Short Communication

Pathogenesis and complications of non-alcoholic steatohepatitis and its management by nutraceuticals

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Abstract

Non-Alcoholic Steatohepatitis (NASH) is a real health problem that is commonly associated with obesity and diabetes. Cardiovascular diseases, liver carcinoma, and liver failure might develop from NASH if not well managed. The present article deals with the pathogenesis of non-alcoholic steatohepatitis and its complications in addition to exploring the importance of using nutraceuticals in its prevention and treatment.

Non-Alcoholic Fatty Liver Diseases (NAFLD) affect more than 20% of the world population. The spectrum of NAFLD includes simple steatosis, steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and hepatic failure. Steatosis is a simple deposition of fat in the liver, steatosis does not represent a health problem however progression to Non-Alcoholic Steatohepatitis (NASH) would be the real health problem since NASH is a risk factor for cardiovascular diseases (CVDs) and on the other hand might be advanced to liver cirrhosis, hepatocellular carcinoma and might be ended by liver failure [1-4].

A sedentary lifestyle, overnutrition, inflammation, oxidative stress, insulin resistance, genetic factors, and lipotoxicity have a strong correlation with the incidence of NASH. Excessive consumption of fructose and saturated fat might exacerbate the induction of NASH. Fructose elevates lipid lipogenesis in the liver through the de novo pathway and produces a reduction of beta-fatty acids oxidation [2,5].

Metabolic syndrome includes a cluster of components comprising fatty liver, dyslipidemia, visceral obesity, glucose intolerance, insulin resistance, and hypertension [6]. Obese and diabetic subjects are more commonly suffering from steatosis than normal. Patients with NAFLD were demonstrated to have high glycosylated hemoglobin, obesity, elevated or normal Alanine Transaminase (ALT) and normal Aspartate Transaminase (AST) however in more advanced stages they might show AST/ALT to be 0.8 [7]. It is worth mentioning that elevations in ALT and AST are indicative of liver damage.

The pathophysiology of NASH is not well understood however insulin resistance has been reported to influence hepatic, muscle, and adipocytes metabolisms of fat and sugar which leads to deposition of lipids in the hepatocytes. Fat deposition by itself in the liver could lead to increased oxidative stress and inflammation. Leptin resistance due to malfunctioning of its receptor might also contribute to NASH development [8]. Reduced adiponectin that induces hepatic inflammation is commonly encountered in obese, NASH, and diabetics [9]. Therefore the role of adipokines, leptin and adiponectin, cannot be ignored in NASH progression which is mediated by elevated oxidative stress [2]. The imbalance of colonic microbiota has been proposed as one of the major causes of NASH due to transforming inflammation in the liver with further modulation of liver pathology by microbiota.
metabolite [10].

So far there is no efficient remedy for NASH [11,12] however insulin sensitizers like biguanides (metformin), lipid-lowering drugs like statins and other therapies such as urodeoxycholic acid and pentoxyfylline might be used [13]. Natural agents that could be beneficial are under experimental investigations. From the natural products; nutraceuticals are functional food ingredients purified from food and are considered safe natural products that could be efficient in mitigating steatohepatitis. There are no internationally agreed definitions of nutraceuticals and functional foods [14]; however, they are considered midway between food and pharmaceuticals. The best definition that I prefer is that nutraceuticals are bioactive constituents prepared from food and can treat or prevent one or more chronic diseases and sold in the form of pharmaceuticals meanwhile functional food is a food rich in bioactive ingredients and can prevent one or more chronic diseases and consumed in form of food. Our research team investigated the potential beneficial effect of nutraceuticals that could be efficient in the protection/treatment of NASH through a series of researches (Figure 1).

Nutraceuticals composed of chitosan, and ferulic acid were shown to be efficient in treating steatohepatitis, the nano-form of such nutraceuticals showed superiority in this respect [15]. The mechanism was related to reducing insulin resistance, oxidative stress, inflammation (represented by high sensitivity C-reactive protein and adiponectin) liver triglycerides and total cholesterol.

*Nigella sativa* crude oil extracted by a screw press machine was shown to prevent inflammatory fatty liver and dyslipidemia in experimental rats and has antioxidant and anti-inflammatory activity [16]. It reduced Low-Density Lipoprotein–Cholesterol (LDL-C), Total Cholesterol (TC), and Triglycerides (TG) and elevated High-Density Lipoprotein–Cholesterol (HDL-C) together with reduction of malondialdehyde and tumor necrosis factor—α and improved liver function which was ascribed to the presence of 1% volatile constituents in the crude oil with major compounds represented by p-cymene and thymoquinone. Phytosterols especially β-sitosterol in addition to gamma and α-tocopherols in crude oil could also participate in the prevention of NASH [17,18].

Quinoa seeds were reported to be a good source of both lipophilic and hydrophilic nutraceuticals that could improve fatty liver due to the presence of α-tocopherols, linolenic fatty acids, phenolic compounds with protocatechuic, para hydroxybenzoic, ferulic and cinnamic acid as the major phenolic acid and rutin, chrysin and luteolin as the prominent flavonoids in two varieties of quinoa. Both nutraceuticals possess *in-vitro* and *in-vivo* antioxidant effects, with hypolipidemic, anti-inflammatory, and liver lipid-lowering effects with the improvement of liver and heart histopathology in rats. They produced a reduction in body weight gain and TC/HDL-C therefore reducing the risk of CVDs [19,20].

Clove essential oil conventional emulsion, eugenol nano-emulsion, the main constituent of the essential oil, and the nano-emulsion of the essential oil were studied in rats with dietary-induced fatty liver. The study showed that the three preparations improved fatty liver and dyslipidemia with protection from cardiovascular diseases and fatty liver complications [21].

The potential protective effect of Basil Essential Oil (BO) and its Nano-Emulsion (BNO) was studied towards NASH in rat models. Both treatments produced significant protection from NASH through a reduction in liver lipids, plasma TC, TG, LDL-C, TG/HDL-C, lipocaline, and interleukin–6. Microbiota represented by *Firmicutes/Bacteriodetes* (F/B) was improved. BNO was superior in reducing the F/B ratio, liver lipids, and liver histopathological changes while BO was more efficient in reducing TC, TG, and LDL-C. The therapeutic effect of BO and BNO was ascribed to the presence of linalool, eugenol, and eucalyptol as bioactive constituents [22].

**Conclusion**

Steatohepatitis is a serious condition that is commonly present in diabetics and obese subjects. Steatohepatitis is accused of developing cardiovascular diseases and might progress to hepatocellular carcinoma and liver failure. Experimental studies showed efficient nutraceuticals for the protection and treatment of NASH. The sources of such nutraceuticals are represented by *Nigella sativa*, quinoa, clove seed, and basil. Consumption of such sources in daily life could be beneficial in the prevention of steatohepatitis. Other nutraceuticals prepared from chitosan and ferulic acid showed efficiency in treating steatohepatitis and prevention of its complications. Prospective clinical studies are needed for confirmation of the efficiency of such nutraceuticals in humans.

**References**


