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Review

Beneficial effects of the Mediterranean spices and aromas on non-alcoholic fatty liver disease

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) can be regarded as the hepatic manifestation of metabolic syndrome (MS), which has a high prevalence in Western-lifestyle countries. NAFLD can progress to more severe pathologies such as cirrhosis and fibrosis, thus worsening individuals' life quality and increasing health costs. In the last decades, many efforts have been made in order to understand the molecular mechanisms of NAFLD and how to cure it. It has become clear that alimentary regimen is of primary importance for preventing/treating MS and NAFLD.

Scope and approach: Beneficial effects of the Mediterranean diet (MedDiet) on MS and NAFLD are now recognized and can be ascribed to low calories intake but also to abundance of anti-oxidant and anti-inflammatory compounds which are present in fruit and vegetables as well as in herbs and spices widely used to flavor traditional Mediterranean dishes. The aim of this review is to summarize briefly NAFLD molecular pathways and therapies, while focusing on the beneficial effects and mechanisms of action of the most used Mediterranean aromatic plants and spices (MAPS).

Key findings and conclusions: All MAPS reviewed here have been documented to exert hepatoprotective actions and almost the totality has a direct or indirect lipid-lowering effect on the liver, accompanied by amelioration of other MS parameters. We suggest that culinary MAPS use can contribute to the health benefits of MedDiet without the danger of adverse effects that can occur when the active compounds are used in pharmacological doses.

1. Introduction

Metabolic Syndrome (MS) is a multifactorial disorder, frequently occurring in obese patients, with a combination of cardiometabolic risk determinants, which can increase morbidity and mortality of individuals (Bruce & Byrne, 2009). Non-alcoholic fatty liver disease (NAFLD) consists in the hepatic manifestation of MS and shows rising prevalence among individuals from different ages and incomes worldwide (Seidell & Halberstadt, 2015). NAFLD encompasses a wide spectrum of diseases ranging from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and fibrosis, in the absence of an excessive alcohol consumption (Anstee, McPherson, & Day, 2011). The incidence of NAFLD, obesity and MS has augmented due to increasing excessive food intake, along with sedentary lifestyle, especially in Western-lifestyle societies.

Although many efforts have been made, no pharmacological treatment is developed to effectively prevent and/or cure NAFLD and liver progression to more severe pathologies.

One of the most effective therapies is to change the lifestyle by increasing physical activity and reducing intake of calories. The Mediterranean diet (MedDiet) is one of the most successful therapeutic tool for treating obesity and NAFLD, thus ameliorating MS outcome. The recipes of Mediterranean-style cooking also include the frequent use of aromatic plants and spices (MAPS), which are widely documented sources of many bioactive and non-nutritive

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compounds, mainly polyphenols (Davis, Bryan, Hodgson, & Murphy, 2015). The latter are flavonoids, water-soluble plant-derived components with widely documented antioxidant properties *in vitro* (Zamora-Ros et al., 2010). The chemical structure of the main anti-steatotic compounds present in MAPS is depicted in Table 1.

In this review, we summarize the mechanisms underlying NAFLD onset and focus on the strengthening effects of MAPS use associated with MedDiet.

1.1. NAFLD and molecular pathways

There are different mechanisms or causes proposed to lead to steatosis: an increase in free fatty acids (FFAs) due to increased lipolysis or increased fat intake by diet; decreased FFA oxidation; increased hepatic *de novo* lipogenesis (DNL) due to excessive dietary fructose or decreased hepatic triacylglycerol (TAG) secretion through very low density lipoprotein (VLDL) (Fabbrini et al., 2008; Lustig, 2013; Stanhope, 2016). It has been shown that more than 60% of the lipid accumulation in the liver is represented by FFA delivery to it (Donnelly et al., 2005). The excessive energy intake yields white adipose tissue (WAT) hypertrophy and hyperplasia, which determines a low grade inflammation and triggers insulin resistance (IR) in obese individuals (Yilmaz, 2012). The consequent hyperinsulinemia leads to enhanced lipolysis in WAT, which diverts excessive FFAs to the liver. Meanwhile, IR reduces β-oxidation capacity within hepatocytes (Angulo, 2007). Whenever hepatic fatty acids input (derived from hepatic DNL and/or uptake of FFAs or chylomicrons/remnants) exceeds hepatic β-oxidation and/or lipoprotein exportation, lipid droplets accumulate within hepatic parenchyma, configuring NAFLD (Angulo, 2007). Genetic aspects can play a role in NAFLD progression as they do in obesity and IR, given that they are all strongly overlapped. In these terms, MS and its components are predictors and also risk factors for NAFLD (Hamaguchi et al., 2005).

In terms of the pathogenesis of NAFLD, gut derived factors, systemic inflammation and both biochemical and psychological stress have been described to play important roles (Demori & Grasselli, 2016).

The two-hit hypothesis postulates that if hepatic inflammation occurs, coupled with enhanced oxidative stress, NAFLD progresses to NASH (Paschos & Paletas, 2009). This condition implies a greater lipid accumulation than NAFLD and morphophysiological alterations that drive hepatocyte injury and predispose to liver fibrosis or even to hepatocellular carcinoma (De Minicis, Day, & Svegliati-Baroni, 2013). The understanding of the molecular pathways related to NAFLD is useful to avoid its harmful progression. In this context, peroxisome proliferator activated receptors (PPARs) are a family of three transcription factors that act through transactivation or transrepression of genes found at the crossroads of many metabolic pathways involved with hepatic β-oxidation of FFAs, hepatic insulin signaling and inflammation. Therefore, the study of their molecular mechanisms and the identification of their agonists and/or antagonists are relevant to NAFLD treatment and/or prevention (Souza-Mello, 2015).

In obesity experimental models, reduced PPARα hepatic expression is a hallmark of NAFLD, provoking reduced mitochondrial β-oxidation owing to decreased carnitine palmitoyltransferase1 (CPT1) expression, which is responsible for FFA transport through the inner mitochondrial membrane. PPARα activation augments mitochondria density *per* area of hepatic tissue and markedly reduces hepatic steatosis percentage in obese mice (Magliano et al., 2013; Souza-Mello et al., 2010). Moreover, PPARα plays a decisive role in preventing hepatic stellate cell activation and liver inflammation, both of which comply with progression to NASH (Berlanga, Guiu-Jurado, Porras, & Auguet, 2014).

Conversely, PPARγ plays a pivotal role in hepatic DNL as it controls the expression of lipogenic enzymes such as fatty acid synthase (FAS) and sterol regulatory element-binding protein 1c (SREBP1c), both overexpressed in lipotoxicity and models of obesity (Barbosa-da-Silva et al., 2015; Magliano et al., 2013). Of note, high-fructose intake increases DNL through the induction of SREBP1c, which elicits an impressive production of acetyl-coA, a DNL substrate. Moreover, fructose induces the carbohydrate response element binding protein (ChREBP), which enhances malonyl-coA production, impairing β-oxidation (Lim, Mietus-Snyder, Valente, Schwarz, & Lustig, 2010; Softic et al., 2016).

Regarding PPARβ/δ activation, it promotes body mass reduction, which alleviates both IR and NAFLD. Also, FFA utilization by hepatocytes is highly influenced by PPARβ/δ target genes such as fatty acid translocation/CD36 (FAT/CD36), involved in long-chain FFA uptake by mitochondria and FFA transport within hepatocytes; pyruvate dehydrogenase kinase 4, which favors FFA oxidation instead of glucose oxidation; and CPT1 (Magliano, Penna-de-Carvalho, Vazquez-Carrera, Mandarim-de-Lacerda, & Aguila, 2015; Salvado, Serrano-Marco, Barroso, Palomer, & Vazquez-Carrera, 2012). Moreover, reduced hepatic glucose production due to reduced forkhead box protein O1 (FOXO-1) expression after PPARβ/δ activation is crucial to tackle IR and NAFLD (Zhang et al., 2012). Of note, an interplay between PPARα and PPARβ/δ happens as the activation of the latter leads to enhanced AMP-activated protein kinase (AMPK) activity, which amplifies the PPARγ coactivator 1-α (PGC-1α)/PPARα signaling and favors CPT1 transcription and FFA oxidation within hepatocytes (Barroso et al., 2011). Fig. 1 summarizes the influence of PPAR modulation on NAFLD pathogenesis as well as the influence of high-fat or high-fructose intake upon NAFLD onset.

1.2. NAFLD treatment

1.2.1. Pharmacological treatment of NAFLD

Weight loss, diet and exercise seem to be the mainstay of NAFLD treatment; nevertheless, different drugs are being used in the attempt to ameliorate metabolic parameters and eventually mend the patient state. Some weight loss medications are effective, but it has been shown that they can exert some side effects if they are not continuously taken. The withdrawal effects of these drugs are variable among substances and need to be further studied (Johansson, Neovius, DeSantis, Rössner, & Neovius, 2009).

Among these, the PPAR targets thiazolidinediones (TZDs) or 'glitazones' are the most studied. These oral drugs improve metabolic control in patients with type 2 diabetes mellitus (T2DM) by ameliorating insulin sensitivity (Hauner, 2002). Unfortunately, the use of TZDs can cause cardiovascular and other adverse effects, demonstrating to be not completely safe as anti-obesity drugs (Juurlink et al., 2009).

Metformin has also demonstrated to improve NAFLD as a result of its impact over insulin sensitivity and body weight; however, as it only exerts effects on these factors and not directly on the liver, it has not been recommended as first-choice treatment for the disease (Chalasani et al., 2012).

A high percentage of the studies about statin treatment shows an improvement in transaminases and steatosis and a slowdown in the progression of NAFLD into NASH. Hence, they are mainly endorsed by literature to be used in patients with NAFLD and hyperlipidemia (Chalasani et al., 2012).

Thyroid hormone natural derivatives, such as 3,5diiodo-L-thyronine (T_2), are promising compounds since they exert direct anti-steatotic effect in both *in vitro* and *in vivo* rat models of NAFLD (Grasselli et al., 2011, 2012, 2014). T_2 has been documented to act