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EDITORIAL

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Natural Extracts as Modifiers of Intracellular Lipid Handling

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Article commented

Rojas A, Gallego P, Gil-Gómez A, Muñoz-Hernández R, Rojas L, Maldonado R, Gallego R, *et al.*
Natural extracts abolished lipid accumulation in cells harbouring non favourable PNPLA3 genotype.
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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions ranging from simple liver fat accumulation to inflammation and fibrosis, and ultimately to cirrhosis and liver cancer. NAFLD prevalence is increasing worldwide and it is expected to be the main reason for liver transplantation in the next decade. Although NAFLD in its early stages can be resolved by dietary modifications and lifestyle changes (weight loss),[1] liver transplantation is the only existing treatment for the later stages of the disease. There is no drug approved as a specific treatment against NAFLD although vitamin E has shown to reduce NAFLD with a modest effect.[2] Based on antioxidant effects, natural compounds including resveratrol, quercetin and anthocyanin have been proposed as treatment against NAFLD.[3]

In this edition of *Annals of Hepatology,* Rojas, *et al.* examined the effect of quercetin and natural extracts from mushroom and artichoke, on reducing intracellular neutral lipid content in human hepatic cells. Specifically, Huh7.5 homozygous for *Patatin-like phospholipase domain-containing 3 (PNPLA3)* I148M (rs738409) variant were incubated with oleic acid to increase intracellular neutral fat. Cells were subsequently treated with quercetin or with natural extracts from mushroom or artichoke, and lipid droplet content and size were measured by fluorescence microscopy. Authors found that quercetin reduces both lipid droplet content and size; aqueous extracts from mushroom and artichoke had similar effects. Next, to understand the mechanism behind the reduction of intracellular neutral fat content, authors measured the expression levels of genes involved in lipogenesis *(SREBP-1c, PPAR γ, ACAT1, FASN, DGAT1,* and *DGAT2)*, lipolysis (*PPARα*), and lipid secretion (*MTTP*, *APOB*, and *APOE*).

The main finding of this study is that quercetin decreases de novo lipogenesis and increases lipolysis in human hepatocytes. In particular, quercetin treatment decreases the expression of *SREBP-1c* and increases the expression of *PPARa.* A similar trend was found with the artichoke extract. Additionally, in this *in vitro* model of steatosis, quercetin down-regulates genes involved in very low density lipoproteins (VLDL) secretion.

A caveat of this study is that Huh7.5 cells are homozygous mutant for the *PNPLA3* (rs738409) I148M variant. The *PNPLA3* I148M represents the most widely replicated genetic variant associated with the entire spectrum of liver disease.[4,5] *PNPLA3* is a membrane-bound protein highly expressed in hepatocytes and hepatic stellate cells. It is a lipase[6] involved in hepatic triglycerides[7] and retinol metabolism,[8,9] and the I148M substitution is a loss of function of the lipase activity. Importantly, in humans the I148M is associated with lower *de novo* lipogenesis and lower expression of the lipogenic transcription factor *SREBP-1c* despite a substantial increased hepatic fat content.[10]

The importance of this study resides in using cells homozygous for the main NAFLD risk gene variant. It would be interesting to know whether the same effect would be found in the same cells with reversion of the *PNPLA3* gene to its wild type form. If this would not be the case, this study reinforces the concept of "one diet does not fit all".

In conclusion, the study by Rojas, *et al.* strengthens the role of quercetin in reducing intracellular fat content in NAFLD, and it helps to understand the molecular mechanisms behind this reduction.

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Further studies are needed to confirm and understand the effect of artichoke and mushroom extracts in other immortalized or primary hepatic cells and *in vivo.* Moreover, as the authors stated, it would be interesting to test the specific effect of each single compound included in the aqueous extracts.

DISCLOSURES

No disclosures.

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