Researchers target Parkinson's disease with kurarinone and sEH inhibitor

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This is Sophora flavescens. A compound from this plant reduce neuroinflammation in an animal model with Parkinson's disease. Credit: Wikipedia/CC0 Public Domain

A natural product from the dried root of a pea-family plant, potentially combined with an enzyme inhibitor discovered in the Bruce Hammock laboratory at the University of California, Davis, may provide hope in alleviating neuroinflammation in Parkinson's disease, an eight-member team of researchers from Dalian Medical University, China, and UC Davis announced today.

Their novel research, published in the current edition of the *Proceedings of the National Academy of Sciences (PNAS)*, shows that a soluble epoxide hydrolase (sEH) inhibitor and kurarinone, a compound from the dried root of Sophora flavescens, reduced neuroinflammation in an animal model with Parkinson's disease (PD). The dried root, also known as kushen, has been used for hundreds of years in traditional Chinese medicines.

"Traditional Chinese medicines play an immeasurable role in the treatment of all kinds of diseases," said lead researcher Cheng-Peng Sun, a Dalian Medical University professor who is partnering with the Hammock lab on the PD research. For the past 35 years, Hammock, a distinguished professor who holds a joint appointment with the Department of Entomology and Nematology and the UC Davis Comprehensive Cancer Center, has researched enzyme inhibitors that dramatically reduce inflammation, inflammatory pain and neuropathic pain.

"We investigated the neuroprotective effects of S. flavescens in Parkinson's disease based on the neuroinflammation," Sun explained.

"Our extensive studies indicated that kurarinone possesses several pharmacological effects, including anti-inflammatory and antioxidative activities."

The research, titled "Kurarinone Alleviated Parkinson's Disease via Stabilization of Epoxyeicosatrienoic Acids in Animal Model (Mice)," may lead to an effective therapy for PD, a progressive neurogenerative or brain disorder that affects more than 10 million people worldwide, including a million in the United States, according to the Mayo Clinic. Most PD patients are 65 or over and most are men. There is no cure.

"Basically, kurarinone targets the soluble epoxide hydrolase (sEH), which is a key regulatory enzyme involved in the metabolism of fatty acids, and inhibitors of the sEH enzyme resolve neuroinflammation," said professor Hammock, corresponding author. "The enzyme regulates a newly studied class of natural chemical mediators, which in turn regulates inflammation, blood pressure and pain."

"We have known for a number of years that the soluble epoxide hydrolase inhibitors, now in human safety trials, are active in reducing the development of Parkinson's disease in several rodent models," Hammock said. "The evidence for this is quite strong, particular based on work of our longterm collaborator Kenji Hashimoto at Chiba University in Japan. Certainly, Parkinson's disease is one of our targets for the sEH inhibitors, but the regulatory path is slow and expensive. This path becomes much faster for a natural product, so the discovery of this natural product from Cheng-Peng's laboratory potentially offers relief to patients far faster than a classical pharmaceutical."

"In addition to its use as a natural product for treating Parkinson's disease, kurarinone provides a new model for the design of still more active compounds to block the neuroinflammation associated with multiple neurodegenerative diseases where sEH inhibitors have shown

efficacy in rodent models, including Alzheimer's, autism, and other disorders," Hammock said. "The fact that kurarinone binds in the sEH enzyme in an adjacent but non-identical site opens the door to new synthetic drugs for these diseases."

"From the standpoint of drug design in general and discovery of natural biologically active compounds in particular," Hammock said, "the Sun laboratory in China used the kurarinone project to pioneer new techniques in discovering natural plant products for disease treatment."

Co-author Christophe Morisseau, a biochemist in the Hammock lab, performed the enzyme kinetics, demonstrating the potency of the compound and how it interacts with the enzyme. "This research is important in two ways," he said. "In lay terms, it demonstrates the use of a natural compound to treat Parkinson's disease. Right now, there is no effective treatment for this disease, so this is pretty cool. And we show that the compound used has a novel mechanism of inhibiting sEH compared to the previous inhibitors published."

UC Davis Health System neurologist and School of Medicine Professor Lin Zhang, who is known for his PD expertise (he was not involved in the study), praised the research as novel. "Although we now have multiple medications to manage the debilitating symptoms of Parkinson's disease, we still don't have a way to stop the progression of the disease, not to mention having a cure," said Zhang, who treats PD patients. "The conventional wisdom believes the reason for that is that we have been only treating the symptoms, not the cause of the disease. One of the contributing causes, as evidenced recently, has been neuroinflammation."

A common Parkinson model comes from mice treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). "This paper shows that when Parkinsonian mice were treated with the natural product

kurarinone, their Parkinson-like behaviors were significantly alleviated by attenuation of neurotoxicity," Zhang said. "The same natural product was able to suppress sEH activities selectively so much so that neuroinflammation was markedly ameliorated. Furthermore, when the same models had their sEH gene knocked out, kurarinone did not provide additional protection against Parkinsonism."

"This paper shows that kurarinone, a natural product, is able to alleviate Parkinson symptoms," Zhang pointed out. "The mechanism for that has something to do with the fact that kurarinone targets soluble epoxide hydrolase (sEH) which mediates neuroinflammation. Products capable of inhibiting sEH like kurarinone can provide a novel yet promising,mechanism to reduce neuroinflammation, subsequently treating neurodegenerative disorders including PD at its core."

"These findings presented in this paper help to solidify the candidacy of sEH as a key player of PD pathogenesis via neuroinflammation, underscoring the role of sEH inhibitors as a new class of anti-neuroinflammatory pharmaceuticals treating neurodegenerative disorders including PD."

What's the next step?

"We hope that the natural herbal medicine will offer some relief from Parkinson's disease," said Sun.

Added Morisseau: "We also hope to increase kurarinone levels in the plant and ensure that the extracts are nontoxic and effective. Possibly we can even find a food plant that is effective."

Hammock lab researcher Sung Hee Hwang, an organic chemist, has been making small molecule inhibitors for Parkinson's disease, "and the crystal structure of sEH bound to kurarinone will be a great help to him,"

Hammock said. "He has been working with Jogen Atone who is just finishing his doctorate in the UC Davis Pharmacology Toxicology program working on basic aspects of Parkinson's disease and environmental chemicals that may cause it."

Sophora (the Arabic name for a pea-flowered tree) is a genus of about 45 species of evergreen trees and shrubs in the pea family, Fabaceae. The species are native to southern Asia, Australasia, various Pacific islands, western South America, the western United States, Florida and Puerto Rico. About fifteen of these species have a long history of use in traditional Chinese medicine.

"Now that we have a lead structure, we hope to screen related species for related compounds and efficacy," Morisseau said.

"Parkinson's disease occurs when nerve cells in the basal ganglia, an area of the brain that controls movement, become impaired and/or die," according to the National Institute on Aging (NIA). "Normally, these nerve cells, or neurons, produce an important brain chemical known as dopamine. When the neurons die or become impaired, they produce less dopamine, which causes the movement problems of Parkinson's. Scientists still do not know what causes cells that produce dopamine to die."

"One clear risk factor for Parkinson's disease is age," NIA says. "Although most people with Parkinson's first develop the disease at about age 60, about 5 to 10% of people with Parkinson's have 'early-onset' disease, which begins before the age of 50. Early-onset forms of Parkinson's are often, but not always, inherited, and some forms have been linked to specific gene mutations."

Hammock expressed hope that a variety of research pathways, such as the one resulting in kurarinone, "can lead to therapies, preventions and

cures of Parkinson's disease and other neuroinflammatory problems associated with aging."

More information: Kurarinone alleviated Parkinson's disease via stabilization of epoxyeicosatrienoic acids in animal model, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2118818119.

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