IIIa, and saponin-related acyltransferases were also found in clade I. These two clades will be the focus of future TEsACT research ([Figure 4A](#)).

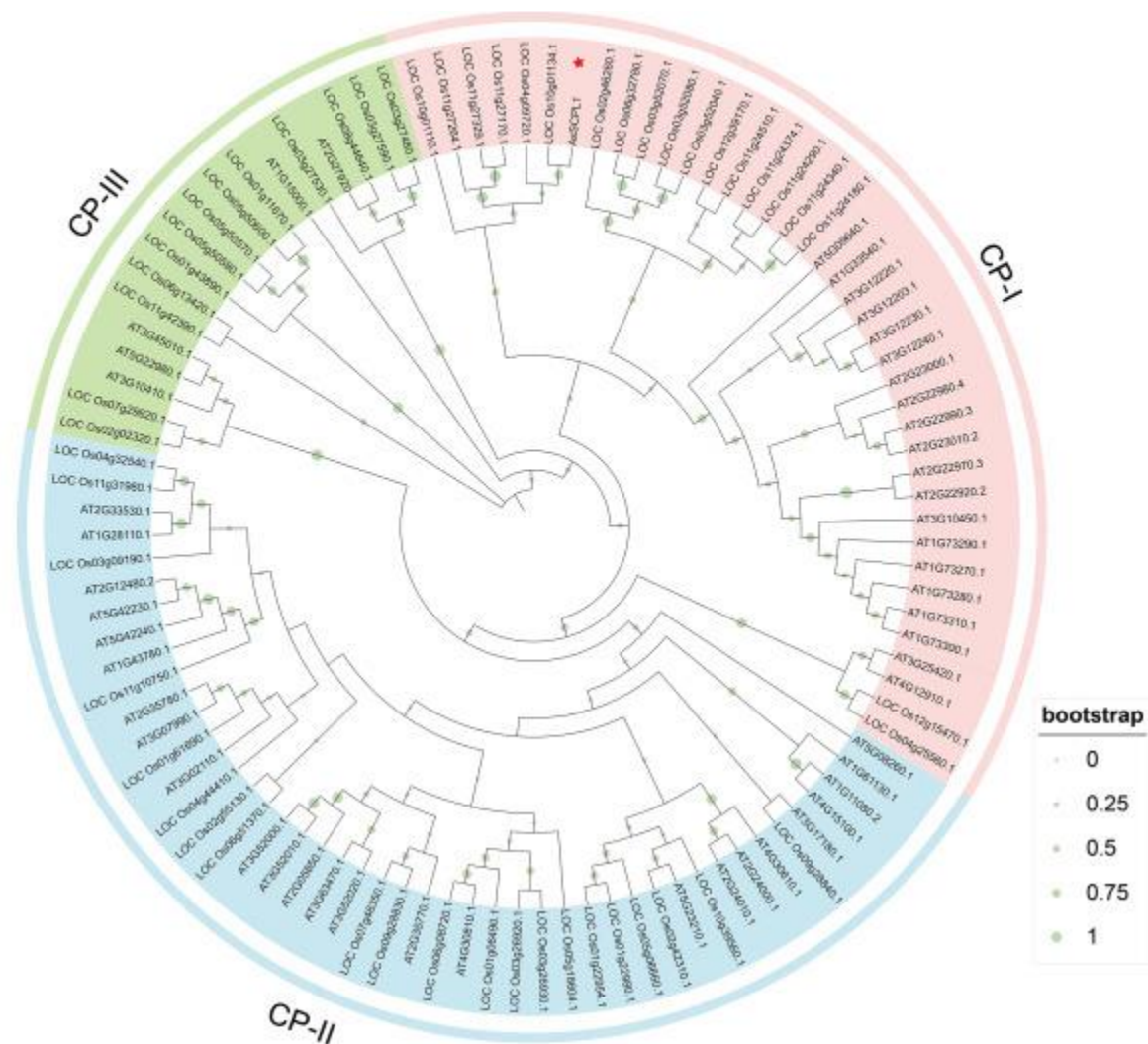
SCPL acyltransferase family

SCPL-ATs are a class of acyltransferases primarily located in the vacuole ([Hause et al., 2002](#); [Bontpart et al., 2015](#)) ([Figure 2](#)). Structurally and functionally, SCPL-ATs closely resemble members of the SCP family, with both belonging to the S10 subfamily of the SC family ([Milkowski and Strack, 2004](#)). SCPL-ATs possess a highly conserved tertiary α/β hydrolase domain ([Milkowski and Strack, 2004](#)). SCPLs and SCPs share a common motif known as the Ser-His-Asp catalytic triplet, consisting of three non-contiguous amino acids. Although these amino acids are arranged differently in the primary structure, they are spatially close to each other in the tertiary structure, relying on folding of the polypeptide chain to form conserved triplets ([Liao and Remington, 1990](#)). This catalytic triplet establishes a hydrogen bond network between the SCPL protein and its substrate ([Milkowski and Strack, 2004](#)). Consequently, SCPL proteins have the ability to cleave carboxy-terminal peptide bonds within their protein or peptide substrates ([Milkowski and Strack, 2004](#)). The significant feature that distinguishes SCPLs from SCPs is that the former have the conserved pentapeptide motif “GDSYS,” whereas SCPs contain “GESYA” instead ([Mugford and Milkowski, 2012](#)) ([Figure 3C](#)).

According to the present study, at least 51 SCPL family members are found in *A. thaliana* ([Fraser et al., 2005](#); [Chen et al., 2020](#)) and 71 in *O. sativa* ([Feng and Xue, 2006](#)); *Camellia sinensis* has 47 members ([Ahmad et al., 2020](#)), and *Triticum aestivum* has 210 ([Xu et al., 2021](#)). A phylogenetic analysis of SCPL-AT family members in rice and *A. thaliana* revealed division of the 121 proteins into three clades. AtSCPLs were predominantly clustered in clades I and II, whereas OsSCPLs were distributed across all three clades ([Feng and Yu, 2009](#)). A subsequent phylogenetic analysis of SCPL family members from poplar, tea, grape, and wheat showed that they also fell within three clades ([Zhu et al., 2018](#); [Ahmad et al., 2020](#); [Wang et al., 2021a](#); [2021b](#); [Xu et al., 2021](#)). We specifically examined the SCPL proteins of *A. thaliana* and rice, focusing on the genes associated with triterpene ester biosynthesis identified to date. However, although acyltransferases of the SCPL family have been reported in multiple species, only one functional TEsACT of the SCPL family, AsSCPL1, has been identified. We observed that AsSCPL1 was classified within the CP-I subfamily ([Figure 5A](#)); it can serve as a reference for the discovery of other

acyltransferases in the SCPL family that potentially participate in formation of triterpene esters.

A



B

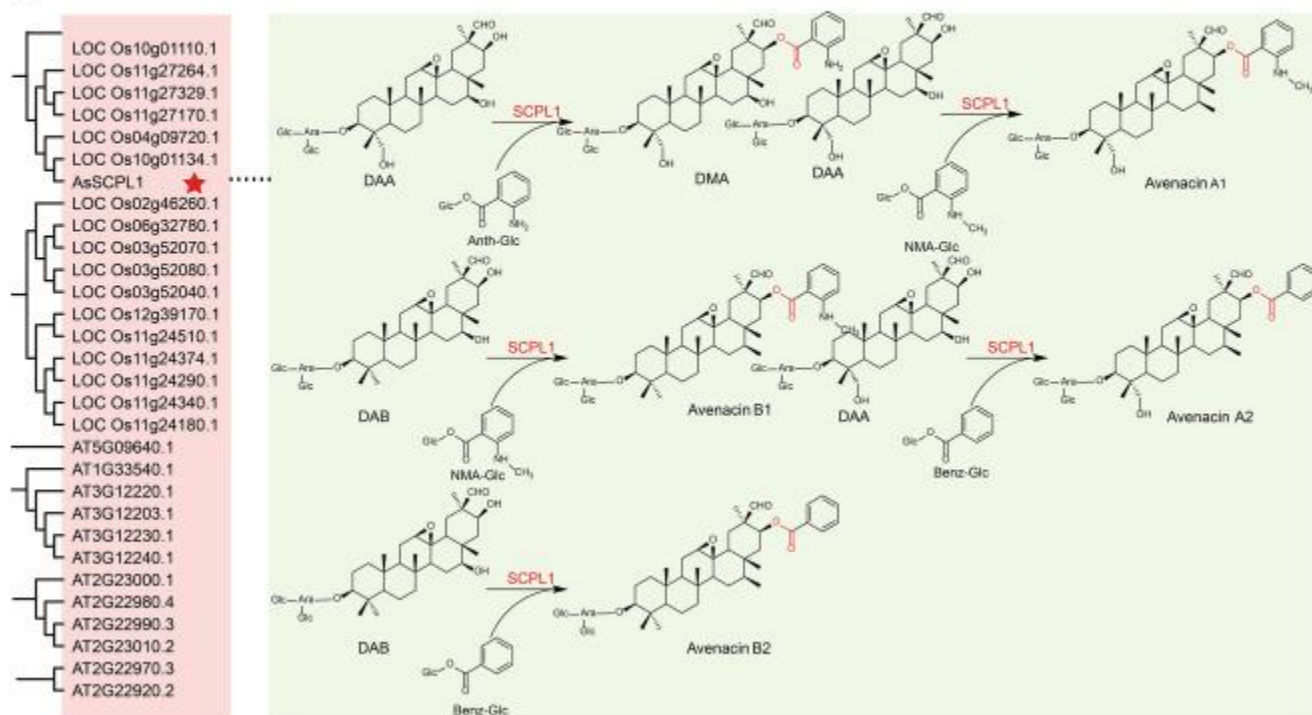


Figure 5 Biosynthetic pathways of triterpene esters involving SCPL acyltransferases.

[Show full caption](#)[Figure viewer](#)

Avenacins, the acylated antibacterial triterpene saponins produced in oat roots, prevent the invasion of pathogenic fungi from the soil ([Mugford et al., 2009](#)). AsSCPL1, an SCPL-AT encoded by *Sad7* in oat, is a crucial enzyme in avenacin biosynthesis ([Mugford et al., 2009](#)) ([Figure 5B](#)). In addition, *Sad9* encodes AsMT1, which catalyzes the production of N-methyl anthranilate (NMA) from anthranilate (Anth) ([Mugford et al., 2013](#)), and *Sad10* encodes AsUGT74H5, which facilitates the formation of N-methyl anthraniloyl-O-glucose (NMA-Glc) and anthranilate-O-glucose (Anth-Glc) derived from NMA and Anth substrates, respectively ([Owatworakit et al., 2013](#)). These processes occur within the cytoplasm. Furthermore, Des-acyl avenacin A (DAA) and Des-acyl avenacin B (DAB) are synthesized within the cytoplasm by SAD1, SAD2, and other enzymes ([Mylona et al., 2008](#); [Mugford et al., 2013](#); [Owatworakit et al., 2013](#)). These molecules are then transported to the vacuole, where AsSCPL1 catalyzes the transfer of an acyl donor and acceptor to produce avenacins ([Mugford et al., 2013](#); [Owatworakit et al., 2013](#)) ([Figures 2](#) and [5B](#)).

Biological functions

Defense

Synthesis of plant secondary metabolites is the result of a lengthy evolutionary process of adaptation to changing environmental conditions. These metabolites afford plants several advantages in responding to adverse environments, competition, co-evolution with other plants, defense against insect pests and herbivorous animal foraging, and protection against pathogenic microorganisms. Triterpene esters also play a defensive role in plant growth and development. For example, the bark of *Boswellia* releases a specialized oleo-gum resin enriched in boswellic acid (BA) in response to wounds. This resin contains acylated derivatives of BAs that contribute to its defensive properties ([Celedon and Bohlmann, 2019](#); [Kumar et al., 2021](#)). Upon attack or injury, the damage-specific acyltransferase BsAT1 interacts with BAs to produce C3 α -O-acetyl-BAs as a response to external damage ([Ammon, 2016](#); [Kumar et al., 2021](#)). Avenacins are a class of triterpene glycosylated esters that exhibit antifungal effects and provide defense against fungal invasion ([Mugford et al., 2013](#); [Owatworakit et al., 2013](#); Qi et al., 2004).

Cucurbitacins, a class of tetracyclic triterpenoids, possess a bitter taste and exhibit toxicity, enabling plants to resist pest and disease invasion. They serve as defense agents as well as attractants for certain polyphagous and predatory insects. The cucurbitin B (CuB) content in the leaves of various Cucurbitaceae species influences the host selectivity of the insect *Liriomyza sativae*. A higher concentration of CuB results in a decrease in the number of *L. sativae* individuals and reduces the extent of leaf damage ([Zhang et al., 2004](#)). Zou et al. found that CuB and CuE act as antagonists of 20-hydroxyecdysone, causing significant molting defects and mortality in *Bombyx mori* and *Drosophila melanogaster* larvae ([Zou et al., 2018](#)). CuB also impeded growth of *Helicoverpa armigera* larvae ([Zou et al., 2018](#)). Although cucurbitacins are toxic to

most animals, they act as feeding attractants for *Aulacophora* spp. and *Diabrotica* spp. beetles ([Lance, 1992](#); [Brust and Foster, 1995](#)). *Luffa acufangula* is rich in CuB and CuE, which stimulate beetles to feed directly ([Da Costa and Jones, 1971](#)).

Cucurbitacins possess strong cytotoxicity, which raises the question of how plants avoid damaging their own cells while synthesizing these compounds for insect resistance. In the case of cucumber leaves, cucurbitacins are synthesized in the cytoplasm and then transported and stored in the vacuole, an organelle responsible for storing various harmful substances within cells. This process may serve as a mechanism by which plants protect themselves ([Zhong et al., 2022](#)). By compartmentalizing cucurbitacins in the vacuole, the plant can effectively isolate and sequester these toxic compounds, preventing them from harming essential cellular components. This detoxification mechanism likely enables plants to balance the role of cucurbitacins as defense agents against pests and diseases without compromising their own cellular integrity.

In addition to serving as defensive compounds when plants are injured, triterpene esters also play an important role as a barrier during plant growth and development. Almost all terrestrial plants have a cuticle, which consists of the cuticle layer, the cuticle proper and the epicuticular wax; the inner cuticle layer contains cutin, a polyester layer of hydroxyl fatty acids crosslinked by ester bonds, and the outer layer of wax consisting of long-chain aliphatic compounds and a diverse array of cyclic compounds ([Müller and Riederer, 2005](#)). The cuticle serves as a protective layer and prevents non-stomatal water loss from plant organs, as well as loss of organic and inorganic substances ([Szakiel et al., 2012](#)). Triterpene esters with non-polar donors may be present in abundance in the exfoliating wax layer and stem skin of some plants ([Müller and Riederer, 2005](#)). Recently, the leaf wax of sorghum was found to be enriched in triterpenes, including pentacyclic triterpene esters, which accumulate spatially under high-temperature conditions to reinforce the cuticle and prevent water loss ([Heupel, 1985](#); [Busta et al., 2021](#)). In addition to the waxy cuticle that covers leaves, fruit surfaces are also protected by a waxy coating. For example, the apple peel contains abundant sterol esters and trichomes that contribute to proper development of the fruit (Belding et al., 2000; [Buschhaus and Jetter, 2011](#); [Jetter and Schäffer, 2001](#); [Poirier et al., 2018](#); [Szakiel et al., 2012](#)). Fatty acid triterpene esters are found in the cuticle, suggesting their potential functions as insect repellents or constituents of the cuticle layer, which helps prevent excessive water loss and loss of organic and inorganic substances. The pollen coat serves a crucial role in protecting the released pollen grain from desiccation, damage, and pathogen attack, ensuring successful pollination. Triterpene esters are present in the pollen coat as well ([Breygina et al., 2021](#); [Chichiriccò et al., 2019](#)), where they play a vital role in preventing dehydration of the pollen grain ([Xue et al., 2018](#)). Consequently, triterpene esters could potentially serve as a novel form of biopesticide for plant protection, reducing reliance on synthetic pesticides and mitigating chemical pollution.

Regulation of rhizosphere microorganisms

In recent years, researchers have made significant findings regarding the crucial role of secondary metabolites produced by plant roots in selectively shaping the rhizosphere

microbiome ([Ling et al., 2022](#)). Among these secondary metabolites, triterpene esters have emerged as a noteworthy class of compounds known for regulating the assembly of the rhizosphere microbiome.

A. thaliana is known to accumulate two tricyclic triterpene esters that are released into rhizosphere soil. Disruption of the arabidin and thalian biosynthetic pathways leads to a change in the composition and diversity of root microorganisms, suggesting that these compounds help to govern root microbiome assembly. *In vitro* experiments have also demonstrated that triterpene esters selectively regulate the growth of root microorganisms ([Huang et al., 2019](#)).

CuB and CuE secreted by melon roots recruit specific rhizosphere flora and enhance plant disease resistance. Specifically, CuB has been shown to selectively enrich two bacterial genera, *Enterobacter* and *Bacillus*, thus modulating the rhizosphere microbiome. This modulation, in turn, leads to robust resistance against the soil-borne fungal wilt pathogen *Fusarium oxysporum* ([Zhong et al., 2022](#)). Together, these studies suggest the role of triterpene esters in shaping the rhizosphere microbiome ([Figure 6](#)).

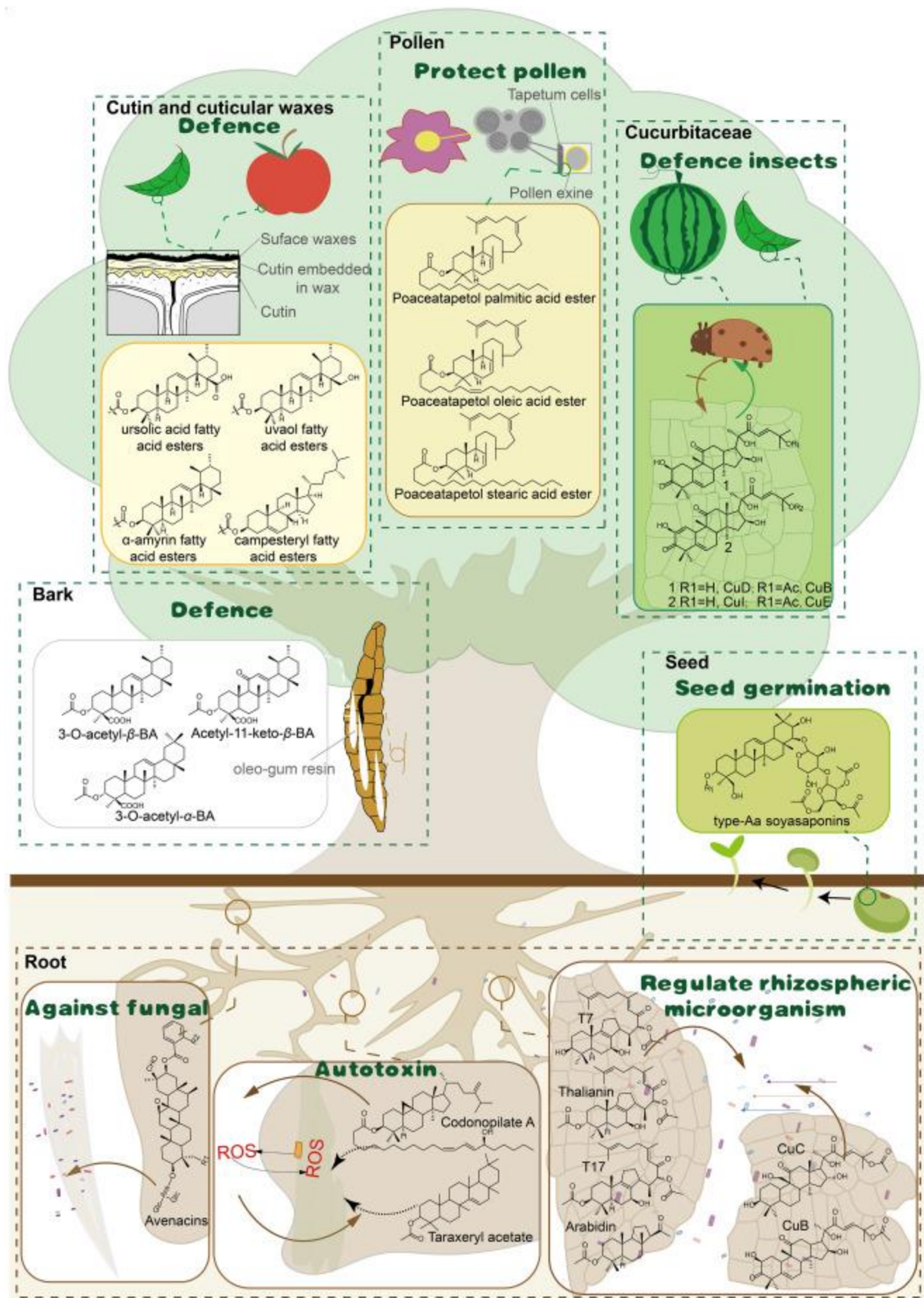


Figure 6 Potential functions of triterpene esters in plant growth, development, and environmental interactions.

[Show full caption](#)[Figure viewer](#)

Autotoxicity in plants

Although secondary metabolites offer various benefits to plants, it is important to note that they can also have toxic effects on plants. For example, production of codonopilate A, a triterpene ester secreted in the roots of *Codonopsis pilosula*, leads to accumulation of reactive oxygen species in the root tips and results in autotoxicity ([Wakana et al., 2011](#)). Another compound, taraxeryl acetate, also exhibits autotoxicity in the roots of *C. pilosula* through a similar mechanism, although its autotoxicity is weaker than that of codonopilate A ([Xie et al., 2017](#)) ([Figure 6](#)).

Triterpene esters have important biological functions in plant defense against pests and diseases, regulation of plant growth and development, and autotoxicity. These roles establish the basis for the future use of triterpene esters as significant biopesticides. Furthermore, heterologous reconstruction of the triterpene ester biosynthetic pathway in appropriate plants offers the potential to enhance crop disease resistance, paving the way for future agricultural productivity and commercial applications.

Regulation of seed germination

Saponins have well-known functions in protecting plants against biotic and abiotic stresses ([Szakiel et al., 2011](#)). In soybean, most saponins accumulate to high levels in seeds and hypocotyls. Type-A soyasaponins are triterpene esters in which the sugar donors are acylated. However, this acylation causes a bitter taste in soy-derived foods, and deacetylated soybean saponins do not result in such bitterness ([Chitisankul et al., 2021](#)). Recently, Yuan et al. identified the acyltransferase GmSSAcT1 in soybean, which is responsible for acetylating the sugar donors of type-A soyasaponins. Interestingly, soybean seeds fail to germinate when this acyltransferase gene is knocked out, suggesting a critical role for type-A soyasaponins in the germination process of soybean seeds ([Yuan et al., 2023](#)). This finding further highlights the significance of terpenoid acylation in plant growth and development.

Concluding remarks and perspectives

In recent years, significant attention has been paid to plant secondary metabolites and their biosynthesis. With the rapid development of life science and sequencing technologies, gene-editing techniques, DNA synthesis technology, etc., more natural products have been discovered and their physiological activities and biosynthetic mechanisms characterized. Compared with other triterpenoids, triterpene esters are less well studied, despite their great potential value for human health and agriculture.

Triterpene esters have multiple roles in biotic and abiotic stress tolerance. They have functions in disease and pest resistance ([Da Costa and Jones, 1971](#); [Dinan et al.,](#)

[1997](#); [Ma, 2017](#); [Metcalf et al., 1980](#); [Zou et al., 2018](#)) and also play important roles in formation of the waxy cuticle ([Szakiel et al., 2012](#); [Busta et al., 2021](#); [Poirier et al., 2018](#)). Thus, synthetic biology could be used to breed new plant varieties that can produce disease-resistant and pest-resistant triterpenes in specific tissues, while removing adverse-flavored compounds from fruits or seeds. Attention has also been paid to the important effects of plant secondary metabolites on rhizosphere microorganisms in recent years ([Hu et al., 2018](#); [Sasse et al., 2018](#); [Stringlis et al., 2018](#); [Huang et al., 2019](#); [Koprivova et al., 2019](#)), and studies have shown that triterpenes can regulate rhizosphere microorganisms ([Huang et al., 2019](#); [Zhong et al., 2022](#)). Because triterpene esters play a crucial role in regulating root microbiota, they may provide a new method for regulating rhizosphere microorganisms in the future ([Bai et al., 2021](#); [Jacoby et al., 2021](#); [Koprivova and Kopriva, 2022](#); [Ling et al., 2022](#); [Zhong et al., 2022](#)). In another aspect, mutation of *OsOSC12* in rice leads to water loss from pollen grains, revealing the important role of triterpene esters in male hygro-sensitive sterility of rice and laying a foundation for related studies in other species ([Xue et al., 2018](#)). Although sorghum and maize are closely related and have similar leaf wax components during the early stage of leaf development, triterpene esters are found only in the leaf wax of sorghum after the transition to adulthood. Triterpene biosynthesis in sorghum leaves is mediated primarily by a single gene, which has lost function in maize. This finding suggests the possibility of reactivating triterpenoid synthesis genes in the corn epidermis and also supports efforts to transfer surface carbon to intracellular storage for bioenergy and bioproduct innovation ([Busta et al., 2021](#)). In addition, vacuoles are known to store large amounts of plant defense compounds, and the synthesis of avenacins in vacuoles provides new insights for exploring biologically functional secondary metabolites in the future. The transporters responsible for movement of avenacin precursors are also of great interest and worthy of further investigation. Currently, triterpenoid saponins are thought to enter the vacuoles via vesicular transport from the endoplasmic reticulum or through transporters on the tonoplast. However, the mechanism for transport of NMA-Glc into the vacuole remains unknown ([Mugford et al., 2013](#)).

Nonetheless, natural triterpene esters also have a number of drawbacks, such as low contents and a lack of plant resources. The biological functions of most triterpene esters have not been clarified, and their biosynthetic pathways have not been deciphered. Further analysis of the biosynthetic pathways of triterpene esters and exploration of their biological functions will promote further utilization of these compounds. Moreover, the rational use of triterpene ester biosynthetic pathways to achieve heterologous synthesis has potential commercial value, and synthesis of triterpene esters as protein inhibitors also provides a new idea for their further study ([Chen et al., 2017](#)). In the future, triterpene esters will play significant roles in pharmaceuticals, biopesticides, and other commercial applications.

At present, there has been relatively little research on TEsACTs, and the development of related research will promote further analysis of triterpene ester biosynthetic pathways. Future analysis of triterpene ester biosynthesis and further exploration of their biological and pharmacological activities will make important contributions to biopesticide development, breeding, energy conservation, and medical resources.

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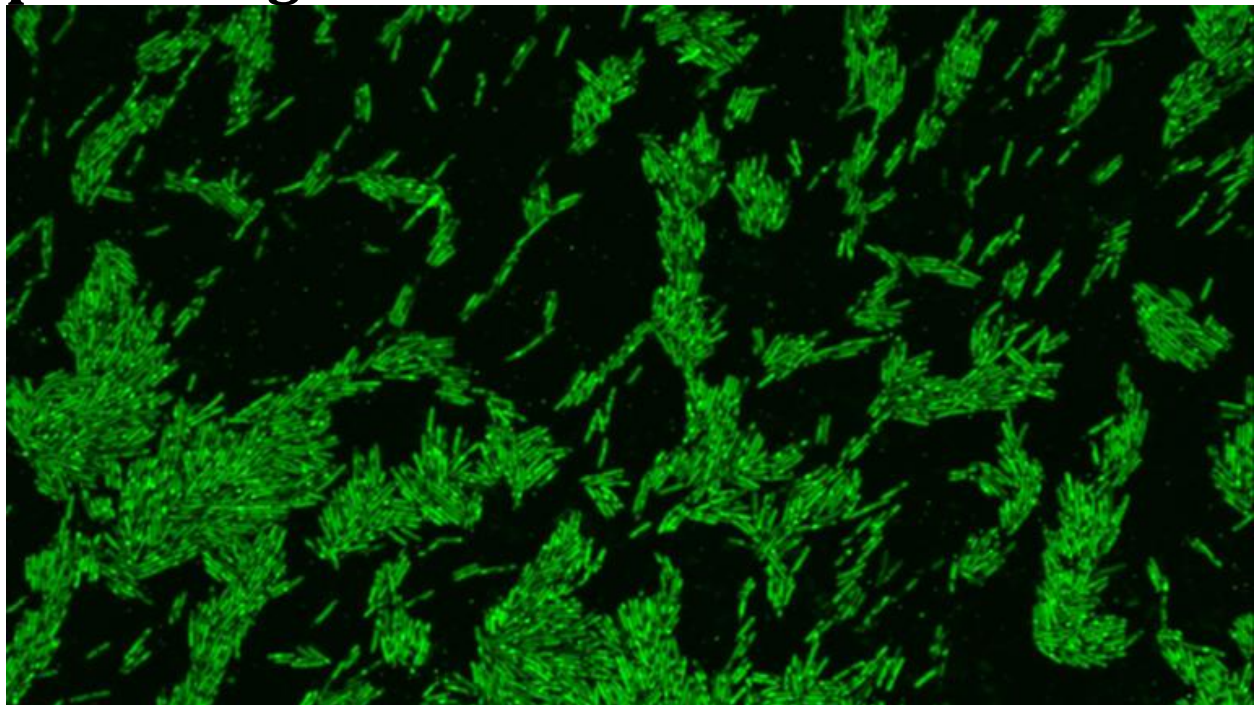
Author contributions

J.L., Writing - Original Draft, investigation; X.Y. and C.K., Investigation; R.T., Review; X.H., Review; Z.X., Conceptualization, Writing - Review & Editing, Supervision, Project administration.

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The authors declare no competing interests.

Cholesterol-gobbling gut bacteria could protect against heart disease



These rod-shaped bacteria were confirmed to gobble up and break down cholesterol (here shown in green).© Ahmed Mohamed

Bacteria present in some people's guts may help break down cholesterol, making them less susceptible to [heart disease](#), a new study suggests.

The link between a high diversity of gut microbes and a lower chance of cardiovascular disease is well established. [Previous research](#) has shown that people with heart-related diseases, such as [atherosclerosis](#), carry different kinds of microbes in their guts than people without the conditions. Researchers thought this may be related to a microbe-made enzyme called [lsmA](#) that breaks down cholesterol.

People whose gut bacteria made lsmA had less cholesterol in their blood than those whose gut bacteria [didn't make this enzyme](#). However, the specific species of bacteria that make cholesterol-gobbling enzymes were not known.

Now, a study published April 2 in the journal [Cell](#) has shown that bacteria in the genus *Oscillibacter* break down cholesterol and that people who carry more of those bacteria have lower cholesterol levels than people with fewer of those microbes.

Related: [9 heart disease risk factors, according to experts](#)

Uncovering the bacteria that metabolize cholesterol is "very interesting and exciting," [Daoming Wang](#), a researcher at the University of Groningen in the Netherlands, told Live Science in an email. Wang, a bioinformatician who studies the human gut microbiome, wasn't involved in the new study.

To understand how gut bacteria influence [heart health](#), the researchers examined stool and blood samples collected from more than 1,400 people in the [Framingham Heart Study](#), a decades-long study of heart disease risk factors.

The team used different techniques to profile the microbial DNA in the stool samples. They also analyzed metabolites — the byproducts left over when chemicals like cholesterol break down. For each participant, the team then correlated these findings with known markers of heart health, like blood-borne cholesterol and [triglyceride](#) levels.

People with lower triglyceride and cholesterol levels had an abundance of *Oscillibacter* bacteria in their poop, the team found. They checked whether this

correlation showed up in another, independent set of people and found that it did.

To confirm that *Oscillibacter* indeed metabolized cholesterol, the researchers grew the bacteria in the lab and exposed them to cholesterol marked with fluorescent tags. Using microscopy, the team looked for fluorescence within the bacterial cells, to see if the microbes sucked up the cholesterol — and they did.

The researchers then tracked the fate of the gobbled cholesterol and found that different bacterial species broke it down into various steroids. These steroids could be absorbed by other gut bacteria, resulting in decreased cholesterol levels overall.

To figure out which genes and proteins might help *Oscillibacter* break down cholesterol, the team used a [machine-learning](#) algorithm. The algorithm analyzes features of genes to predict how proteins encoded by these genes will look. This analysis revealed that genes that encoded proteins similar to lsmA were likely responsible for metabolizing cholesterol.

These results take us closer to understanding the "dark matter" of the microbiome, meaning the large number of gut microbial genes whose functions aren't yet known, Wang said. "This dark matter hinders us from seeing the whole picture of gut bacterial functionality."

In theory, tweaking the gut microbiome to boost cholesterol breakdown could be a strategy to reduce people's cholesterol levels, the study authors proposed. But before that can be done, we need follow-up investigations to better understand exactly how these bacteria break down cholesterol and how this can be used as a therapy, Wang said. We need detailed studies in lab animals, followed by clinical trials in humans, he said.

Nonetheless, Wang added, "it's very exciting to further explore the potential of manipulating *Oscillibacter* species as therapeutic interventions for managing cholesterol levels."

Revolutionary new smart masks can diagnose health conditions



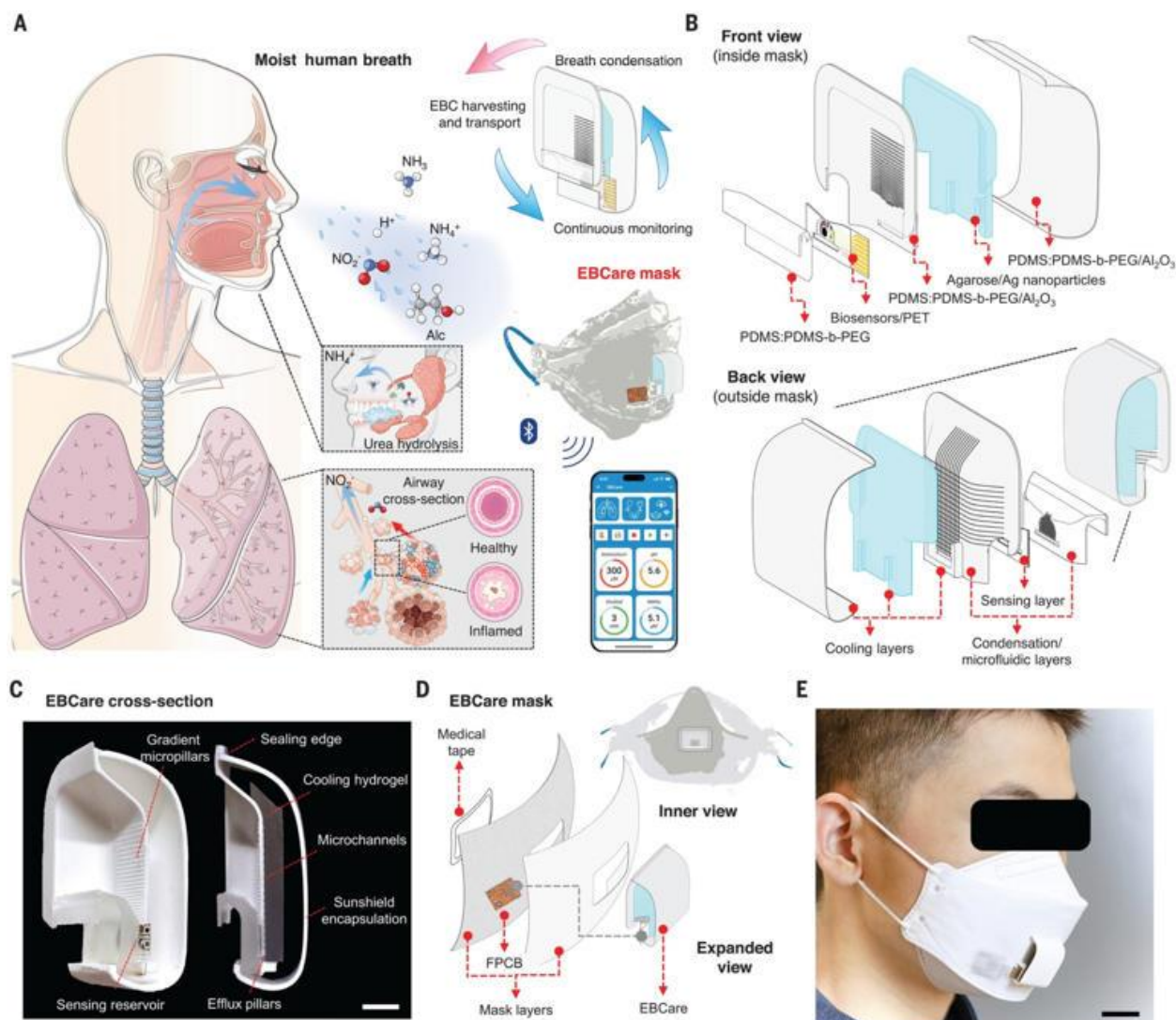
EBCare, a smart mask by Caltech, analyzes breath to monitor respiratory and metabolic health. Explore its groundbreaking potential in personalized healthcare. (CREDIT: Caltech/Wei Gao and Wenzheng Heng)© The Brighter Side of News

[Wearable devices](#) for health monitoring have evolved significantly in recent years, with innovations ranging from watches and patches to sensors that track heart activity and inflammation. These devices empower individuals to manage their health from the comfort of home.

Among the latest advancements is EBCare, a smart mask designed to monitor respiratory and [metabolic health](#) by analyzing exhaled breath condensate (EBC) in real time. This high-tech mask not only collects breath samples but also analyzes their chemical composition to detect health markers.

Developed by Wei Gao, a professor of medical engineering at [Caltech](#), and his team, EBCare introduces a groundbreaking approach to health monitoring. Unlike existing devices that monitor physical parameters such as breath rate or temperature, EBCare targets the molecular information embedded in breath.

This innovation opens new possibilities for managing conditions like asthma, chronic obstructive pulmonary disease (COPD), and post-COVID-19 respiratory issues.



A smart EBCare (exhaled breath condensate analysis and respiratory evaluation) mask for efficient harvesting and continuous analysis of exhaled breath condensate. (CREDIT: Science)© The Brighter Side of News

"Monitoring a patient's breath is routinely done in clinics for conditions like [asthma](#). However, it requires physical visits and waiting for lab results," Gao explains. "Since COVID-19, mask use has become more common, presenting an

opportunity for remote, personalized health monitoring. EBCare enables real-time feedback on health from anywhere.”

The mask’s design tackles a significant challenge in EBC analysis—cooling and condensing breath into liquid for [chemical analysis](#). Traditionally, this step involves bulky equipment like ice buckets or refrigeration units. EBCare incorporates a self-cooling mechanism using hydrogel evaporative cooling and radiative cooling, making the process portable and efficient.

“This mask marks a paradigm shift in respiratory and metabolic disease management,” notes Wenzheng Heng, a graduate student at Caltech and the study’s lead author. “Breath condensate contains a wealth of data, including metabolic substances, inflammatory markers, and [pathogens](#), which can now be analyzed seamlessly in daily life.”

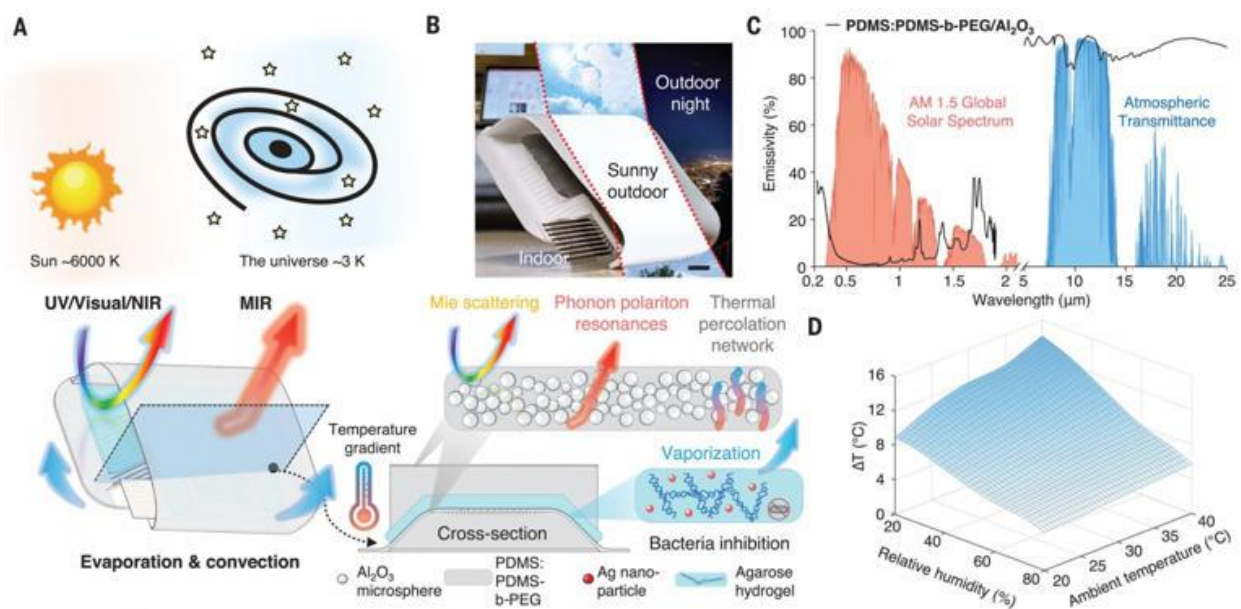
Once the breath is converted to liquid, the mask employs bioinspired microfluidics to transport the sample to sensors for immediate analysis.

Drawing inspiration from how plants transport water, this system ensures rapid and efficient delivery of samples to electrochemical biosensors. The results are then transmitted wirelessly to a [smartphone](#), tablet, or computer. Notably, the material costs for each mask are estimated at just \$1, making the technology accessible.

In human trials, EBCare demonstrated its potential across various applications. The team focused on patients with asthma and COPD, monitoring nitrite levels in breath as an [inflammation](#) biomarker. The mask reliably detected these levels, highlighting its precision in tracking airway inflammation.

The mask’s versatility extends beyond [respiratory health](#). It has shown promise in detecting blood alcohol levels, suggesting potential applications in on-site alcohol monitoring. Similarly, it could aid in managing kidney disease by evaluating blood urea levels through breath analysis.

Urea, a byproduct of protein metabolism, accumulates in blood as [kidney function](#) declines. The study confirmed that EBCare accurately measures ammonium levels in breath, which correspond to blood urea levels.



Characterization of EBCare's tandem cooling design for breath condensation. (CREDIT: Science)© The Brighter Side of News

"These initial studies provide a proof of concept," Gao states. "Our goal is to expand the technology to include a broader range of health markers, establishing a versatile health-monitoring platform."

The smart mask's comfort has also been tested, with participants, including those with respiratory conditions, reporting positive experiences.

"The platform represents a significant leap in real-time [lung](#) health monitoring," says Harry Rossiter, a co-author and professor at UCLA. "The potential to add biosensors for diverse compounds underscores the game-changing nature of this technology."

EBCare's real-time monitoring capabilities promise to transform health diagnostics. By integrating advanced cooling, microfluidics, and biosensing into a low-cost, wearable device, the mask provides an unprecedented level of convenience and precision.

As researchers work to incorporate additional health markers, EBCare could become an essential tool for managing a wide range of medical conditions, paving the way for a new era in personalized healthcare.

The Hidden Culprit Behind Alzheimer's Revealed: Microglia Under the Microscope

BY ADVANCED SCIENCE RESEARCH CENTER, GC/CUNY DECEMBER 23, 2024 [NO COMMENTS](#) 4 MINS READ



Exciting findings from CUNY researchers reveal a novel target in the fight against Alzheimer's — harmful microglia activated by cellular stress. This could lead to therapies that reverse the damaging effects on the brain, offering new hope for patients. Credit: SciTechDaily.com

Researchers at the CUNY Graduate Center have made a groundbreaking discovery in Alzheimer's disease research, identifying a critical link between cellular stress in the brain and disease progression.

Their study focuses on microglia, the brain's immune cells, which play dual roles in either protecting or harming brain health. By targeting harmful microglia through specific pathways, this research opens new avenues for potentially reversing Alzheimer's symptoms and providing hope for effective treatments.

Key Cellular Mechanism Driving Alzheimer's Disease Identified

Researchers with the Advanced Science Research Center at the CUNY Graduate Center (CUNY ASRC) have unveiled a critical mechanism that links cellular stress in the brain to

the progression of Alzheimer's disease (AD). The study, published in the journal *Neuron*, highlights microglia, the brain's primary immune cells, as central players in both the protective and harmful responses associated with the disease.

The Role of Microglia in Alzheimer's

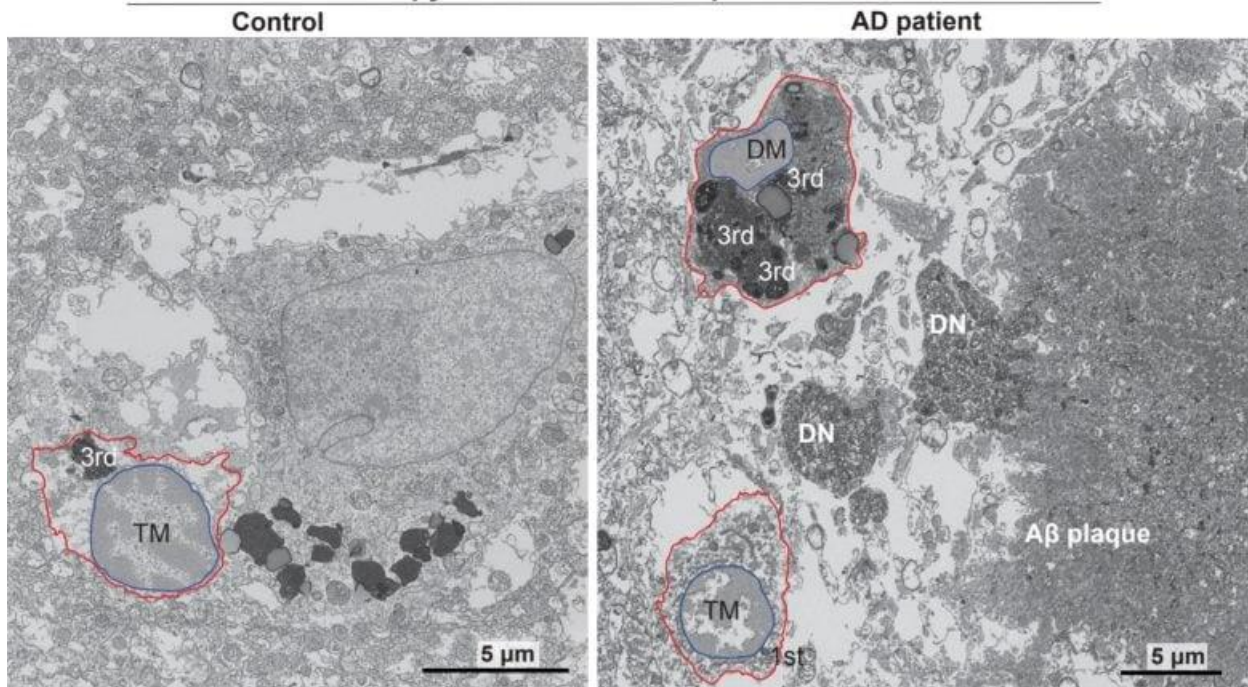
Microglia, often dubbed the brain's first responders, are now recognized as a significant causal cell type in Alzheimer's pathology. However, these cells play a double-edged role: some protect brain health, while others worsen neurodegeneration. Understanding the functional differences between these microglial populations has been a research focus for Pinar Ayata, the study's principal investigator and a professor with the CUNY ASRC Neuroscience Initiative and the CUNY Graduate Center's Biology and Biochemistry programs.

"We set out to answer what are the harmful microglia in Alzheimer's disease and how can we therapeutically target them," said Ayata. "We pinpointed a novel neurodegenerative microglia phenotype in Alzheimer's disease characterized by a stress-related signaling pathway."

Key Findings in Alzheimer's Research

The research team discovered that activation of this stress pathway, known as the integrated stress response (ISR), prompts microglia to produce and release toxic lipids. These lipids damage neurons and oligodendrocyte progenitor cells—two cell types essential for brain function and most impacted in Alzheimer's disease. Blocking this stress response or the lipid synthesis pathway reversed symptoms of Alzheimer's disease in preclinical models.

Electron microscopy of the cortex from postmortem human brains



Electron micrographs show typical microglia in the prefrontal cortex of a 92-year-old healthy female (left) and dark microglia a 91-year-old female patient with Alzheimer's disease (right). Credit: Anna Flury

Key Findings

- **Dark Microglia and Alzheimer's Disease:** Using electron microscopy, the researchers identified an accumulation of "dark microglia," a subset of microglia associated with cellular stress and neurodegeneration, in postmortem brain tissues from Alzheimer's patients. These cells were present at twice the levels seen in healthy-aged individuals.
- **Toxic Lipid Secretion:** The ISR pathway in microglia was shown to drive the synthesis and release of harmful lipids that contribute to synapse loss, a hallmark of Alzheimer's disease.
- **Therapeutic Potential:** In mouse models, inhibiting ISR activation or lipid synthesis prevented synapse loss and accumulation of neurodegenerative tau proteins, offering a promising pathway for therapeutic intervention.

"These findings reveal a critical link between cellular stress and the neurotoxic effects of microglia in Alzheimer's disease," said the study's co-lead author Anna Flury, a member of Ayata's lab and a Ph.D. student with the CUNY Graduate Center's Biology Program. "Targeting this pathway may open up new avenues for treatment by either halting the toxic lipid production or preventing the activation of harmful microglial phenotypes."

Implications for Alzheimer's Treatment

This research underscores the potential of developing drugs that target specific microglial populations or their stress-induced mechanisms. “Such treatments could significantly slow or even reverse the progression of Alzheimer’s disease, offering hope to millions of patients and their families,” explained co-lead author Leen Aljayousi, a member of Ayata’s lab and a Ph.D. student with the CUNY Graduate Center’s Biology Program.

The study represents a major leap forward in understanding the cellular underpinnings of Alzheimer’s and emphasizes the importance of microglial health in maintaining overall brain function.

Reference: “A neurodegenerative cellular stress response linked to dark microglia and toxic lipid secretion” 23 December 2024, *Neuron*.

[Alzheimer's DiseaseBrainCity University of New YorkDementiaNeuroscience](#)

World’s first Fertilo baby born, eggs mature outside body with stem cell tech

A new fertility technology developed by Gameto, using stem cells to help embryos mature outside the body, has led to the world’s first live human birth.

This new technique, called Fertilo, offers a faster, safer, and more accessible alternative to traditional IVF.

The evolution of IVF and its challenges

Since the world’s first “test tube baby” was born in 1978, in vitro fertilization (IVF) has become a common treatment for couples struggling with infertility. While IVF has helped millions of people become parents, it does have its challenges.

The process can be lengthy, expensive, and emotionally taxing. It also carries risks such as ovarian hyperstimulation syndrome, which causes painful swelling in the ovaries.

Typically, [IVF](#) involves collecting mature eggs from a woman’s ovaries, fertilizing them in a laboratory, and then transferring the fertilized embryos into the uterus. The process usually requires hormone injections to stimulate egg production, which can add up to 90 shots per treatment cycle.

While IVF has a relatively high success rate, it's not without its drawbacks, including the physical strain of repeated hormone injections and the emotional toll of the process.

Fertilo: A safer and more efficient alternative

Gameto's Fertilo procedure uses an innovative approach to improve the IVF process. Instead of relying on hormone injections to mature eggs, Fertilo takes ovarian support cells (OSCs) derived from human induced pluripotent stem cells (iPSCs) and uses them to help immature eggs mature in the lab.

This method mimics the natural egg maturation process, making the procedure faster and less invasive.

A 2023 study showed that [Fertilo](#) significantly improved egg maturation and embryo formation. Gameto claims that the Fertilo procedure eliminates 80% of the hormone injections required in traditional [IVF](#) and shortens the treatment cycle to just three days.

Dr. Luis Guzmán, the lead researcher at Pranor Laboratories in Peru, was in charge of the Fertilo procedure that resulted in the first live birth.

He [explained](#), "The ability to mature eggs outside the body with minimal hormonal intervention significantly reduces risks such as ovarian hyperstimulation syndrome and alleviates the side effects caused by high hormone doses."



The first successful birth and global expansion

The first live [human birth](#) using the Fertilo method took place in Lima, Peru, at the Santa Isabel Clinic. The mother of the baby shared her gratitude for the Fertilo approach. "The Fertilo method was the preferred option compared to traditional approaches," she said.

"With fewer injections and a gentler, less invasive egg retrieval process, it gave me hope and reassurance during a deeply personal journey."

Recently, Gameto announced a partnership with IVF Australia, making the Fertilo method available at select IVF clinics across the country. Fertilo is now approved in several countries, including Australia, Japan, Argentina, Paraguay, Mexico, and Peru. The company is also preparing for Phase 3 trials in the United States, which could make the technology available to a wider population.

Gameto's CEO and co-founder, Dr. Dina Radenkovic, celebrated the milestone, saying, "We are delighted to celebrate the world's first live birth conceived using Fertilo."

She highlighted that the technique overcomes key challenges of traditional IVF, such as long treatment cycles, significant side effects, and emotional and physical strain.

Fertilo, she said, offers a faster, safer, and more accessible solution for families, marking a significant milestone in reproductive health. This achievement also demonstrates the first application of induced pluripotent stem cell (iPSC) technology in IVF, showcasing its immense potential.

13 proteins tied to brain aging seem to spike at ages 57, 70 and 78

Scientists have identified 13 proteins that may be linked to [brain](#) aging and could one day be targeted with anti-aging treatments.

However, experts say that more research is needed to know exactly why these proteins are tied to brain aging, and whether they point to specific solutions for diseases like dementia.

In a new study, scientists analyzed [magnetic resonance imaging](#) (MRI) brain scans from nearly 11,000 people ages 45 to 82. They used the scans to estimate each participant's "brain age gap" — essentially how much their "brain age" differs from their chronological age.

The team determined people's brain ages using [artificial intelligence](#) to look at specific physiological features, such as brain volume and surface area. This revealed the extent to which their brains were undergoing accelerated aging.

The team then assessed the concentration of approximately 3,000 proteins in the blood of nearly 5,000 of the participants. The blood [connects the brain to the rest of the body](#), so changes in the concentration of proteins within the blood should reflect [similar alterations in the brain](#).

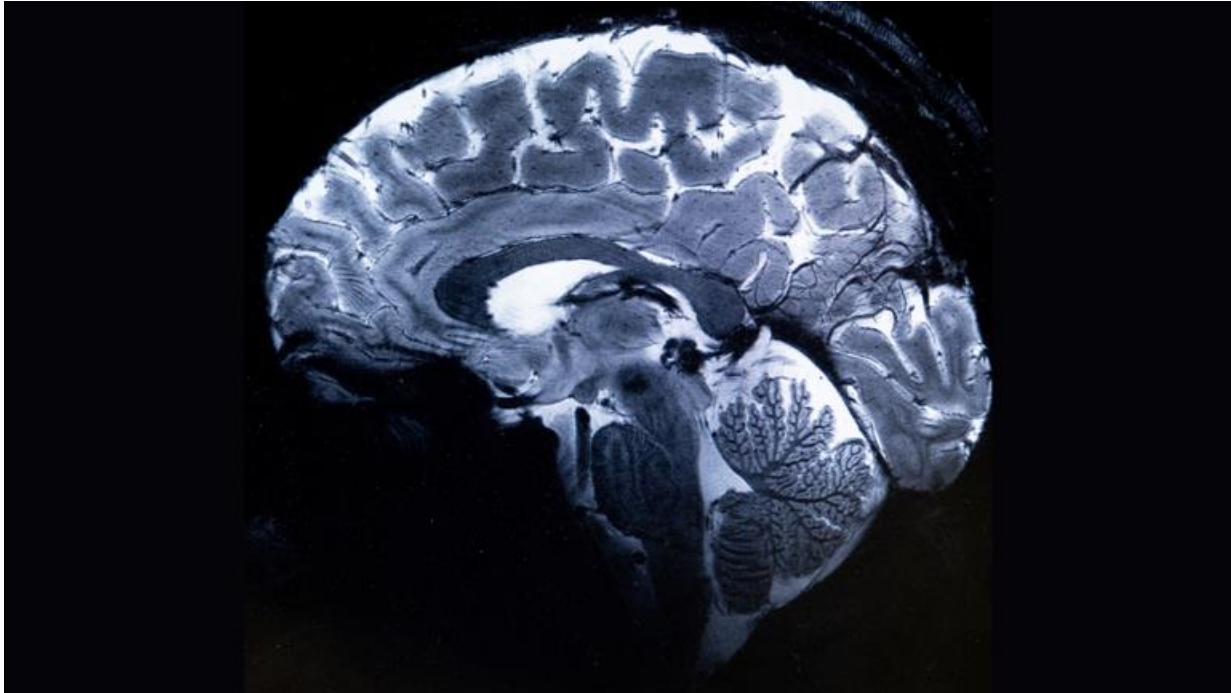
Across the board, the researchers identified 13 proteins whose blood concentrations were significantly associated with biological brain age. Proteins that were linked to factors involved in aging — such as cellular stress and [inflammation](#) — increased in the blood as biological brain age rose. Meanwhile, levels of proteins that help maintain the brain's function, including those involved in cellular regeneration, decreased as people aged.

Of the proteins that the team identified, one known as [brevican](#) showed one of the strongest links with biological brain age — it decreased in concentration as people aged, and those falling numbers showed a strong correlation with conditions such as dementia and [stroke](#).

Brevican is known to help neurons [communicate with one another](#), so this finding supports previous research that suggested the protein could act as a [measurable marker for the development of neurodegenerative diseases](#).

Furthermore, the scientists found that the concentrations of the 13 proteins peaked in the blood at specific chronological ages: 57, 70 and 78. This might reflect "waves" of brain aging that could be used as a reference point to target future anti-aging interventions, the team wrote in a paper published Monday (Dec. 9) in the journal [Nature Aging](#).

However, other experts have voiced concerns about rushing to such conclusions.



The team used MRI scans to predict participants' biological brain ages; they compared these ages to the concentration of thousands of proteins in their blood. (The image above is stock and not from the new study.) (Image credit: ALAIN JOCARD / Contributor via Getty Images)

The "brain waves" findings are not only "unexpected" but "go against pretty much everything that is known about brain aging," during which there is a continuous, gradual decline in brain function and associated changes in cells, [Mark Mattson](#), an adjunct professor of neuroscience at Johns Hopkins School of Medicine who was not involved in the research, told Live Science in an email.

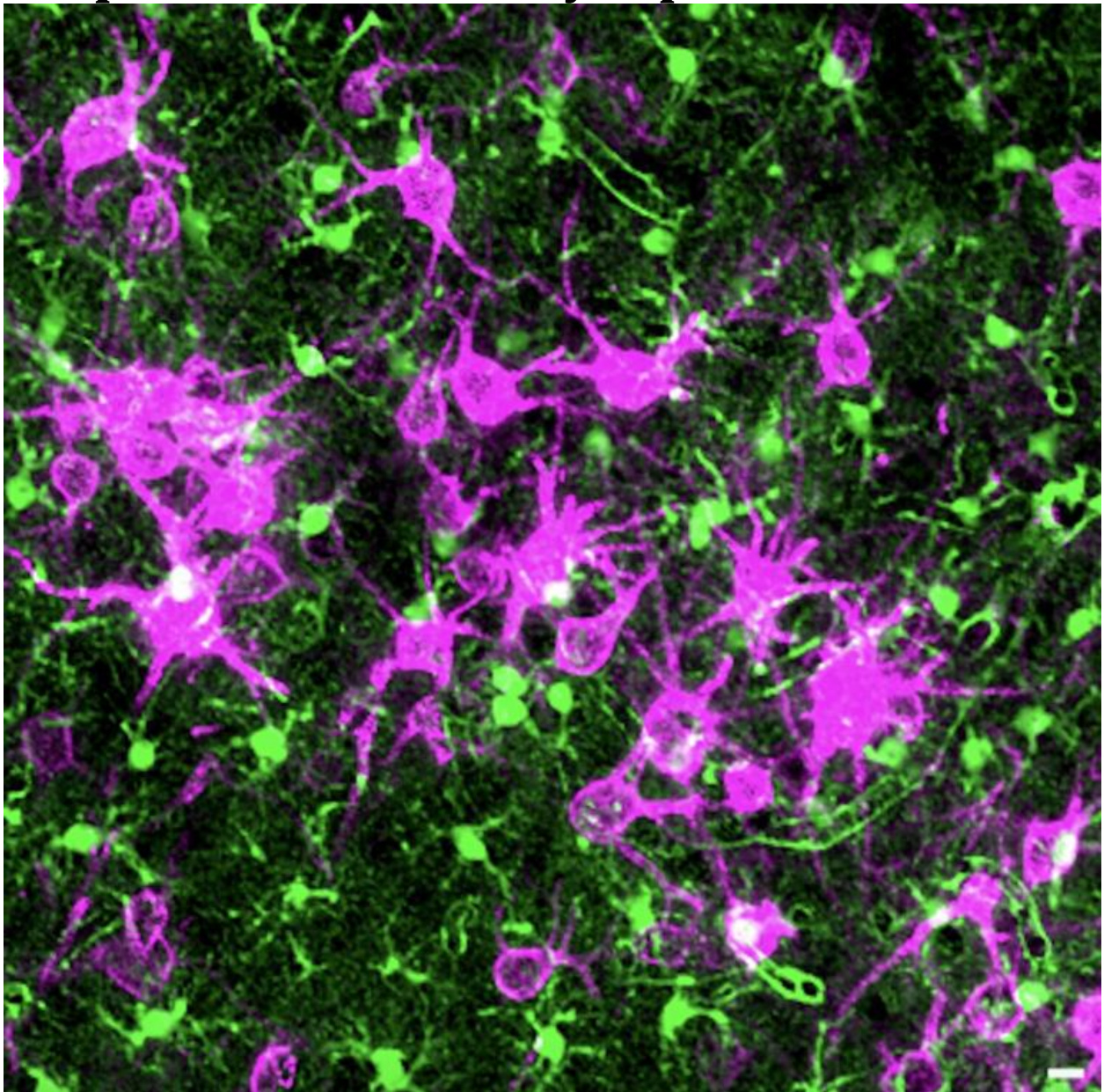
Many questions about the study also remain.

"The correlation between several proteins in blood samples and an MRI image-based indicator of brain aging are interesting," Mattson said. "However, the implications for using measurements of blood levels of those proteins to diagnose brain dysfunction or for developing specific interventions are unclear."

The team acknowledged several limitations of the study in their paper. For instance, they only used data from older people who were mainly of European descent, because their data was drawn from the [U.K. Biobank](#) database. More research is needed to see if the proteins fluctuate in the same ways in individuals of different races and ethnicities, as well as how they may change across the entire human life span.

It is also still unknown where in the brain these 13 proteins come from, Mattson added. "Until levels of those proteins in the brain are established, it will be unclear whether they actually play a role in brain aging," he said.

How astrocytes and perineuronal nets cooperate to sustain synaptic homeostasis



Confocal micrographs showing close association between Perineuronal nets (magenta) and astrocytes (green) in mouse cerebral cortex. Credit: Bhanu Tewari© Provided by Medical Xpress

Synapses are small gaps between neurons through which signals are transmitted. This transmission of signals is what allows neurons to communicate and ultimately produce complex internal processes, such as thoughts and feelings, as well as actions and behaviors.

The loss or deterioration of synapses is typically accompanied by a decline in brain function and cognitive impairments, such as those observed in patients diagnosed with Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. Better understanding the neural processes that ensure the stability and function of synapses could thus inform the development of more effective therapeutic interventions for these disorders.

Researchers at University of Virginia School of Medicine recently carried out a study investigating the combined role of astrocytes, a class of glial cells with many known neuroprotective functions, and perineuronal nets (PNNs), structures that form a coating around some neurons, in regulating synaptic activity over time. Their findings, [published](#) in *Nature Neuroscience*, show that astrocytes and PNNs cooperate to maintain synaptic homeostasis in the mouse brain.

"My laboratory has been studying brain support cells called astrocytes for the past 30 years," Harald Sontheimer, senior author of the paper and Harrison Distinguished Professor at University of Virginia, told MedicalXpress. "Astrocytes serve many functions in the brain but one of the most important ones is the removal of the neurotransmitter glutamate."

Glutamate is the primary neurotransmitter that nerve cells in the brain use to communicate with one another. Past neuroscience studies showed that astrocytes surround synapses, ensuring that glutamate remains at each synapse, without spilling over onto nearby synapses.

"Over 125 years ago, Camillo Golgi discovered a net-like structure of extracellular molecules that covers the surface of some neurons," Sontheimer said. "He called these structures perineuronal nets (PNNs), albeit he and many scientists since have not been able to figure out what these structures do. In the 1970s, it was discovered that they are important in brain development when they ensure that certain synapses between cells of the sensory system stay in place once they are formed."

Previous studies have concluded that PNNs play a key role in stabilizing synapses over time, yet they failed to examine their possible link to astrocyte activity. Given their interest in astrocytes and their role in regulating synapses, Sontheimer and his colleagues set out to investigate whether astrocytes are related to PNNs and specifically if they are also stabilized by these structures.

"PNNs are constantly turned over in the healthy brain," Sontheimer said. "In other words, neurons synthesize them and enzymes produced by neurons and support cells degrade them. PNNs are also degraded by a bacterial enzyme called Chondroitinase ABC. In our first experiments, we took this enzyme and injected it into the brains of mice, and within 40 minutes the PNNs disappeared."

By degrading PNNs using the enzyme Chondroitinase ABC, the researchers were able to observe how damage to these structures impacted synapses and astrocytes. Interestingly, they found that synapses remained in place, while astrocytes extended their processes, covering all the membrane laid bare after the removal of PNNs.

"These experiments also allowed us to study what happens functionally to such synapses after PNNs were removed," Sontheimer explained. "Much to our surprise, we found that glutamate now spilled out of them and activated receptors far away, thereby compromising the signaling between adjacent nerve cells."

Sontheimer and his colleagues observed that after PNNs had degraded, the adult mice started experiencing epileptic seizures. This suggests that the net-like structures act as containers that prevent the dispersion of glutamate from synapses, thus ensuring that astrocytes dispose of the neurotransmitter before it can activate neighboring nerve cells.

"Our findings suggest that the function of synapses can be affected by enzymes that are released in conjunction with tissue inflammation and disease," Sontheimer said. "We show that in a mouse model of Alzheimer's disease, and in epilepsy, enzymes released break down the PNNs and alter neuronal signaling, even causing seizures."

The results gathered by this team of researchers offer new valuable insight into the unique contributions of PNNs and astrocytes to synaptic homeostasis. In addition to inspiring further studies focusing on the neural processes they

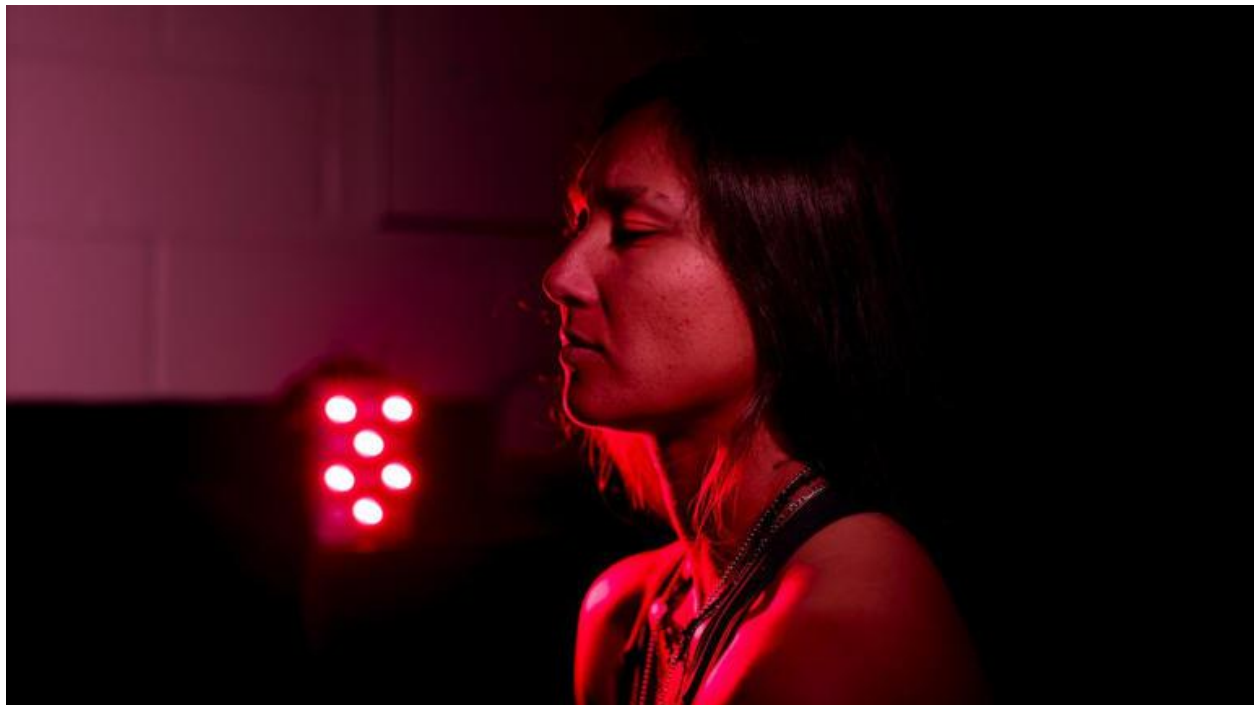
uncovered, they could pave the way for the development of new therapeutic interventions, such as enzyme inhibitors that prevent the breakdown of PNNs in patients diagnosed with Alzheimer's or epilepsy.

"We are now trying to understand how the loss of PNNs comes about at the cellular level, as well as how and when it is best to prevent it," Sontheimer added.

More information: Bhanu P. Tewari et al, Astrocytes require perineuronal nets to maintain synaptic homeostasis in mice, *Nature Neuroscience* (2024). [DOI: 10.1038/s41593-024-01714-3](https://doi.org/10.1038/s41593-024-01714-3)

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Red light is everywhere. We asked doctors what's real



Red light is everywhere. We asked doctors what's real

Red light is one type of light doctors aren't shielding us from.

Why it matters: It's a therapy surging in popularity, especially for the treatment of wrinkles and acne. Red light therapy has also shown promise in a variety of other areas, including [wound healing](#), [pain management](#) and [cancer care](#).

Doctors say it's generally safe to use.

- "It can be used across a variety of skin types, even in the most sensitive individuals," says dermatologist Joshua Zeichner of Mount Sinai Hospital in New York.

Yes, but: Amit Om, a dermatologist in Charlotte, North Carolina, told Axios, he doesn't recommend it to anyone with photosensitizing conditions, like lupus. People with [melasma](#) also might not benefit.

How it works: LED light directed at the skin triggers a process called photobiomodulation, a noninvasive way to stimulate certain cells that rejuvenate skin.

- That's what stimulates collagen to reduce wrinkles and scarring.

Fun fact: NASA was a red light therapy [pioneer](#).

Reality check: While red light can improve the appearance of skin, "it's not powerful enough to replace anything that we currently have," Om told Axios.

- In other words, red light can plump aging skin, but don't expect Botox-like results. In most cases, a doctor recommends red light therapy to complement other treatment options.
- Also, at-home red light devices require use at least several times a week or daily.

Another caveat: Devices you buy for home use won't give you the same results as an in-office laser treatment, Samantha Karlin with the American Academy of Dermatology told Axios.

Before buying a red light device, you can check the U.S. Food and Drug Administration's [database](#) for clearance claims.

- Low-level light devices can only be "cleared," not "approved," according to the way FDA categorizes medical devices.

Zoom out: Red light is one type of several LED therapies. Blue light is another option that is best for acne-prone skin because it can reduce levels of acne-causing bacteria.

- Blue light is also used in neonatal intensive care units to [prevent jaundice](#).
- A note for people with darker skin tones: Blue light may worsen [hyperpigmentation](#).

What's next: Red light therapy will likely shine brighter in 2025.

- Praveen Arany, who has been studying how light can help [heal wounds](#), predicts we'll see more red light uses for post-surgical healing, more athletes using it to improve performance, and more at-home devices in various forms like helmets and panels.
- "It is a fantastic new type of treatment," but do your research before buying in, Arany cautions. "The marketing is all over the place."

"Concierge wellness" becomes a new primary care

A routine checkup in some parts of the country may now come with a side of Botox, a weight-loss drug or a comprehensive blood screening to suss out medical conditions, all usually offered on a cash-only basis.

Why it matters: Primary care and the quest for longevity are converging into a multibillion-dollar business fueled by lifestyle influencers, do-it-yourself wellness enthusiasts and millennials seeking biohacks.

- But experts say there's little evidence many of the services have clinical benefits and warn the demand for care could provide a potential harbor for unqualified or under-qualified clinicians peddling dangerous or untested treatments.

The big picture: The trend is further evidence that patients with resources can pay for better access in a glutted medical system.

- Fitness club giant Equinox, which made splashy headlines earlier this year with its \$40,000 health concierge program, is a key example of concierge wellness, said Kate Festle, director of health care and life sciences for consulting firm West Monroe.
- Equinox recognized that a subset of its high-income clientele would be willing to invest in optimizing their health.
- "It's that whole-body health: physical fitness, but also nutritional supplements, wellness, hormone and blood panel monitoring, all of those things are what the upper crust of Americans are starting to have as a status symbol," Festle said.
- While still largely fragmented, the concierge wellness segment is drawing more private equity interest. "We're working with a couple small regionals right now who are on track to grow 50% year over year," Festle said.

Between the lines: Much of the growth in aesthetic and wellness services is driven by the proliferation of anti-obesity drugs, and by independent physicians looking for options that don't involve battling insurers and wrestling with crushing caseloads, said Sam Patel, founder of Astra Culture, which helps doctors transition to aesthetic and wellness care.

- "I just worked with a bariatric surgeon who's been working for years of doing surgeries ... when he removes a gallbladder, as an example, he only makes \$168," Patel said.
- "He's like, 'Why am I doing this? I'd rather do provide services like medical weight loss, hormone replacement therapy, body contouring. It will still help my patients, and I don't have to worry about ... minuscule reimbursements.'"
- Primary care docs, as well as OB-GYNs and even dentists are looking to diversify their income streams and get more time back, he said. And it's attractive for patients who get access to services from a trusted provider.

Zoom in: Private equity-backed Formula Wellness has grown to 15 locations around the country in upscale neighborhoods and features pay-as-you-go medical aesthetics and longevity services.

- Rather than turning to drugs to treat chronic illness, they search for holistic methods to address the underlying concerns, said CEO Michael Bennett.
- The client base is high-powered executives craving peak performance and wellness faddists who expect easy access to a doctor when they're unwell.
- They don't promote themselves as a primary care but say many of their clients use them in that way because of the array of services and the convenience offered.
- "I want to text my provider through a HIPAA-compliant secure link that goes directly to their phone," Bennett said, describing the patient experience. "Say, 'I need to be on the phone with you in 15 minutes. Can you or one of your colleagues be available?' We can make that happen."

Go deeper: Such customized services are attracting backing from bold-faced names.

- Function Health, co-founded by prominent doctor and author Mark Hyman, [raised \\$53 million](#) earlier this year from celebrities such as Kevin Hart and Matt Damon and boasts a 300,000-patient waitlist. It's also partnered with Equinox.
- Its providers do not diagnose but say their goal is to "empower" members to "live 100 healthy years" through the information from their annual lab tests and comprehensive personalized results delivered online. It costs \$499 a year.
- "People are just dying to get their own information and not have to go through their doctor and insurance and get caught up in the health care system that's mostly focused on diagnosing and treating disease," Hyman said.

The intrigue: The timing may be right as more people gravitate toward [DIY medicine](#).

- "People are exploring the realms of peptides and supplements, plasmapheresis and all kinds of stuff at the margins because people are looking for not just 'How do I treat disease,' but 'How do I actually become healthy?'" Hyman said.

Reality check: When conventional doctors prescribe obesity drugs or hormone therapy, they're generally following evidence-based guidelines for treating an identifiable disease, as opposed to providing therapies without a clear illness.

- Experts say while many of the recommendations — healthy diets, exercise, adequate sleep — are generally beneficial, there may be little direct evidence of improved outcomes.
- It may also come with risks, Alexa Mises Malchuk, a Durham, N.C.-based family medicine doctor, told Axios. Some providers may automatically look to hormones or nutrient deficiencies as the drivers of symptoms and overlook more obvious diagnoses.
- The "more and more you deviate from [evidence-based guidance], it just becomes riskier because the risk-benefit analysis is now not so clear," she said.
- That means it's up to patients to exercise due diligence, including asking about a provider's level of experience or even reading online reviews.
- "Just because someone has a certain degree doesn't mean that they're competent at a skill, especially when it comes to aesthetic procedures," Mises Malchuk said.

What to watch: The trend could widen health disparities as doctors flee to cash-pay businesses and cherry-pick patients.

- There's also the perennial concern of whether consumer-driven care is directing scarce medical resources to the "worried well."
- "It is going to impact the health care system," Patel said. "I can't really blame the health care providers."

Editor's note: This story has been corrected to reflect that West Monroe is a consulting firm (not an investment firm).

• The Virus That Could've Ended Us is Now Saving Lives, Thanks to AI

- **Viruses** are nature's master engineers, capable of **encapsulating** and delivering **genetic material** with remarkable precision. These natural systems have long been a source of inspiration for scientists seeking to revolutionize gene therapy. Yet, replicating the intricate functionality of viral protein shells—known as **capsids**—has proven challenging. Artificial **nanocages**, modeled after viruses, have fallen short due to limited capacity and lack of complexity.
- Now, a collaboration between **Professor Sangmin Lee** from **POSTECH** and **2024 Nobel Chemistry Laureate Professor David Baker** from the **University of Washington** has transformed this field. Their groundbreaking research, published in *Nature* on December 18, uses **artificial intelligence (AI)** to mimic and enhance viral structures, offering a new frontier in therapeutic delivery.

• The Power of AI in Redefining Protein Design

- Traditional gene therapy vectors, such as **adeno-associated viruses (AAVs)**, are limited by their small genetic payload capacity. To overcome this, the research team turned to **AI-driven computational design**, reimaging nanocages in tetrahedral, octahedral, and icosahedral shapes.
- The standout is the **icosahedral nanocage**, with a diameter of 75 nanometers and the capacity to hold three times more genetic material than AAVs. By incorporating subtle asymmetries found in natural viruses, these AI-designed nanostructures achieve levels of functionality previously unattainable with traditional methods.

• Key Features of Ai-Designed Nanocages:

- • **Geometries:** Tetrahedral, octahedral, and icosahedral shapes.
- • **Size:** Up to 75 nanometers in diameter.
- • **Capacity:** Holds three times more genetic material than traditional AAVs.
- • **Complexity:** Includes six distinct protein-protein interfaces.
- • **Precision:** Symmetry confirmed via electron microscopy.

• **Precision Meets Performance: Testing the Nanocages**

- The AI-designed nanocages aren't just efficient—they're transformative. Electron microscopy validated the accuracy of these designs, and functional experiments proved their ability to deliver [therapeutic genes directly to target cells](#). This combination of precision and performance redefines what's possible in medical biotechnology.

• **Potential Applications:**

- • Gene therapy for genetic disorders.
- • Development of next-generation vaccines.
- • Precision-targeted drug delivery.
- These multifunctional nanocages challenge the status quo, offering a platform for breakthroughs that go beyond current limitations.

• **Collaboration at the Forefront of Innovation**

- This achievement highlights the value of interdisciplinary collaboration. **Professor Lee**, who spent nearly three years working in **Professor Baker's** lab before joining POSTECH, brought a unique perspective to this partnership. Supported by funding from the **Ministry of Science and ICT of Korea** and the **Howard Hughes Medical Institute (HHMI)**, the research exemplifies how global collaboration can drive scientific breakthroughs.

• **Contributions to the Research:**

• **Reimagining the Future of Medicine**

- "[Advancements in AI have opened the door to a new era](#) where we can design and assemble artificial proteins to meet humanity's needs," said **Professor Lee**. These AI-designed nanocages represent a leap beyond mimicking nature—they redefine it. Their potential spans far beyond gene therapy, promising innovations in **next-generation vaccines**, targeted drug delivery, and beyond.
- [This research is more than a milestone](#); it's a bold statement that challenges conventional thinking. By leveraging the power of AI, scientists are not just learning from nature—they're improving upon it, ushering in a

new era of precision medicine. The question now is not whether AI can reshape biotechnology, but how far it can take us.

Harvard nutritionist and psychiatrist: I've studied brain foods for 20+ years—here are 5 of my favorite breakfasts

Breakfast provides the brain with its first source of energy every morning. Fueling the brain is key for focus, clarity, and optimal functioning throughout the day. Even if you happen to follow [intermittent fasting](#), it's important to [pick something nourishing](#) at the start of your eating window.

Today, most people in the U.S. associate breakfast with [colorful cereals](#), overloaded bagels and breakfast sandwiches, baked goods that border on dessert, and coffee drinks that are barely distinguishable from milkshakes.

These popular items are frequently loaded with sugars and simple carbohydrates that cause an initial spike in blood sugar followed by a crash. They also contribute to the neuroinflammation (inflammation around the brain) that's associated with brain fog and poor concentration.

Fortunately, as the Director of Nutritional, Lifestyle and Metabolic Psychiatry at Massachusetts General Hospital, my research and clinical work has helped me learn that there are plenty of other options for your [morning routine](#) that can help enhance your mental fitness.

And as a chef, I know those healthier choices can be delicious and easy to prepare.

I always suggest [a glass of water when you wake up](#) to combat dehydration and anxiety. After that, here are five of my favorite breakfast brain foods. They're rich in key nutrients and functional compounds that promote better energy, clarity, and mental health.

1. Chia pudding

One of my go-to breakfasts is [homemade chia seed pudding](#). It contains tons of [fiber](#), which nourishes healthy bacteria in the gut and results in a [less inflamed microbiome](#), optimized [gut-brain communication](#), and the production of mood-supporting [neurotransmitters](#).

It contains [omega-3 fatty acids](#) that have strong [anti-inflammatory effects on the brain](#), which helps boost mood, ward off stress, and maintain healthy cognition and memory.

The pudding is easy to make the night before: Combine three tablespoons of chia seeds with a cup of coconut milk (or your unsweetened milk of choice), [a drop of honey](#), and a pinch each of cinnamon and sea salt. Top it in the morning with nuts, berries, and/or coconut flakes.

2. Scramble, omelet, or baked frittata

If eggs are part of your diet, consider starting the day with a scramble, omelet, or baked frittata.

Eggs are loaded with healthy fats, proteins, and vitamins that are essential for a healthy brain. The yolks, for example, are rich in [vitamin D](#) and serotonin, which help you reach the optimal balance of neurotransmitters to regulate your mood.

I always encourage people to pick eggs from pasture-raised, cage-free chickens when possible for the highest quality and purest nutrients.

Your breakfast doesn't have to be fancy. In my first book, "[This Is Your Brain On Food](#)," I share a recipe for my "On-the-Go Scrambled Egg in a Mug" that you can prepare with eggs, a splash of milk, and salt and pepper. It takes just a couple of minutes in the microwave and you can toss in some spinach or kale if you'd like.

3. Tofu scramble

Tofu is an excellent, versatile protein that's rich in [tryptophan](#) and soy isoflavones, which have a [demonstrated association](#) with reduced symptoms of depression.

As an alternative to eggs, I love a savory tofu scramble spiced with turmeric, black pepper, and a pinch of sea salt.

4. Green smoothie

A bright green smoothie is a quick and easy way to start the day with fiber and folate.

We need folate for [the production of neurotransmitters](#) in the brain — folate deficiency is implicated in a number of psychiatric conditions, including [depression](#), while optimal levels are associated with improved [mood](#).

Blend up your favorite leafy greens like spinach along with a few berries, your favorite clean protein powder (or silken tofu for a creamy twist), and a bit of fat from hemp seeds or almond butter for a nutrient-dense smoothie you can take with you as you run out the door.

Avoid adding too much fruit or any fruit juices to keep it low sugar and avoid disrupting the microbiome or experiencing blood sugar spikes and fatigue.

5. Turmeric latte

While not necessarily a meal in itself, my golden milk turmeric latte is a nourishing beverage and an incredible way to kick off your morning.

Combine a cup of your favorite unsweetened plant milk with turmeric and a pinch of black pepper.

What you get is a potent [anti-inflammatory](#) that helps reduce symptoms of anxiety, boost energy, and clear brain fog for focus throughout the day.

[Dr. Uma Naidoo](#) is a Harvard-trained nutritional psychiatrist, professional chef, and nutritional biologist. She is also the author of the bestselling "[This is Your Brain on Food](#)" and most recently, "[Calm Your Mind with Food](#)." Follow her on [Instagram](#) or subscribe to her [newsletter](#) on Substack.

Aging ‘hotspot’ found in brain, researchers say: ‘Major changes’



The brain plays a big part in the [aging process](#), and scientists think they've pinpointed the specific cells that control it.

In a study of mice, researchers at the Allen Institute identified certain cells that showed "major changes" with age, particularly in one specific "hotspot," according to a press release.

Mice were chosen because their brains share "many similarities" to [human brains](#).

The researchers used RNA sequencing and brain-mapping tools to analyze more than 1.2 million brain cells from young mice (2 months old) and older mice (18 months old).

The 18-month-old mice are roughly equivalent to a "late middle-aged human," the researchers indicated.

The researchers grouped the cells into 847 different types and also identified nearly [2,500 genes](#) that changed with aging, according to Zeng.

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WARDING OFF DEMENTIA MEANS MORE READING, PRAYING AND LISTENING TO MUSIC: STUDY

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Mice (not pictured) were chosen because their brains share "many similarities" to human brains, the researchers said.
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The cells that were linked to aging showed an increase in inflammation and a decrease in "neuronal function."

"Changes in these genes point to deteriorated neuronal structure and function in many neuronal and glial cell types, as well as increased immune response and inflammation in the brain's immune and vascular (blood vessel) cell types," Zeng detailed.

The cells that experienced the biggest changes were the ones in the hypothalamus, the part of the brain that is linked to food intake, energy balance and metabolism, the researchers noted.

This suggests that this area is a "hotspot for aging," Zeng noted, and that there could be a connection between diet, [lifestyle factors](#), brain aging and risk of age-related cognitive disorders.

"The findings from the study reinforce the notion that maintaining a [healthy lifestyle](#), promoting a healthy metabolic state, and reducing inflammation in the body and brain could slow down or delay the aging process and reduce the risks of aging-associated brain diseases," he said.

The hope is that this discovery could lead to new age-related therapies to improve the function of these cells and help prevent neurodegenerative diseases, according to the researchers.

"Aging is the most important risk factor for many brain diseases," Zeng noted.

"Our study provides a highly detailed genetic map for which brain cell types may be most affected by aging and suggests new gene and cell targets for developing new treatments for aging-related brain diseases."

The study did have some limitations, the authors acknowledged.

"The main limitation of our study is that the findings are correlational," Zeng said.

Inflammation plays a role in chronic age-related diseases such as Alzheimer's, a neurologist noted. AP Images© AP Images

"We don't know yet if the gene expression changes observed in specific cell types are causal to brain aging. Our study lays the groundwork by providing a detailed genetic map and cell targets."

Zeng called for [future studies](#) to investigate the cells' roles in aging and determine whether the reversal of the changes could delay the aging process.

Dr. Earnest Lee Murray, a [board-certified neurologist](#) at Jackson-Madison County General Hospital in Jackson, Tennessee, commented that the new research adds to existing evidence supporting the role of diet in human brain health.

The detailed "brain roadmap" will be very beneficial for future research into aging and possible therapeutics, according to Murray, who was not involved in the study.

The detailed "brain roadmap" discovered in the study will be very beneficial for future research into aging and possible therapeutics, experts agree. iStock© iStock

It's been known for some time that inflammation plays a role in chronic age-related diseases [such as Alzheimer's](#), the neurologist noted.

"More and more evidence is pointing to the fact many chronic diseases can be prevented, and it often comes down to [diet and exercise](#)," he told Fox News Digital. "Altering diet to exclude processed foods and initiating some habits such as intermittent fasting have been shown to reduce this cellular inflammation that appears to be leading to so many diseases."

Original article source: [Aging 'hotspot' found in brain, researchers say: 'Major changes'](#)

5 major Alzheimer's discoveries scientists made in 2024

The Alzheimer's Association shares some of its most significant dementia findings

Published December 27, 2024

[Drug shows promise in treating Alzheimer's](#)

Gillian Turner reports how BAN2401 might help slow the mental decline of Alzheimer's patients.

With an estimated 6.9 million Americans aged 65 and older currently living with [Alzheimer's disease](#), the road to a cure seems long and uncertain.

But as the year comes to a close, experts are reflecting on some of the hopeful advances in diagnosis, treatment and risk management that have been made in 2024.

The Alzheimer's Association — a Chicago-based nonprofit committed to [Alzheimer's research](#), care and support — shared its top five significant discoveries from the year.

[DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80](#)

1. Third new Alzheimer's drug is approved

2024 saw a new drug enter the dementia landscape, as the U.S. Food and Drug Administration (FDA) approved Kisunla (donanemab) in July.

This was the third new approval since 2021.



The Alzheimer's Association — a Chicago-based nonprofit committed to Alzheimer's research, care and support — shared its top five significant discoveries from the year. (iStock)

Kisunla, which is made by Eli Lilly, is designed to "slow progression and change the underlying course of the disease," according to the Association's press release.

The [once-monthly injection](#) is intended for adults with early symptomatic Alzheimer's disease.

This is the first medication to target amyloid plaques — the proteins that build up in the brains of Alzheimer's patients, often impairing memory and cognitive function — with evidence to support stopping therapy when amyloid plaques are removed, a company release stated.

'HIDDEN' FAT COULD PREDICT ALZHEIMER'S DISEASE UP TO 20 YEARS BEFORE SYMPTOMS, RESEARCH FINDS

"This is real progress," said Alzheimer's Association President and CEO Dr. Joanne Pike in a statement shared with Fox News Digital at the time.

"[This FDA] approval allows people more options and greater opportunity to have more time. Having multiple treatment options is the kind of advancement we've all been waiting for."

2. Blood tests could improve speed and accuracy of diagnosis

Research this year has helped move Alzheimer's blood tests closer to being used in [physicians' offices](#).

Studies have shown that blood tests can achieve a higher accuracy of diagnosis, which could help fast-track patients' access to clinical trials and treatments, according to the Alzheimer's Association.

"This is real progress."

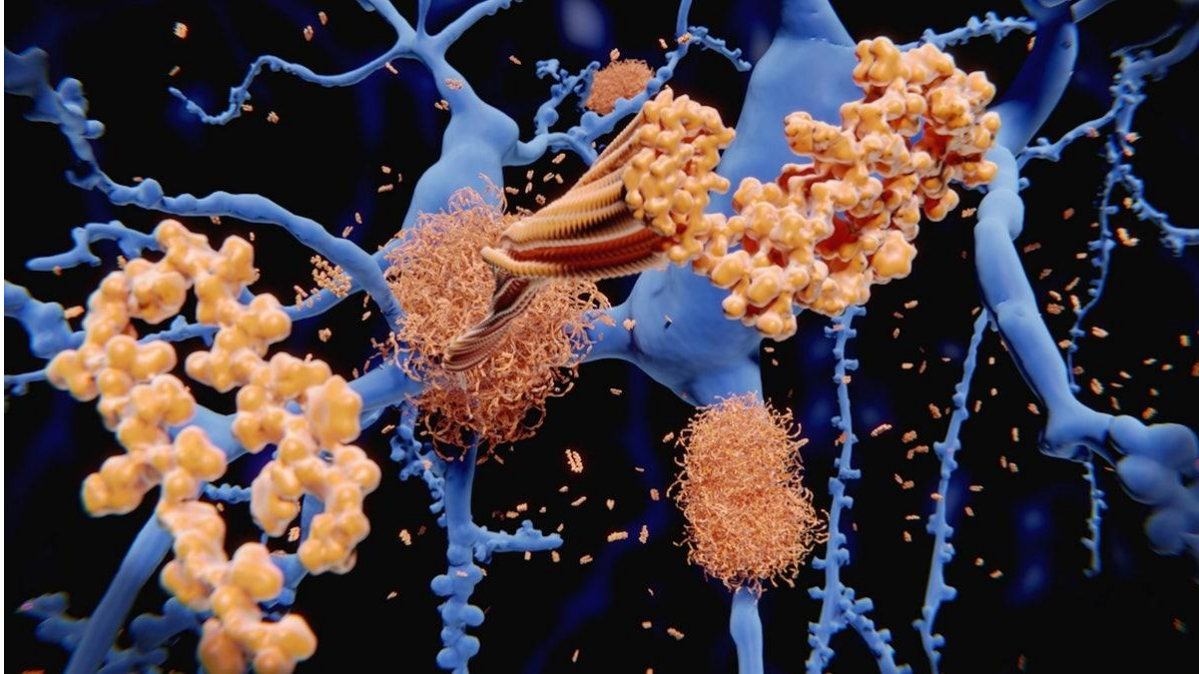
"Blood tests for Alzheimer's are demonstrating in research that they could significantly improve a clinician's accuracy and confidence, provide greater accessibility and a reason for more communication," the same source stated.

In one study reported this year, a specific blood test was around 90% accurate in identifying Alzheimer's in patients with cognitive symptoms seen in [primary care](#) and at specialized memory care clinics, per the Association.

3. Individuals and caregivers want more support post-diagnosis

People who are newly diagnosed with Alzheimer's and their caregivers need more support in navigating the health care system.

That's according to a 2024 Alzheimer's Association survey, which found that 97% of dementia caregivers expressed a desire for those support systems.



2024 saw the approval of the first medication to target amyloid plaques, the proteins that build up in the brains of Alzheimer's patients and often impair memory and cognitive function. (iStock)

A majority of dementia caregivers (70%) also noted that "coordination of care is stressful."

To help address this, the Centers for Medicare & Medicaid Services in July 2024 launched an eight-year pilot program in dementia care management, called the Guiding an Improved Dementia Experience (GUIDE) model.

[DEMENTIA RISK COULD BE LINKED TO WALKING SPEED, STUDY SUGGESTS](#)

The program aims to work with [health care systems](#) to provide supportive services to people living with dementia and their caregivers, with a focus on helping patients remain in their homes and communities, according to the Alzheimer's Association.

4. Wildfire smoke raises risk of dementia

Air pollution has been linked to an increased risk of dementia, according to 2024 research.

The 10-year study, which was presented during the Alzheimer's Association International Conference in Philadelphia in July, found that wildfire smoke can be "particularly hazardous" for [brain health](#).

A 2024 Alzheimer's Association survey found that 97% of dementia caregivers expressed a desire for those support systems. (iStock)

The research included more than 1.2 million people in southern California, an area that experiences frequent wildfire activity.

Air pollution produced by wildfires could be more hazardous to health because it is produced at higher temperatures, contains a greater concentration of toxic chemicals, and is smaller in diameter than other sources, the Alzheimer's Association stated.

5. Alzheimer's causes physical changes in the brain

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer's disease. "Defining diseases by the biology has long been standard in many areas of medicine — including cancer, [heart disease](#) and diabetes," the Alzheimer's Association wrote.

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer's disease. (iStock)

"The new publication defines Alzheimer's as a biological process that begins with brain changes before people exhibit memory and thinking problems."

These brain changes were found to come ahead of the typical outward symptoms, such as memory loss, confusion, disorientation and trouble with planning or organizing.

Warding off dementia means more reading, praying and listening to music: study

Downtime decisions may have profound health impacts, say researchers

Published January 1, 2025

[Could being bilingual help prevent dementia?](#)

Fox News medical contributor Dr. Nicole Saphier joins 'Fox & Friends Weekend' to weigh in on a new report that being bilingual could help people ward off dementia.

For long-term brain health, [older adults](#) might want to carefully consider how they spend their downtime, according to a new study. Researchers from the University of South Australia assessed the 24-hour activity patterns of nearly 400 people over age 60. When it comes to brain health, the study found that the context or type of activity individuals engage in matters, news agency SWNS reported.

[DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80](#)

Some sedentary behaviors are better for [cognitive function](#) than others, according to the findings, which were published in The Journal of Gerontology Series A. Mentally stimulating behaviors, [such as reading](#), listening to music, praying, crafting and playing a musical instrument — as well as social behaviors like chatting with others — are beneficial for memory and thinking abilities, the study noted.

Mentally stimulating behaviors such as reading, listening to music, praying, crafting and playing a musical instrument are beneficial for memory and thinking abilities, a new study noted. (iStock)

The research team referred to the "valuable insights" that could help reduce instances of cognitive impairment. More passive activities, like playing video

games or watching TV, do not offer the same benefits as reading, [praying and other activities](#), they noted. More than 55 million people around the globe have dementia, according to estimates from the World Health Organization. Another 10 million new cases are diagnosed each year. Dr. Maddison Mellow, researcher at the University of South Australia, said that not all sedentary behaviors are equal when it comes to memory and cognitive health.

"The context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." (iStock)

"In this research," she said, "we found that the context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." She said that scientists "already know that physical activity is a strong protector against dementia risk, and this should be prioritized if you're trying to [improve your brain health](#)," as SWNS reported.

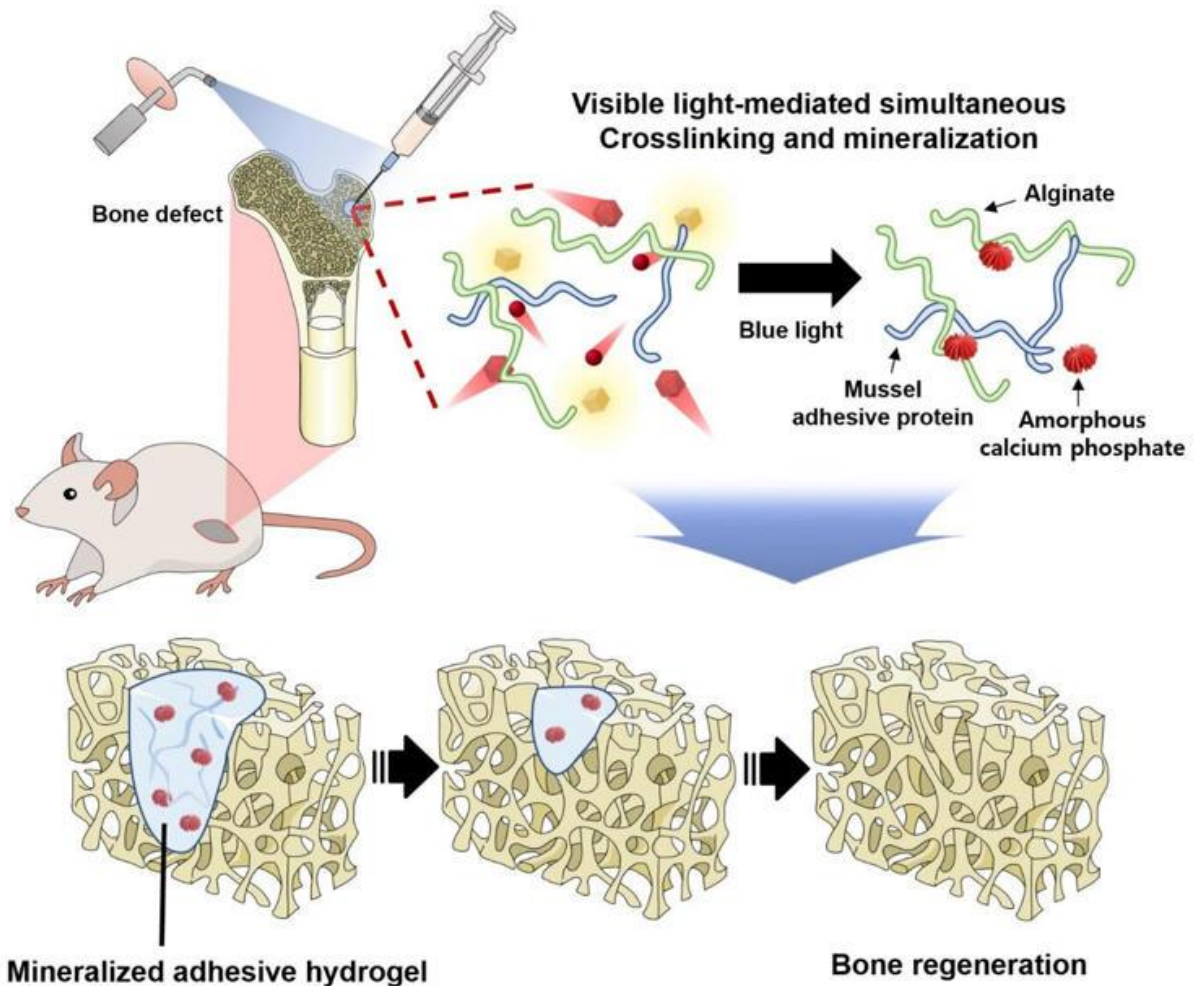
"Even small, 5-minute time swaps can help."

"But until now, we hadn't directly explored whether we can benefit our brain health by swapping one sedentary activity for another." She went on, "And while the 'move more, sit less' message certainly holds true for cardiometabolic and brain health, our research shows that a more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." It's wise to "prioritize movement that's enjoyable and gets [the heart rate](#) up," she also said. And "even small, 5-minute time swaps can help."

"A more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." (iStock)

A recent study published by the RAND Corporation in California also identified several major predictors occurring around age 60 that could likely lead to cognitive impairment and dementia in individuals [by age 80](#), as Fox News Digital previously reported. Researchers evaluated 181 potential risk factors, including demographics, socioeconomic status, lifestyle and health behaviors, health history, psycho-social factors and more. The list of predictors, according to RAND, included "never exercising" and "low engagement in hobbies." The study results suggested that "[maintaining good physical](#) and mental health is beneficial not just to staying in shape, but also to staying sharp and delaying cognitive decline," study co-author Peter Hudomiet, a RAND economist in California, told Fox News Digital.

Injectable hydrogel uses harmless visible light to achieve bone regeneration and adhesion



Injectable adhesive hydrogel for bone regeneration that simultaneously induces cross-linking and mineralization with visible light. Credit: POSTECH

A research team has developed an innovative injectable adhesive hydrogel for bone regeneration. This hydrogel utilizes harmless visible light to simultaneously achieve cross-linking and mineralization without the need for bone grafts. The research was recently [published](#) in the journal *Biomaterials*.

Bone defects, which arise from various causes such as trauma, infection, and congenital abnormalities, are becoming increasingly common in aging societies.

Conventional treatments often involve bone grafts combined with serum or bioadhesives to fill the defect.

However, existing injectable hydrogels face challenges such as difficulty in maintaining their shape within the body and limited adhesive strength. Moreover, traditional methods using bone grafts with adhesive materials often fail to achieve simultaneous "bone regeneration" and "adhesion."

The POSTECH team has introduced a novel system that addresses these limitations. This new hydrogel system employs visible light—safe for the human body—to facilitate cross-linking, where the main components of the hydrogel bond and harden, and to simultaneously boost mineralization where bone-building minerals like calcium and phosphate form within the hydrogel.

While earlier studies have explored the use of light in similar applications, they encountered issues such as requiring separate preparation and mixing of bone grafts and adhesive materials, as well as weak bonding of the main components, which often degraded over time.

The newly developed hydrogel precursor comprises alginate (natural polysaccharide derived from brown algae), RGD peptide-containing mussel adhesive protein, calcium ions, phosphonodiols, and a photoinitiator. The coacervate-based formulation, which is immiscible in water, ensures that the hydrogel retains its shape and position after injection into the body.

Upon visible light irradiation, cross-linking occurs, and amorphous calcium phosphate, which functions as a bone graft material, is simultaneously formed. This eliminates the need for separate bone grafts or adhesives, enabling the hydrogel to provide both bone regeneration and adhesion.

In experiments using animal models with femoral bone defects, the hydrogel was successfully injected, adhered accurately, and effectively delivered components essential for bone regeneration.

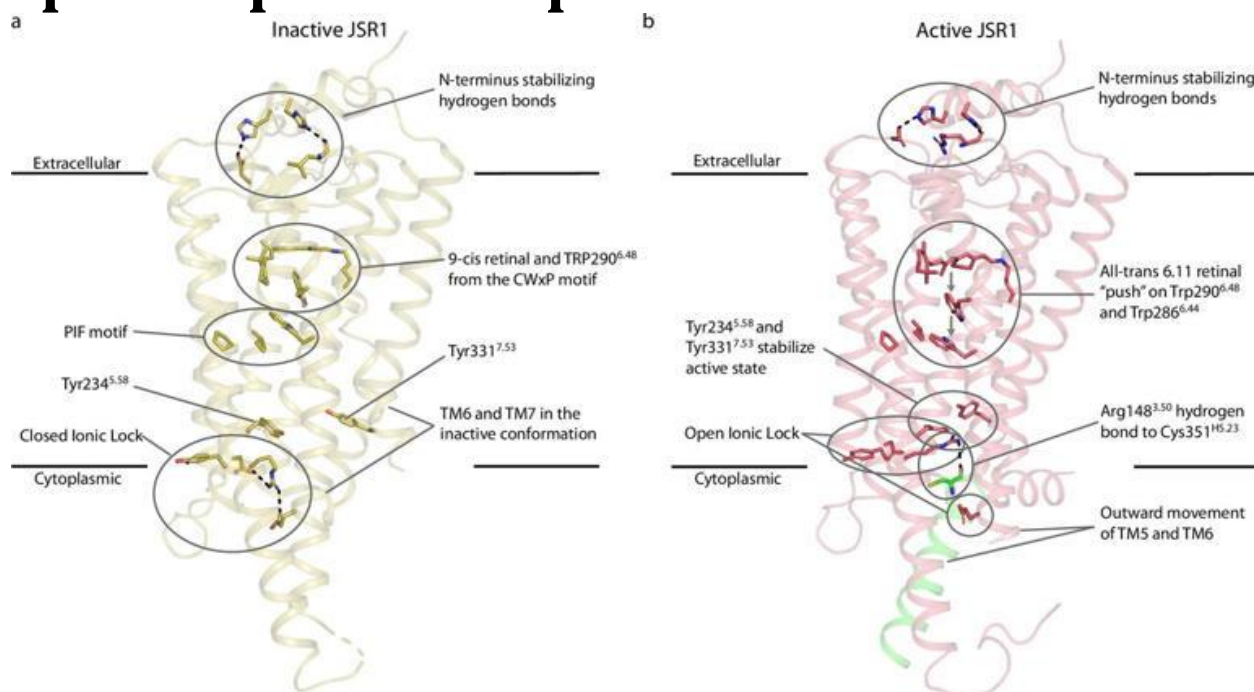
Professor Hyung Joon Cha from POSTECH commented, "The injectable hydrogel system for bone regeneration developed by our research team represents an innovative alternative to conventional complex treatments for bone diseases and will greatly advance bone tissue regeneration technology."

The research team included Professor Cha from POSTECH's Department of Chemical Engineering and Graduate School of Convergence Science and Technology with a specialization in Medical Science, along with Dr. Jinyoung Yun and Integrated Program student Hyun Taek Woo from the Department of Chemical Engineering.

More information: Jinyoung Yun et al, Visible light-induced simultaneous bioactive amorphous calcium phosphate mineralization and in situ crosslinking of coacervate-based injectable underwater adhesive hydrogels for enhanced bone regeneration, *Biomaterials* (2024). DOI: [10.1016/j.biomaterials.2024.122948](https://doi.org/10.1016/j.biomaterials.2024.122948)

Provided by Pohang University of Science and Technology

On the way to light-controlled medicine: Researchers elucidate the structure of specific photoreceptors



Activation of JSR1 by the agonist all-trans 6.11 retinal. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-53208-2

Researchers in biology and medicine have long dreamed of controlling the activities of cells without, for example, having to use chemicals. After all, in a structure as complex as an entire organism, unwanted side-effects can often arise.

The ideal solution would therefore be a type of remote control for cells, which would allow the functions of individual organs to be better examined and understood, and could even be used for therapeutic purposes. Remote control using light would be ideal for this, as it would enable organs and tissues deep inside the body to be influenced in a very selective and non-invasive way.

However, such a process also requires a cellular light receiver in the relevant organs. The receptors that receive light impulses in the retina of our eyes—called rhodopsins—could be suitable for this. With such photoreceptors, it might be possible to switch certain cell functions on and off using a light impulse.

This would work more rapidly and in a more targeted manner than drugs, which take a long time to take effect and often have unwanted side-effects because they cannot simply be activated in just one specific organ.

In the neurosciences, something similar is already working and is currently being tested in animal models to investigate brain diseases such as Parkinson's and epilepsy: Light-controlled ion channels from single-celled organisms are being incorporated into neurons using genetic engineering.

In the animal model, these ion channels in the cell membrane open when exposed to blue light, for example, and allow positively charged ions to flow into the neuron. In a chain reaction, further channels open, creating an electrical signal—the neuron becomes active.

A new kind of optogenetics

But such light-controlled ion channels only work in nerve cells. The goal of this research, however, is to stimulate other cells and organs in the organism to control a variety of bodily functions. For example, one could investigate the heart's natural pacemaker, or the mechanisms of chronic pain, anxiety, depression, and other mental illnesses.

It might be possible to develop effective cell therapies for hormonal malfunctions as well as immune, heart, and other diseases, including cancer.

To this end, researchers led by Gebhard Schertler of the PSI Center for Life Sciences are working on a new kind of optogenetics. In this approach, it is light receptors similar to the rhodopsins in our retina that become active: Triggered by a light pulse, they couple to proteins in the cell and thus initiate specific cellular signaling processes that take place in all organs.

The PSI researchers have joined forces with leading colleagues in Germany and England. Their project, Switchable rhodOpsins in Life Sciences (SOL), has three goals:

1. Find rhodopsins that can do this and elucidate their structure to better understand how they work.
2. Modify such rhodopsins, using molecular biological methods to optimize them for switching processes in various bodily functions.
3. Use the switches to better understand the signaling mechanisms of the proteins; use them as a tool in research and, on that basis, develop gene therapeutics.

The structural elucidation of proteins is a core competence of PSI, thanks to its high-resolution large research facilities. And PSI researchers have now made two significant steps towards SOL's first goal, as they report in two new studies.

First, they succeeded in finding a suitable rhodopsin and modifying it in such a way that it remains stable in the active state and thus can be examined. And second, the structure of this active state was clarified using a cryo-electron microscope at ETH Zurich.

A switch that bends and stretches

Rhodopsins are proteins. They are among the most important photoreceptors in the animal world. They have an elongated molecule in the middle, called retinal, that is derived from vitamin A. When a light pulse hits this molecule, it absorbs the energy and changes its shape within a quadrillionth of a second. A curved molecule—called the 11-cis form—becomes an elongated one—called the all-trans form. Through this transformation, the retinal also changes the structure of

the entire rhodopsin so that it can now bind to other proteins in the cell membrane, so-called G proteins.

Therefore these light-sensitive rhodopsins also belong to the GPCRs (G protein-coupled receptor) family, as rhodopsin-G protein complexes stimulate other proteins to react, triggering a whole series of biochemical processes leading, for example, to the transmission of a visual signal to the brain.

The human body possesses hundreds of different types of GPCRs, which are located in the cell membranes, receive signals from the outside, and pass them along to the inside of the cell. In this way, they control many bodily functions. That's why roughly 40% of all medications target GPCRs with active ingredients that dock onto their receptors.

The advantage of simple photoreceptors

Rhodopsins are found in the retina of the human eye. In the rod cells, for example, they are responsible for distinguishing between light and dark at night. However, like those of most vertebrates, these rhodopsins are monostable.

This means that once the retinal is changed by light, it leaves the protein and has to be regenerated. Only then is it available for the next switching process. This is too complicated to allow this molecule to be used effectively as an optogenetic switch, since enzymes would also have to be used to regenerate it.

Many invertebrates, such as squid, insects, and spiders, have bistable rhodopsins. "From an evolutionary perspective, these are actually a more primordial form of rhodopsins, and less sensitive," says Gebhard Schertler. They offer advantages for optogenetics, however: The retinal remains in the protein after being switched on, and with a second light pulse it can immediately return to its original form and switch the cellular process off again.

The rhodopsin of a jumping spider species, for example, proved to be robust and easy to produce, unlike other bistable rhodopsins. This qualified it as a possible optogenetic switch.

With the Swiss Light Source SLS at PSI, it was possible to determine the molecular structure of this spider rhodopsin in its inactive ground state. But before it could

be used as an optogenetic switch, its structure in the active form also had to be known precisely. This state, however, when the retinal is stretched and the rhodopsin binds to the G protein, is extremely short-lived.

How to make proteins happy

In one study, which was recently published in the [Proceedings of the National Academy of Sciences](#), lead author Matthew Rodrigues now reports how they managed to stabilize the active state to be able to elucidate its structure: by making a tiny modification to the retinal.

"The properties of the retinal remain the same, but the modification—one small additional molecular ring—ensures that it apparently fits better into the binding pocket of the protein," reports Rodrigues. "It stays there for hours. As we structural biologists say, it's happy." Now the conditions were in place to examine the structure of the active rhodopsin in conjunction with a G protein.

A mixed protein

In a second study, now published in [Nature Communications](#), first author Oliver Tejero and last author Ching-Ju Tsai did exactly that. "However, as expected, it was found that a spider protein (rhodopsin) naturally never fits optimally with a human protein (the G protein)," says Tsai. "So we compared spider G proteins with those of humans and assembled a chimera from both forms."

The researchers replaced the end part of the gene sequence of the human protein, which contains the code for the docking site, with that of the spider.

With additional genetic modifications in the actual light receptor, they addressed another problem: The spider rhodopsins are both activated and deactivated by light of the same wavelength.

"This means that a light pulse produces a hopeless hodgepodge of activated and deactivated states in a cell sample," says Tsai. Naturally, this is bad for a switch that is intended to turn on or off in a targeted manner. "With our modifications, we have ensured that switching on and off now takes place with different colors of light."

However, such "color tuning" by means of genetic engineering is only just beginning. The next step in the fundamental research into these new optogenetic switches will now be to find out how the proteins involved need to be designed to enable control using other colors of light.

This would then make it possible to selectively switch different cell functions on or off. It is also a matter of constructing the switches so that they are not only sensitive to blue, orange, and green light, but also, for example, to infrared light.

"The big question remains, if optogenetics is actually to be used in everyday medical practice, how the light will get to the rhodopsin," says Rodrigues. "You could implant the light source into the body. But the much more elegant and gentler method would be to work with infrared light. This can penetrate body tissue."

The largest part of the protein engineering, project leader Schertler confirms, is still to come, now that the structural basics are known. Ultimately, the goal is to put together a whole assembly kit of light-activated GPCRs that can be used for various purposes in the organism.

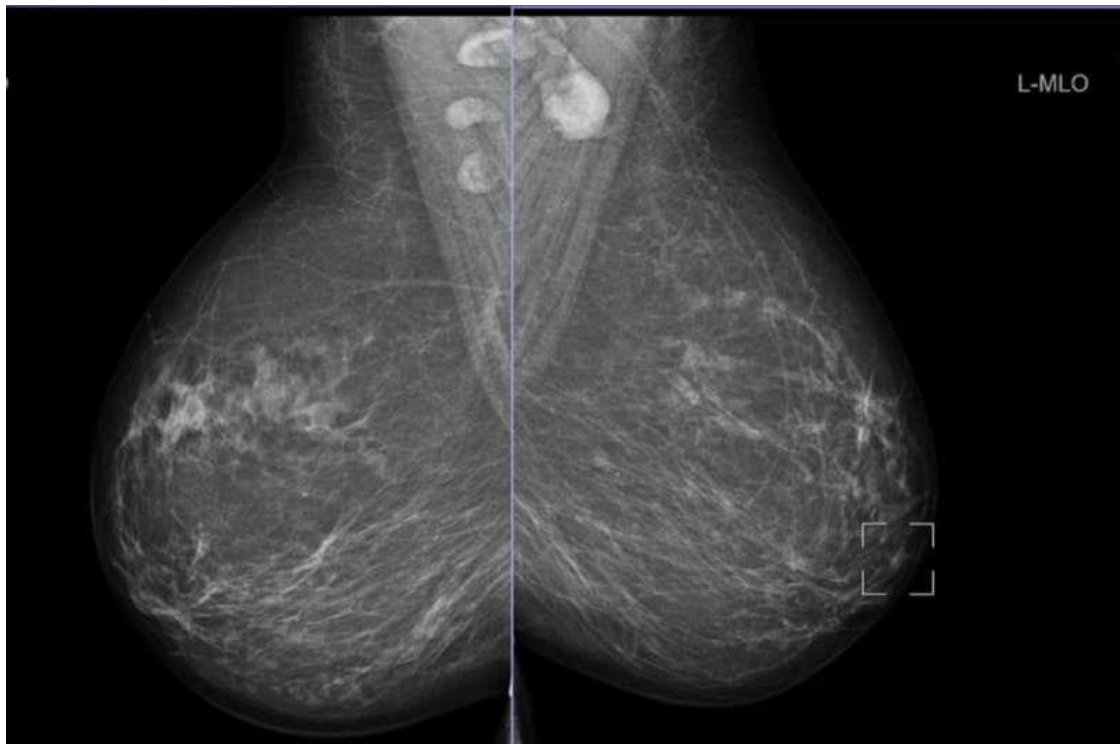
More information: Matthew J. Rodrigues et al, Activating an invertebrate bistable opsin with the all-trans 6.11 retinal analog, *Proceedings of the National Academy of Sciences* (2024). [DOI: 10.1073/pnas.2406814121](https://doi.org/10.1073/pnas.2406814121)

Oliver Tejero et al, Active state structures of a bistable visual opsin bound to G proteins, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-53208-2](https://doi.org/10.1038/s41467-024-53208-2)

Provided by Paul Scherrer Institute

AI improves mammography cancer detection rates in large cohort study

by Justin Jackson , Medical Xpress



a) The screenshot shows a worklist with subset of examinations tagged as normal. Radiologists can also choose to read only normal examinations or only not normal examinations ('potentially suspicious'). Names and dates of birth are not real and were sampled randomly from a list of common first and last names. **b)** and **c)** When radiologists assess a case as normal (BI-RADS 1 or 2) but the safety net triggered, an alert is shown (**b**) and a suspicious region is highlighted in the viewer (**c**), asking the radiologists to reconsider. Credit: *Nature Medicine* (2025). DOI: 10.1038/s41591-024-03408-6

An observational, multicenter, real-world study conducted at 12 screening sites in Germany has reported a 17.6% higher cancer detection rate among women aged 50–69 who received AI-supported double-reading mammography screenings compared to those who received standard double-reading. Recall rates remained unchanged.

Mammography [screening](#) programs often rely on double reading to identify [breast cancer](#) at earlier stages. Radiologists face substantial workloads interpreting mammograms, most of

which include cases with no signs of cancer. Screening centers struggle to keep up with providing efficient and accurate assessments, a problem only getting more urgent with a growing shortage of trained radiologists.

Many breast cancers elude early detection only to be diagnosed at later stages, reflecting ongoing issues with current screening methods. False positive results burden both participants and health care systems with needless worry and unnecessary follow-up (recall) appointments. Efforts to boost early detection sensitivity and lower unnecessary false positives are top priorities.

In a study titled "Nationwide real-world implementation of AI for cancer detection in population-based mammography screening," [published](#) in *Nature Medicine*, researchers compared screening results of a large cohort with and without AI-assisted prediction software.

Investigators enrolled 463,094 women in the German mammography screening program (PRAIM study). Participants were divided into an AI group (260,739) and a control group (201,079). AI-based software classified certain examinations as normal and triggered a "safety net" alert for high-suspicion cases.

Results showed a higher breast cancer detection rate of 6.7 per 1,000 in the AI group compared to 5.7 per 1,000 in the control group. The recall rate was 37.4 per 1,000 with AI and 38.3 per 1,000 without AI. Recall rate measures how many participants return for further tests and includes correct initial detections as well as false positives.

Positive predictive value, the portion of suspicious findings that truly represent cancer, reached 17.9% for AI-supported reading versus 14.9% in the control group. The [positive predictive value](#) of follow-ups resulting in biopsy was 64.5% in AI-assisted screening, compared to 59.2% under standard double reading.

While the false positives were slightly lower, the researchers considered these to be comparable to existing double reading methods. That AI-supported mammograms detected more cancers without increasing recall rates in a large cohort is considered the more critical threshold for recommending further development and greater widespread use of the technology.

More information: Nora Eisemann et al, Nationwide real-world implementation of AI for cancer detection in population-based mammography screening, *Nature Medicine* (2025). [DOI: 10.1038/s41591-024-03408-6](https://doi.org/10.1038/s41591-024-03408-6)

Journal information: [Nature Medicine](#)

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JANUARY 13, 2025

Discovery of MCJ protein's role in converting brown fat to heat could combat obesity

by [The Spanish National Cancer Research Centre](#)



Credit:

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Obesity, which affects 650 million people worldwide, influences the development of cardiometabolic diseases and increases the risk of cancer.

Guadalupe Sabio, head of the Organ Crosstalk in Metabolic Diseases Group at the National Cancer Research Center (CNIO), and Cintia Folgueira, from CNIO and the National Center for Cardiovascular Research (CNIC), have discovered one of the ways in which the body "burns" brown fat and converts it into heat. This mechanism protects against obesity and related metabolic diseases.

The mechanism now identified is controlled by the [protein](#) called MCJ, present in mitochondria (the organelles of the cell where energy is produced).

Sabio and Folgueira have discovered that, when the MCJ protein is removed from obese mice, these animals produce more heat and lose weight. The researchers have also

managed to reduce the weight of obese mice just by having them transplanted with fat without that protein.

Brown fat and obesity

"Obesity is the result of either excessive food intake or inadequate total energy expenditure. We now know that adipose tissue body fat, in addition to storing energy, plays a crucial role in the management of that energy by the body. Adipose tissue is a complex organ that acts as a regulator of the whole body's metabolism, and therefore modulating its function could well be a way to combat obesity," the authors write in [Nature Communications](#).

There are two types of fatty or adipose tissue: white and brown. White adipose tissue mostly stores energy, while brown fat (its cells have more mitochondria and that gives them a brown hue) is responsible for heat generation or thermogenesis, the process that maintains body temperature and which is triggered by cold or other stimuli.

Several studies in the last decade have shown that activating brown fat protects against obesity and metabolic disease. "For some time," explains Sabio, "it has been thought that obesity could be prevented by getting this fat to spend more energy by generating heat. So the first thing is to understand how it works."

"Discovering new mechanisms of heat production in brown fat is one of the most interesting targets in the study of obesity," says Sabio.

How to burn brown fat

For a long time it was thought that brown fat used a single mechanism to generate heat, but today we know that this is not the case. There are several mechanisms involved. The [research](#) led by Sabio and Folgueira has discovered one of them, controlled by a mitochondrial protein called MCJ.

The research conducted at CNIO has discovered that when the MCJ protein is removed from [obese mice](#), these animals produce more heat and lose weight. Moreover, it was enough to transplant into the animals brown fat without the MCJ protein to reduce their weight.

Avoiding pathologies associated with obesity

The researchers also observed that "animals without MCJ in brown fat are protected against health problems caused by obesity, such as diabetes or increased blood lipids," explain the two scientists. Therefore, they believe that the MCJ protein could be a new therapeutic target to correct diseases associated with obesity.

"This protection," explains CNIO researcher Beatriz Cicuéndez, lead author of the article, "is due to the activation of an essential signaling pathway to adapt to the stress caused

by [obesity](#). Known as the catabolic pathway, it causes an increase in the consumption of fats, sugars and proteins to produce [heat](#) in brown fat. It is a mechanism that also happens in people with very active [brown fat](#)."

Blocking the MCJ protein in obese patients

The research is now seeking to develop a therapy to block this protein in obese patients, but to do so they must first investigate whether the MCJ protein has vital functions in other tissues.

At the same time, Guadalupe Sabio says, "we are trying to see if these changes in fat affect tumor growth or cachexia—loss of muscle and fat—which is also sometimes linked to cancer."

More information: Beatriz Cicuéndez et al, Modulation of brown adipose tissue thermogenesis by MCJ/DnaJC15, *Nature Communications* (2025). [DOI: 10.1038/s41467-024-54353-4](https://doi.org/10.1038/s41467-024-54353-4)

Journal information: [Nature Communications](#)

Provided by [The Spanish National Cancer Research Centre](#)

JANUARY 13, 2025

Introducing FDI, the Florey Dementia Index for Alzheimer's onset prediction

by Justin Jackson , Medical Xpress

Credit: Unsplash/CC0 Public Domain

A predictive tool for determining the age at which individuals may develop mild cognitive impairment (MCI) or Alzheimer's dementia (AD) has demonstrated the ability to predict MCI onset within 2.78 years and AD onset within 1.48 years.

Developed by Florey Institute of Neuroscience and Mental Health researchers, collaborating with the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarker, and Lifestyle (AIBL) study, the team has released validation results of the Florey Dementia Index (FDI).

FDI predicts the age at onset of MCI and AD with high accuracy, potentially enabling patients and clinicians to better plan care and prioritize early treatment before the presentation of classic symptoms.

Alzheimer's disease is a progressive neurodegenerative disorder that develops gradually from MCI to dementia, leading to significant loss of independence. While previous research has seen early indication signals related to the [gut microbiome](#), no clinical tools currently exist for reliably predicting the age at onset.

Transitioning from MCI to AD escalates the need for comprehensive care. Reliable methods to forecast the onset age of these conditions, especially in preclinical phases, would allow for interventions with emerging disease-modifying therapies.

In the study "Development and Validation of a Tool to Predict Onset of Mild Cognitive Impairment and Alzheimer Dementia," [published](#) in *JAMA Network Open*, researchers introduce the FDI statistical modeling approach for predicting disease onset and test the index in an Alzheimer's-specific cohort.

The FDI model incorporates age and Clinical Dementia Rating Sum of Boxes (CDR-SB) scores, relying solely on noninvasive data collection methods to balance predictive accuracy with accessibility.

The prognostic study utilized data from 3,694 participants across the AIBL and ADNI cohorts, from October 2004 to March 2023. Data from 93 participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer (A4) study were also employed in a simulated trial to assess the FDI's applicability. The study excluded individuals with MCI or dementia not associated with Alzheimer's disease.

Results indicate that among AIBL and ADNI participants, the FDI accurately predicted the onset of MCI and AD. The mean absolute error (MAE) for predicting the age of MCI onset was 2.78 years, with an MAE of 1.48 years for AD onset. Lower prediction errors were observed in the simulated A4 trial, a group with preclinical Alzheimer's disease, with MAEs of 1.57 years for MCI and 0.70 years for AD.

No adjustments were made initially for medical comorbidities or demographic factors, including sex, and results still demonstrated consistency across datasets, supporting the model's robustness and generalizability.

When well-characterized comorbidities (hypertension, stroke, neurologic disorders, psychiatric disorders) were included in the assessment, FDI showed a slightly enhanced performance over the generalized version. Adjustments for sex slightly improved performance for predicting AD onset but not MCI onset.

Survival analysis revealed a sharp decline in dementia-free probability at specific FDI thresholds. MCI onset was linked to an FDI threshold of 79, while AD onset corresponded to a threshold of 85.

FDI offers a novel approach to predicting the onset of MCI and AD, providing clinicians with a low cost, accessible tool that relies on noninvasive, widely available metrics. In clinical

terms, it could allow early planning of treatment options, or prioritize patients for emerging treatments such as disease-modifying monoclonal antibody drugs.

It would also be useful for patients planning for future challenges with dementia and [home care](#), allowing them to make autonomous decisions while they are best able to do so.

Though validation in broader and more diverse cohorts is necessary, this tool holds promise for advancing personalized [dementia](#) care and improving patient outcomes.

More information: Chenyin Chu et al, Development and Validation of a Tool to Predict Onset of Mild Cognitive Impairment and Alzheimer Dementia, *JAMA Network Open* (2025). [DOI: 10.1001/jamanetworkopen.2024.53756](#)

Journal information: [JAMA Network Open](#)

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Distinct neural circuits mediate anti-anxiety and hallucination-like effects of psychedelics, research reveals

by [UC Davis](#)

Working in a mouse model, UC Davis researchers are able to distinguish brain cells activated by a psychedelic drug. This image shows the prefrontal cortex of a mouse injected with scFLARE2 (purple) which drives the expression of a light-responsive channel in psychedelic-activated neurons (green or red). This allows researchers to visualize and artificially reactive these neurons at a later time point. Credit: Christina Kim, UC Davis

New research suggests that it could be possible to separate treatment from hallucinations when developing new drugs based on psychedelics. The anti-anxiety and hallucination-inducing qualities of psychedelic drugs work through different neural circuits, according to research using a mouse model. The work is [published](#) in *Science*.

The research shows that decoupling the beneficial effects of psychedelics from their hallucinogenic effects isn't just a matter of chemical compound design. It's a matter of targeted [neural circuitry](#).

"In the past, we did this using chemistry by making new compounds, but here we focused on identifying the circuits responsible for the effects, and it does seem that they are distinct," said study co-author David E. Olson, director of the Institute for Psychedelics and Neurotherapeutics (IPN) and a professor of chemistry and of biochemistry and [molecular medicine](#) at the University of California, Davis.

"This is an important mechanistic study that validates our earlier results."

Measuring anti-anxiety behaviors in mice

The researchers measured anxiety in mouse models with two tests: the elevated plus maze and the marble burying test.

In the elevated plus maze, mice are placed in a cross-shaped maze raised a couple of feet off the ground. Two arms of the maze have high walls while the other two arms remain open and have no walls. Mice with high anxiety tend to stay in the closed arms with high walls, not willing to explore the open arms.

In the marble burying test, mice with high anxiety tend to continuously and compulsively bury marbles in their bedding.

"It is well known that in mice, psychedelics induce reduced marble burying and promote exploration of the open arms of the plus maze," said Christina Kim, the study's corresponding author and an assistant professor of neurology, core member of the Center for Neuroscience and IPN affiliate. "But there is also an intoxicating or hallucinogenic-like effect, which can be measured through head twitches in mice."

In the study, the team dosed mouse models with the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI). They found that six hours after the dose, the mice still exhibited reduced marble burying and increased open arm time in the elevated plus maze. However, the head twitches associated with hallucinations had disappeared.

"We thought that if we could identify which neurons activated by DOI were responsible for reducing anxiety, then we might be able to reactivate them at a later time to mimic those anti-anxiety-like effects," Kim said.

To identify the specific neural circuits associated with anti-anxiety effects, the team used a molecular tagging tool called scFLARE2 to highlight the neurons activated by DOI in the [medial prefrontal cortex](#)—a brain region known to be involved in reducing anxious behavior in mice.

The tagging allowed the team to isolate a psychedelic responsive network that extends beyond 5-HT_{2A}R expressing neurons, the main receptor avenue through which psychedelics promote neuroplasticity.

Using light to promote anti-anxiety effects

Equipped with a fluorescent map of the neurons activated by DOI, the team then used optogenetics, or light, to reactivate those neurons.

"When we performed the scFLARE2 tagging and reactivation of these specific prefrontal cortex cells, we could still drive a reduction in anxiety-like behaviors, measured as decreased marble burying and increased open arm exploration in the elevated plus maze," Kim said. "We could do this just by targeting the DOI-activated cells and then reactivating them the next day."

The team also used single nucleus RNA sequencing to genetically profile the specific types of neurons in the DOI-activated network. Of the nine neuron group types identified, three exhibited high activation.

"While some of the [cell types](#) activated by DOI had strong 5-HT2AR expression, there were others that did not," Kim said. "What is likely happening is that we are getting direct activation of cells that express 5-HT2AR, and then they go on to activate additional downstream cells that can trigger behavioral changes."

"It is important to realize that the cells that we are tagging and reactivating extend beyond just those that express the receptor for the drug," she added.

The finding emphasizes how activating single touchpoints in the brain spirals out into the rest of the network.

"While DOI is a potent [psychedelic](#), it is not being explored as a potential therapeutic drug in the clinic. Thus the findings here are focused on dissecting the basic circuit mechanisms of this important class of drugs," Kim said.

Elucidating exactly how psychedelics affect the brain is a major goal of the IPN.

"Understanding which neural circuits psychedelics activate to elicit their effects is the kind of basic science needed to ultimately develop targeted therapeutics with better safety profiles," Olson said.

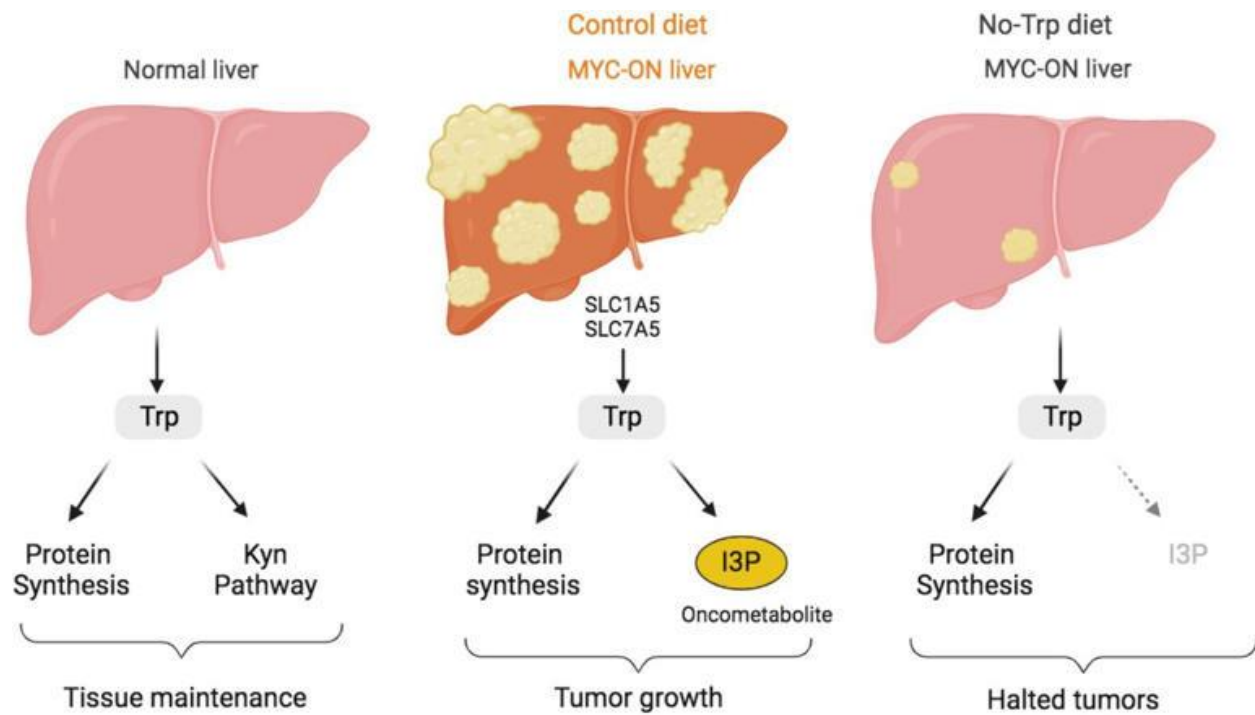
Co-authors Jessie Muir, a postdoctoral researcher at the Center for Neuroscience, and Sophia Lin, a junior specialist at the Center for Neuroscience, spearheaded the DOI study. Additional authors on the study include I.K. Aarrestad, H.R. Daniels, J. Ma and L. Tian.

More information: J. Muir et al, Isolation of psychedelic-responsive neurons underlying anxiolytic behavioral states, *Science* (2024). [DOI: 10.1126/science.adl0666](#). www.science.org/doi/10.1126/science.adl0666

Journal information: [Science](#)

Provided by [UC Davis](#)

Liver cancer growth tied to tryptophan intake



Summary of our findings on Trp dependency and vulnerability in MYC-driven tumors. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-47868-3

Researchers at UT Southwestern Medical Center have discovered that a diet free of the amino acid tryptophan can effectively halt the growth of liver cancer in mice. Their findings, [published](#) in *Nature Communications*, offer new insights for dietary-based cancer treatments and highlight the critical role of the tryptophan metabolite indole 3-pyruvate (I3P) in liver tumor development.

"This work demonstrates that tailored dietary modulation may serve as a powerful adjuvant in cancer treatment," said study leader Maralice Conacci-Sorrell, Ph.D., Associate Professor of Cell Biology and Children's Medical Center Research Institute at UT Southwestern (CRI) and a member of the Cellular Networks in Cancer Research Program of the Harold C. Simmons Comprehensive Cancer Center. "It builds on our lab's discovery that the universal oncogene MYC increases the demand for tryptophan in liver tumors."

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related mortality worldwide, according to 2020 data from the World Health Organization, with limited options for effective treatment and a five-year survival rate of about

30%. The study shows that growth of liver cancers driven by the MYC oncogene is particularly dependent on tryptophan, which is converted into I3P as well as other metabolites.

By removing tryptophan from the diet of mice, researchers stopped the growth of MYC-driven liver tumors and restored normal gene expression in liver cells. Notably, this dietary intervention did not affect protein synthesis in normal cells, suggesting a targeted therapeutic approach that spares healthy tissues.

"Liver tumors require large amounts of tryptophan to generate the oncometabolite I3P," Dr. Conacci-Sorrell said. "A tryptophan-free diet prevents liver tumor growth by a mechanism that depends on I3P but is independent of translation, the process by which proteins are synthesized from amino acid building blocks. Because tryptophan is the amino acid with the lowest abundance in the proteome, short-term dietary manipulation is safe for healthy tissues but not for cancer cells."

Among foods high in tryptophan are turkey, red meat, pork, chicken, tofu, milk, soybeans (including edamame), quinoa, oats, and fish.

The research highlights the complex role of tryptophan metabolism in cancer. While tryptophan is known to be metabolized into several important compounds, including the neurotransmitter serotonin and kynurenine, a precursor of the B vitamin niacin, the study showed that MYC-driven liver tumors preferentially utilize tryptophan to produce I3P rather than kynurenine. This shift underscores the potential for targeting specific metabolic pathways in cancer treatment.

The researchers also found that supplementation with I3P restored the growth of tryptophan-starved liver cancer cells, further emphasizing the critical role of this metabolite in cancer development. These findings suggest that targeting I3P or its production pathway could be a viable therapeutic strategy.

"This study not only advances understanding of liver cancer biology but also suggests a promising approach for developing personalized cancer therapies," Dr. Conacci-Sorrell said.

More information: Niranjana Venkateswaran et al, Tryptophan fuels MYC-dependent liver tumorigenesis through indole 3-pyruvate synthesis, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-47868-3](https://doi.org/10.1038/s41467-024-47868-3)

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