Compounds derived from hops show promise for metabolic syndrome patients

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Pharmacy professor Fred Stevens and graduate student Ines Paraiso examine a ball-and-stick model of the hop-derived compound xanthohumol. Credit: Oregon State University

A group of compounds derived from hops can likely improve cognitive

and other functions in people with metabolic syndrome, new research at Oregon State University and Oregon Health & Science University suggests.

That's good news for the estimated 35 percent of the U.S. adult population that suffers from the syndrome.

A patient is considered to have metabolic syndrome if he or she has at least two of the following conditions: abdominal obesity, high blood pressure, high blood sugar, low levels of "good" cholesterol, and high levels of triglycerides.

A diet high in saturated fat results in chronic low-grade inflammation in the body that in turn leads to the development of metabolic syndrome, a serious condition associated with cognitive dysfunction and dementia as well as being a major risk factor for cardiovascular disease and type 2 diabetes.

Led by corresponding authors Fred Stevens and Jacob Raber, the research focused on xanthohumol (XN), a prenylated flavonoid from hops, and two of its hydrogenated derivatives: DXN and TXN.

"We've studied xanthohumol for many years," said Stevens, professor of pharmaceutical sciences in the OSU College of Pharmacy and a principal investigator at Oregon State's Linus Pauling Institute. "We think what we have now is a big improvement."

Stevens explained that while earlier research had suggested XN could be an effective treatment for metabolic syndrome, the problem is that it transforms into 8-prenylnaringenin, or 8-PN, an estrogenic metabolite. Estrogens are the female sex hormones.

"We were always criticized about the potential side effects because 8-PN

is one of the most potent phytoestrogens known in nature, and that's not good news," he said. "If someone took XN over longer periods of time, it could lead to estrogenic side effects, potentially."

Those include endometriosis and breast cancer – most types of breast cancer are sensitive to estrogen, meaning that estrogen helps tumors grow.

"A double bond in the XN molecule is responsible for that 8-PN metabolism to be possible, so I thought if I could get rid of that double bond by hydrogenating the molecule, then that metabolite cannot be formed anymore," Stevens said. "I thought maybe this is the solution to the problem."

Stevens was right. Testing in a mouse model showed that XN and its hydrogenated derivatives, XN and TXN, improve glucose intolerance and insulin resistance, and sensitivity to leptin – a hormone that tells you to feel full when you've eaten enough and also helps regulate energy expenditure.

Best of all, the derivatives were even more effective than the original compound, without leading to that worrisome estrogenic metabolite or showing much affinity themselves for estrogen receptors.

"TXN is especially potent in reducing insulin resistance in mice made obese by feeding a high-fat diet," said Cristobal Miranda, an associate professor at the Linus Pauling Institute who was involved in the research.

"Probably the bioavailability of the hydrogenated derivatives is better than for XN itself – that would explain why they work better," Stevens added. "Now we have compounds that still have the original beneficial effects but not the side effects. There are no adverse estrogenic effects, and the liver toxicity induced by the high-fat diet is mitigated. Our

mouse study showed that XN, DXN and TXN are not hepatotoxic."

Testing mice in a water maze, researchers found XN and its derivatives ameliorated impairments in spatial learning and memory induced by the high-fat diet the mice had been fed.

"These findings could be important for people suffering from cognitive impairments associated with a high-fat diet and metabolic syndrome," said Raber, professor of behavioral neuroscience, neurology and radiation medicine at the OHSU School of Medicine.

Raber is also an affiliate scientist in the division of neuroscience at the Oregon National Primate Research Center.

"Our findings with rodents suggest that that it may be possible to reduce or even prevent learning and memory impairments through a derivative of the same chemical compound found in beer," he said.

Results were recently published in *Scientific Reports*.

Provided by Oregon State University

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