

Grapefruit's bitter taste holds a sweet promise for diabetes therapy

August 25 2010

Naringenin, an antioxidant derived from the bitter flavor of grapefruits and other citrus fruits, may cause the liver to break down fat while increasing insulin sensitivity, a process that naturally occurs during long periods of fasting.

A team of researchers from the Hebrew University of Jerusalem and Massachusetts General Hospital (MGH) report that naringenin activates a family of small proteins, called nuclear receptors, causing the liver to break down [fatty acids](#). In fact, the compound seems to mimic the actions of other drugs, such as the lipid-lowering Fenofibrate and the anti-diabetic Rosiglitazone, offering the advantages of both. If the results of this study extend to human patients, this dietary supplement could become a staple in the treatment of hyperlipidemia, type-2 diabetes, and perhaps [metabolic syndrome](#). The report appears in this week issue of the online journal [PLoS ONE](#).

"It is a fascinating find," says Yaakov Nahmias, PhD, of the Hebrew University of Jerusalem the paper's senior author. "We show the mechanism by which naringenin increases two important pharmaceutical targets, PPAR α and PPAR γ , while blocking a third, LXR α . The results are similar to those induced by long periods of fasting".

The liver is the main organ responsible for the regulation of carbohydrate and lipid levels in the blood. Following a meal, the blood is flushed with sugars, which activate LXR α , causing the liver to create fatty acids for long-term storage. During fasting, the process is reversed;

fatty acids are released by fat cells, activate PPAR α in the liver, and are broken down to ketones.

A similar process, involving PPAR γ , increases sensitivity to insulin.

"It is a process which is similar to the Atkins diet, without many of the side effects," says Martin L. Yarmush, MD, PhD, director of the MGH Center for Engineering in Medicine and one of the paper's authors.

"The liver behaves as if fasting, breaking down fatty acids instead of carbohydrates." Yarmush is the Helen Andrus Benedict Professor of Surgery and Bioengineering at Harvard Medical School.

"Dual PPAR α and PPAR γ agonists, like naringenin, were long sought after by the pharmaceutical industry," says Nahmias, "but their development was plagued by safety concerns. Remarkably, naringenin is a [dietary supplement](#) with a clear safety record. Evidence suggests it might actually protect the liver from damage."

Grapefruit's bitter taste is caused the presence of the flavonoid naringin, which is broken down in the gut into naringenin. Earlier evidence has shown the compound has cholesterol lowering properties and may ameliorate some of the symptoms associated with diabetes. The researchers demonstrated that the compound activates PPAR α and PPAR γ by dramatically increasing the levels of a co-activator peptide of both, called PGC1 α . At the same time, naringenin bound directly to LXR α , blocking its activation. These effects culminated with increased fatty acid oxidation and the inhibition of vLDL ('bad cholesterol') production.

More information: Goldwasser J, Cohen PY, Yang E, Balaguer P, Yarmush ML, et al. (2010) Transcriptional Regulation of Human and Rat Hepatic Lipid Metabolism by the Grapefruit Flavonoid Naringenin: Role of PPAR α , PPAR γ and LXR α . PLoS ONE 5(8): e12399.

[doi:10.1371/journal.pone.0012399](https://doi.org/10.1371/journal.pone.0012399)

Provided by Public Library of Science

Citation: Grapefruit's bitter taste holds a sweet promise for diabetes therapy (2010, August 25)
retrieved 4 April 2024 from

<https://medicalxpress.com/news/2010-08-grapefruit-bitter-sweet-diabetes-therapy.html>

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