Repairing mitochondrial dysfunction: potential mechanisms of natural products in the treatment of NAFLD

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Non-alcoholic fatty liver disease (NAFLD), also known as MAFLD, is a chronic liver disease characterized by dyslipidemia and excessive steatosis in hepatocytes [1]. With the acceleration of urbanization, the problems of physical activity reduction and nutritional imbalance are becoming increasingly prominent. The prevalence of NAFLD has reached 25% globally [2], and it is also showing a trend of continuous growth and younger onset age[3]. Although numerous studies have confirmed that the pathogenesis of NAFLD may be related to genetic susceptibility, gene polymorphism, intestinal microenvironment disorder, insulin resistance, and other factors [4], the "two-hit" theory also reveals the mechanism of the occurrence of some NAFLD, there is still a lack of effective and stable drugs that can inhibit the progression of NAFLD to liver fibrosis and even liver cancer in the treatment of NAFLD [5], which poses a serious threat to human health and imposes a heavy burden on the socio-economy [6]. It is particularly important to further explore the etiology and pathogenesis of NAFLD, providing ideas and directions for the development of new drugs against NAFLD [7].

Mitochondria are double-membrane organelles with multiple important biological functions and interconnections within cells, including mtDNA, which encodes 13 proteins and auxiliary RNAs related to mitochondrial oxidative phosphorylation in the mitochondrial matrix [8]. They participate in the biosynthesis of nucleotides, fatty acids, cholesterol, amino acids, and heme, and have functions such as regulating lipid metabolism, oxidative phosphorylation, and oxidative stress [9]. They play an important role in maintaining the dynamic balance between fat oxidation and ROS production in the liver, promoting stress responses such as autophagy to protect hepatocytes [10]. Mitochondria are crucial for the normal functioning of the liver, including a series of processes ranging from substrate metabolism and energy production to cell signaling, and then to the biotransformation of exogenous substances [11]. Accumulated recent studies revealed the importance of mitochondrial dysfunction during the progression of NAFLD. A recent review published in "Journal of Hepatology" by Bernard Fromenty et al. summarized the role of mitochondrial dysfunction in NAFLD pathogenesis. Excessive fatty acid could contribute to the dysfunction of hepatic mitochondria, characterized by abnormal morphological changes, reduced respiratory chain activity, ATP depletion, increased outer and inner membrane permeability, excessive ROS production, oxidative stress-mediated double-stranded circular mitochondrial DNA (mtDNA) deletion, and mitochondrial β oxidation damage, these abnormal manifestations could further aggravate the dysfunction of lipid metabolism in liver. When mitochondria are dysfunctional, it will promote the excessive production of ROS, induce oxidative stress, damage liver cells, and further promote the occurrence of inflammatory reactions and oxidative stress [12]. Therefore, by directly or indirectly intervening to repair the dysfunction of liver mitochondria, it can have beneficial effects on the prevention and treatment of NAFLD. Rector RS et al. [13] also confirmed this point. The research results found that mitochondrial dysfunction occurred before NAFLD in the liver of obese OLETF (a spontaneous type 2 diabetes model) rats, indicating that progressive mitochondrial dysfunction may be an important link in promoting the natural course of NAFLD (Figure 1).

Figure 1. The association between mitochondrial dysfunction and NAFLD. (By Pigdraw.)

Natural products are an important source for the development of new drugs, including extracts from animals, plants, or components or metabolites from microorganisms. They have the characteristics of diverse structures and a wide range of sources. Studies have shown that natural polyphenols represented by curcumin [14] and resveratrol [15], natural flavonoids represented by nobiletin [16] and silymarin [17], natural alkaloids represented by tomatidine [18] and berberine [19], and natural polysaccharides represented by angelica polysaccharide and Lycium barbarus polysaccharide [20] can alleviate the occurrence and development of NAFLD by regulating lipid and cholesterol metabolism, insulin sensitivity, liver oxidative stress, and liver inflammation in NAFLD model mice/rats. However, it has also been pointed out that the results of clinical trials targeting the treatment of NAFLD with natural products are not completely consistent with the results of animal experiments. For example, Heeboll S et al. [21] found that resveratrol intervention in NAFLD patients not only failed to benefit patients by improving insulin resistance, and may also cause some adverse reactions such as fever and dual blood cell reduction. Therefore, it is important to explore new potential therapeutic targets and verify the safety and effectiveness of these natural products in clinical applications. This will provide new possibilities for the search for biomarkers and the treatment of NAFLD.

Hymavathi R et al. [22] conducted an experiment using green tea extract (polyphenols) to intervene in NAFLD rats. The experimental results showed that green tea polyphenols can repair the damage to mitochondrial DNA in rat hepatocytes by reducing ROS levels, reducing the frequency of D-loop mutations in mtDNA, and affecting mitochondrial replication, transcription, and/or biogenesis, thereby
affecting mitochondrial function as a whole. Zhu Y et al. [23] also found that after intervention with ginsenoside Rg5 in NAFLD mice, mitochondrial mass in hepatocytes significantly increased, and the Sirt1/PGC-1α/mitofusin-2 mitochondrial biosynthesis pathway was activated, leading to significant improvement in liver oxidative stress and inflammation in mice, thereby exerting therapeutic effects on NAFLD. Sirt3 is mainly located in mitochondria and has a key role in regulating mitochondrial energy metabolism by deacetylating and modifying multiple mitochondrial proteins. Zhang L et al. [24] found that resveratrol can upregulate Sirt3 expression, improve mitochondrial ATP synthase activity and basal respiratory rate, thereby reducing fatty acid oxidation and triglyceride accumulation, and reducing ROS expression, stopping the vicious cycle of "mitochondrial dysfunction-oxidative stress-mitochondrial damage" in NAFLD to protect the liver, without any adverse reactions. Therefore, it can be inferred that repairing mitochondrial dysfunction may be a potential effective mechanism for natural products to treat NAFLD.

In recent years, people have gradually realized that NAFLD may be a 'mitochondrial disease', and the functional changes of liver mitochondria run through the occurrence and development of NAFLD, among which mitochondrial oxidative stress is a key factor in the progression of NAFLD. It will provide new ideas for the treatment of NAFLD and related metabolic diseases such as obesity, type 2 diabetes, cardiovascular disease to carry out in-depth research on promoting lipid peroxidation, inhibiting the generation of reactive oxygen species, maintaining mitochondrial homeostasis, protecting mitochondria, and develop natural products to target the intervention of NAFLD disease progress.

References

Competing interests
The authors declare no conflicts of interest.
Abbreviations
NAFLD, Non-alcoholic fatty liver disease.

Citation

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