Review Article

Polyphenols treatment in patients with nonalcoholic fatty liver disease

Ludovico Abenavoli[1], Natasa Milic[2], Francesco Luzza[1], Luigi Boccuto[3], Antonino De Lorenzo[4]

[1]Department of Health Sciences, University Magna Græcia, Campus Germaneto, Viale Europa, 88100 Catanzaro, Italy;
[2]Department of Pharmacy, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia;
[3]Greenwood Genetic Center, 113 Gregor Mendel Circle, 29646 Greenwood, SC, USA;
Clemson University School of Health Research, 101 Calhoun Drive, 29634 Clemson, SC, USA;
[4]Division of Clinical Nutrition and Nutrigenomics, Department of Biomedicine and Prevention, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) affects 25–30% of the general population worldwide and this high prevalence is linked with lifestyle and dietetic changes, not only in Western countries, but also in the urban areas of developing countries. Several pharmacological approaches were proposed in the treatment of NAFLD, but the reported results are inconclusive. International guidelines recommended the reduction of dietary fat and fructose, in association with some physical activity. In this context, it was reported that the protective effects of traditional Mediterranean diet, related to the high concentration of antioxidant compounds, particularly of polyphenols. Polyphenols are a heterogeneous class of plant derived compounds, with some proven hepatoprotective effects. Our opinion is that the adherence to traditional Mediterranean diet characterized by the consumption of antioxidant-rich foods in general and of polyphenols in particular, can be considered as a potential new approach in the treatment of NAFLD.

Key words: nonalcoholic fatty liver disease, steatosis, polyphenols, Mediterranean diet, antioxidant

Address for Correspondence:
Dr. Ludovico Abenavoli, M.D. Ph.D., Professor, Department of Health Sciences, University Magna Græcia, Viale Europa - Germaneto, 88100, Catanzaro, Italy.
Email: l.abenavoli@unicz.it

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INTRODUCTION

In the last few decades, the term nonalcoholic fatty liver disease (NAFLD) has been evoked increasingly in research frameworks and in clinical practice. It defines the presence of significant fat accumulation in the liver (> 5% of hepatocytes), in the absence of alcohol abuse and any other cause of liver diseases.[1] The term NAFLD includes different clinical entities, and in particular, the fat accumulation in liver, also known as simple fatty liver and nonalcoholic steatohepatitis (NASH); it is characterized by steatosis along with necroinflammation, fibrosis and finally cirrhosis with its complications. NAFLD is a pathological entity histologically characterized by the presence certain symptoms in the liver, such as cellular ballooning, lobular inflammation, perisinusoidal and perivenular fibrosis, features hardly distinguishable from the ones detected in cases with alcoholic liver disease.[2] Insulin resistance, visceral fat mass, obesity, dyslipidemia, diabetes, and metabolic syndrome are well known risk factors largely associated to NAFLD.[3] Studies on genetic and molecular mechanisms predisposed to NAFLD highlight the role of variants enhancing oxidative stress, pro-inflammatory profile of circulating cytokines, and abnormalities in the metabolism of glucose and fatty acids.[4,5] NAFLD affects 25–30% of the general population; however, prevalence change in function of gender, age, ethnicity and metabolic features.[6]. The worldwide spread of NAFLD diagnosis is clearly linked with changes in dietary profiles and increased sedentary lifestyle, not only in Western countries but also in urban area of developing countries.[6]

Several pharmacological treatments have been proposed for the treatment of NAFLD, but the reported results are

inconclusive.[7] International recommendations indicate that the first therapeutic step for the treatment of NAFLD is to reduce the intake of total fat, saturated fatty acids, trans fatty acids and fructose, along with undergoing physical activity.[8]

MEDITERRANEAN DIET

The profile of NAFLD patients is characterized by higher dietary energy and higher simple carbohydrate intake, as compared with the healthy controls.[3,9] The standard care to treat NAFLD patients is focused on lifestyle interventions, and in particular, healthy diet and physical exercise. In this way, literature has reported the benefits of Mediterranean diet. In November 2010, UNESCO officially recognized the Mediterranean diet as an Intangible Cultural Heritage of Humanity and defines it as a "set of traditional practices, knowledge and skills passed on from generation to generation, providing a sense of belonging and continuity to the concerned communities".[10] Mediterranean diet is a way of eating, rather than a formal diet plan. The exact Mediterranean diet is difficult to define precisely, if considered that Mediterranean region is a virtual geographic area that represents many cultures and lifestyles. There are major differences in the dietetic profile between different countries and between some regions within a country, for example, as found in Italy. However, the traditional Mediterranean diet can be represented by a pyramid characterized by high consumption of cereals and vegetables, such as salads, pulses/legumes, bread, pasta, fruits and nuts, and lower intakes of eggs and sweets[11,12] (Figure 1). Extra-virgin olive oil is the main source of fat with a moderate intake of fish, poultry, eggs and dairy products. In addition, moderate amounts of red wine are usually consumed with meals in the European region of the Mediterranean area.[13]

Adherence to the traditional Mediterranean diet is associated with low mortality risk and reduced incidence of chronic diseases, and in particular, cardiovascular and metabolic disorders, neurodegenerative diseases, depression and several types of cancer.[14,15] These protective effects are related to the high concentration of antioxidants in compounds of this diet. Since the 1950s, Ancel Keys and his co-workers have been studying the Mediterranean diet effects on health, and they found that Greek people, especially belonging to the island of Crete, had the longest life expectancy in the world until the 1960s, followed by the people of Southern Italy, Spain and France.[16] These data were confirmed by subsequent studies on the elderly population in Greece and other European Countries, and showed that the Mediterranean dietary pattern *in toto* influenced the longevity rather than a single nutrient in the diet, with a significant reduction in the overall mortality.[17] This assumption is a cornerstone for public health, and in particular, in the context of prevention policy based on the Mediterranean style in the primary prevention of major chronic diseases not only in Western Countries, but also in all urban area worldwide.[18]

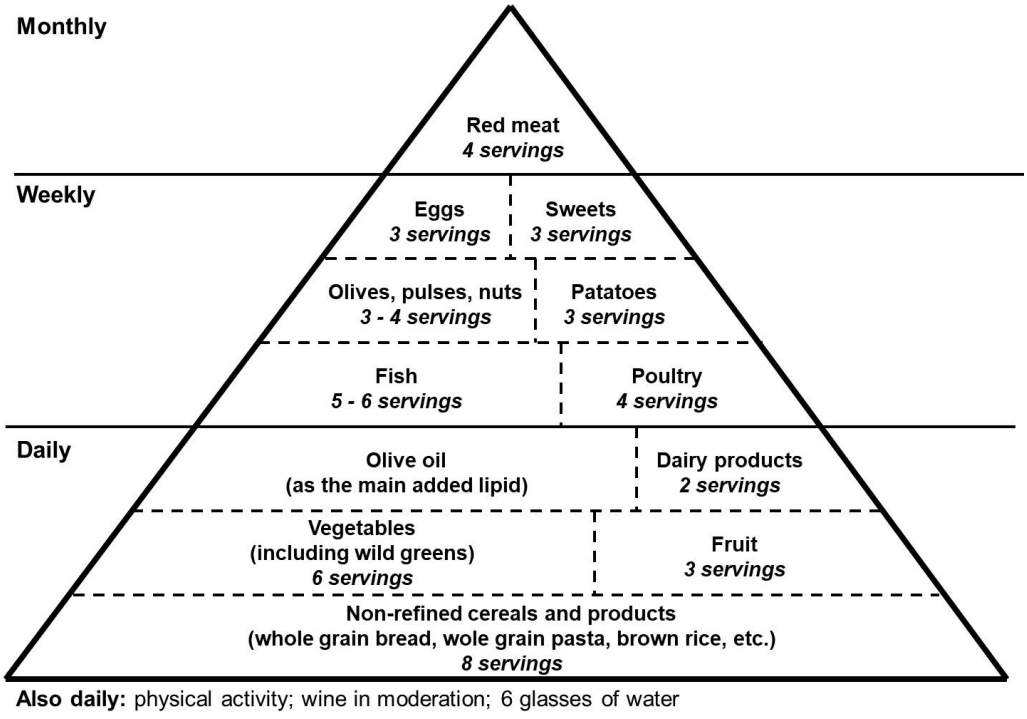

Figure 1: the traditional Mediterranean diet pyramid.

POLYPHENOLS AND NAFLD

Polyphenols are a heterogeneous class of plant derived compounds, that include several hydro soluble antioxidants reported as health promoting agents and proposed in the treatment of different metabolic disorders.[19,20] Fruits, vegetables, beverages including coffee, tea, red wine, and dark chocolate are the important sources of these bioactive compounds. On the basis of their chemical structure, two categories of polyphenols are described: the flavonoids containing a common diphenylpropane skeleton (e.g., flavonoids, flavones, flavanols, flavonols, isoflavones, proanthocyanidins and anthocyanins); the non-flavonoids, mainly comprising mono-phenols alcohols (e.g., hydroxytyrosol) or stilbene phenolic acids (e.g., resveratrol).[20] In the short-term, polyphenols are not essential for life such as vitamins, however, nowadays they are considered responsible for the beneficial effects of fruits and vegetables. Their potential role in the prevention and treatment of oxidative stress and inflammation has been investigated recently.[21] In particular, polyphenols may present hepatoprotective effects by increasing the fatty acid oxidation and modulation of insulin resistance, oxidative stress and inflammation, which are the main pathogenetic factors linked to the progression from simple fat accumulation to NASH.[20] Several evidences *in vitro,* pre-clinical and emerging clinical trials reported beneficial effects on liver steatosis and its pathogenic and clinical setting.[20-23]

Few clinical studies were focused on the polyphenols use in NAFLD patients. Three were undertaken with 500 mg and 600 mg resveratrol daily for 12 weeks, or 3000 mg daily for 8 weeks respectively.[24-26] Other two studies were carried out using 150 mg polyphenols (1.43% of flavonoids, 2.5% anthocyanins and 1.7% phenolic acid) extract of *Hibiscus sabdariffa* L. or 1350 mg of bayberry juice, daily for 12 weeks and 4 weeks in overweight and in young adults with NAFLD, respectively.[27,28] Finally, one study utilized 250 mL of pomegranate juice or orange juice per day associated with hypocaloric diet over a period of 12 weeks.[29] Some studies reported a significant impact of polyphenols' importance on NAFLD. Chang *et al.* and Ekhlasi *et al.* showed a significant improvement of anthropometric parameters after treatment with polyphenols.[27,29] Faghihzadeh *et al.* observed a reduction in weight, body mass index, waist circumference, liver enzymes, and steatosis degree, while resveratrol was associated with lifestyle changes and particularly with physical activity.[24] The reduction of serum transaminase levels was also noted by Chen *et al.* in association with a significant improvement of insulin resistance assessed by homeostasis model assessment insulin resistance index.[25] The polyphenols used by humans through consumption of the bayberry juice and resveratrol showed anti-inflammatory effects, with a reduction in serum cytokines and in particular of TNF-α, interelukin-6 and -8, and increased serum levels of adiponectin.[24,25,28] In addition, Faghihzadeh *et al.* described a reduction in NF-ϰB activity in the peripheral blood mononuclear cells.[24] Finally, Ekhlasi *et al.* reported the reduction of high liver enzymes and improvement of total antioxidant capacity in the NAFLD patients treated with pomegranate juice.[29] Nowadays, data on the effects of polyphenols in the histology of NAFLD, assessed by liver biopsy, are absent. However, the information obtained by non-invasive tools like the liver ultrasound reported a significant improvement of liver damage and liver steatosis degree when polyphenol supplementation is associated with lifestyle changes.[24,25,28]

CONCLUSION

NAFLD is the liver board of over nutrition and an upcoming challenge for hepatologists and health systems worldwide. Patients with liver steatosis have an increased prevalence of chronic diseases. Therefore, the treatment of NAFLD patients should be focused on reducing predisposing factors, such as insulin resistance, oxidative stress, and dyslipidemia. In this way, nutraceuticals may have an important role in the treatment of NAFLD. Supported by literature data, it can be concluded that adherence to the traditional Mediterranean diet characterized by the consumption of antioxidant-rich foods in general and of polyphenols in particular, can be considered as a potential new approach in the treatment of NAFLD, and even a valuable instrument of prevention of this disorder. Further studies are needed to define the achievable doses of individual polyphenols or select their combination.

Conflict of Interest

Authors declare no conflict of interest related to this publication.

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