

# Protective Effect of Polyphenols on Non-alcoholic Fatty Liver Disease

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Abstract: The incidence rate of non-alcoholic fatty disease (NAFLD) has increased in recent years due to poor dietary habits and lifestyle. However, there is no effective ways for the treatment of NAFLD. Therefore, looking for therapeutic agents for NAFLD has become a research hotspot. Polyphenols have attracted increasing attention for the treatment of NAFLD due to its excellent antioxidant and anti-inflammatory properties. They have been proved to exhibit the therapeutic potential for NAFLD. In this study, we aim to present an overview of the effect of polyphenols in the treatment of NAFLD.


## 1 INTRODUCTION


Nonalcoholic fatty liver disease (NAFLD) is the main cause of liver disease. It is closely related to a group of metabolic syndrome such as obesity, hyperlipidemia and insulin resistance (IR). It is a clinicopathological syndrome characterized by steatosis and fat accumulation of hepatic parenchymal cells. NAFLD is caused by excessive fat accumulation in the liver, especially triglycerides (TG) (Gaggini 2013, Labrecque 2014). The main cause of excessive liver fat is central obesity, which is closely related to insulin resistance (Gaggini 2013) NAFLD is the most common in liver diseases, with up to 27% of patients with fatty liver in China, and the age of onset is becoming younger and younger. In the past two decades, its prevalence has increased year by year and even doubled (Gaggini 2013, Labrecque 2014, Della Corte 2014, Karim 2015). The role of inflammatory cytokines, mitochondrial dysfunction and the damage of reactive oxygen free radicals can further worsen it (Labrecque 2014,


Byrne 2015). NAFLD, as a multisystem disease, may affect other organs and regulatory pathways, while increasing the risk of several other chronic diseases, such as type 2 diabetes, heart disease and chronic kidney disease (Gaggini 2013, Byrne 2015).


Polyphenols are a kind of natural metabolites produced by plants, which have a variety of protective effects on liver diseases and related diseases. After ingestion of polyphenols, polyphenols and their metabolites in human body can regulate lipid metabolism, improve oxidative stress, slow down the development of inflammatory response and insulin resistance, reduce liver fat content and enhance the expression of antioxidant enzymes through circulation (Al-Dashti 2018, Li 2014, Nguyen 2017). Therefore, our aim was to outline the role of polyphenols in the treatment of NAFLD. Moreover, compared with self-discipline methods such as improving eating habits, adjusting lifestyle and strengthening exercise, drinking more polyphenols has become a more attractive, simple and easy method to improve nonalcoholic liver injury.


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## 2 PROTECTIVE EFFECT OF NATURAL POLYPHENOLS ON NAFLD

### 2.1 Flavonoids

Silymarin is one of the most effective and common herbs in the treatment of NAFLD (Abenavoli 2010). Silymarin, a common flavonoid extracted from silymarin fruit, is the most important component with the largest content of silymarin. Silybin has shown biological effect on the protection of liver disease. Because silymarin has the characteristics of potential antioxidant, anti-inflammatory and anti fibrosis, it has been widely used in clinic as the main component of liver protection drugs (Abenavoli 2010, Federico 2017).

A mouse experiment has proved that silibinin can improve nonalcoholic liver injury caused by high-fat diet. The NAFLD model of C57BL / 6J mice was successfully established through 8 weeks of high-fat diet. Silibinin (50 or 100 mg / kg / day) was administered by gavage in the last 4 weeks. Through the biochemical indexes of blood and liver homogenate and the metabolomic analysis of serum and liver samples, silibinin reduced the accumulation of liver lipids and improved lipid metabolism. It protects mice from metabolic abnormalities and nonalcoholic liver injury caused by high-fat diet (Sun 2019). The protective effect of silibinin on the liver was also confirmed in a clinical trial, which tested 180 patients with NAFLD, analyzed the data of patients, and proved that the administration of silibinin vitamin E phospholipid complex (188 mg silibinin / day) for 12 months can reduce the level of serum aminotransferase and improve the degree of hepatic steatosis (Loguercio 2012).

Tea is a traditional beverage in China. Now it is also accepted and loved by many countries in the world. The flavonoids in tea have been proved to have a variety of biological activities. Catechin is one of the most important components in flavonoid species and has strong antioxidant activity (Masterjohn 2012). At the same time, the metabolites of catechin in the body also show antioxidant, anti-inflammatory and antioxidant stress effects (Feng 2006, Zhou 2014).

In the clinical trial of NAFLD patients, patients were divided into control, high-density catechin and low-density catechin groups. They took corresponding capsules every day for 12 weeks to maintain a healthy lifestyle. After 12 weeks, serum index examination showed that high-density catechin

could reduce the level of serum liver enzyme alt, urinary 8-Isoprostaglandin excretion and body fat. Experiments have proved that the intake of at least 1g catechin per day can reduce the liver fat content and inflammation in patients with NAFLD by reducing the level of oxidative stress (Sakata 2006).

### 2.2 Curcumins

Curcumin is a bioactive component extracted from the rhizomes of Zingiberaceae and Araceae plants. The content of turmeric is about 3% - 6%, which is a diketone compound and is used as food flavor and pigment (Ganjali 2017). Natural polyphenols in curcumin have become natural compounds for the treatment of NAFLD because of their lipid modification, antioxidant, anti-inflammatory, insulin sensitivity, anti steatosis and anti fibrosis properties (Zabihi 2016).

Some animal experiments also provide evidence that curcumin has become an effective drug for the treatment of NAFLD. Intragastric administration of curcumin can reduce the transaminase activity in serum, regulate lipid metabolism, and reduce the proinflammatory and oxidant effects of mouse liver macrophages (Inzaugarat 2017). Another mouse experiment proved that curcumin intervention can significantly reduce liver steatosis induced by high-fat diet, reverse the abnormalities of serum biochemical indexes, and control lipid synthesis by controlling the expression of CD36, SREBP-1c and Fas (Yan 2018). In addition, in a clinical randomized controlled trial, 102 patients with NAFLD were randomly divided into two groups and received 1000 mg curcumin (intervention group) or lactose placebo (control group) twice a day for 8 weeks. The results showed that curcumin intervention treatment could significantly reduce serum total cholesterol, alt, AST, liver enzyme activity and other biochemical indexes, and reduce body mass index and waist circumference. In addition, liver lipid content was reduced in 75% of patients in the intervention group (Panahi 2016, Panahi 2017).

### 2.3 Stilbenes

Resveratrol (RSV) is the most representative substance of stilbene polyphenols. It is a natural plant polyphenol with two phenolic rings found in red wine and various foods such as grapes, blueberries, peanuts and berries. It mainly has biological activities such as anti-inflammatory, anti proliferative and antioxidant (Brown 2010, Charytoniuk 2016).

Resveratrol can improve the disorder of lipid metabolism induced by high-fat diet and prevent the pro-inflammatory response of liver, such as reducing TNF in liver- $\alpha$ , IL-6 and NF- $\kappa$ B mRNA expression reduces liver adipogenesis markers, such as triglyceride, body fat, total cholesterol, transaminase and plasma insulin levels. These effects are related to the up regulation of SIRT1 (Andrade 2013). In addition, the clinical trial also proved the positive effect of resveratrol on NAFLD. In the clinical trial participated by NAFLD patients, the patients took 500g resveratrol capsule every day for three consecutive months, and the control group took placebo capsule, and both groups maintained a healthy diet. After three months, the examination showed that resveratrol supplementation could reduce ALT, AST enzyme activity, inflammatory cytokines and nuclear factors in serum  $\kappa$ B activity and improve lipid accumulation in the liver (Faghihzadeh 2014, Faghihzadeh 2015).

## 2.4 Phenolic Acids

Ellagic acid (EA) is one of the most representative natural phenolic acids. It widely exists in various plant tissues, such as nuts, soft fruits, etc. pomegranates, berries and other fruits also contain a large amount of ellagic acid (Kang 2016). Ellagic acid has strong antioxidant functions, such as scavenging oxygen and hydroxyl radicals and inhibiting lipid peroxidation (Zhang 2014).

A study also showed that EA can alleviate the production of new fat in the liver. Mice were injected with mouse thymoma virus oncogene homologue (a substance that can improve mouse sterol regulatory element binding protein-1 and adipogenesis regulatory factor). After EA intervention, the transcription and translation of fatty acid synthase (FASN) in mice were inhibited, reducing the accumulation of lipids in mouse hepatocytes. And it can alleviate the steatosis of human hepatoma cells induced by oleic acid in vitro (Zhang 2019). 150mg / kg EA treatment could significantly reduce the activities of antioxidant enzymes cat, GSH Px, SOD and T-AOC caused by 8-week D-gal diet. The enzyme activities of cat and SOD returned to normal level, and the enzyme activities of T-AOC exceeded (Peng 2018).

## 3 CONCLUSIONS

The incidence rate of NAFLD is increasing year by year due to unhealthy diet and work habits. There is

no definite drug for NAFLD, and there is a poor compliance between bad eating habits and daily life and regular exercise. However, many natural plant polyphenols have shown the protective effect and potential for NAFLD. Polyphenols and their metabolites in human body can regulate lipid metabolism, improve oxidative stress, slow down the development of inflammatory response and insulin resistance, reduce liver fat content, and enhance the activity of antioxidant enzymes through circulation. Most foods rich in polyphenols have low calories. Eating more foods rich in polyphenols in daily diet, common polyphenols and their sources are listed in Table 1. Attention to a reasonable and balanced diet of other micronutrients can effectively alleviate NAFLD.

Table 1: Common polyphenols and main sources.

Polyphenol	Group/Subgroup	Source
Catechin	Flavonoids	Green tea (Masterjohn 2012)
Delphinidin	Flavonoids	Blueberry, Raspberry, Strawberry (Hosseini 2007)
Pelargonidin	Flavonoids	Blackberries, Strawberries, Plums (Andersen 2013)
Cyanidin	Flavonoids	Grapes, Bilberry, Berries, Cherry, Elderberry, Hawthorn (Tulio 2008)
Malvidin	Flavonoids	Black rice, Red grapes, Blueberries (Somerset 2008)
Curcumins	Curcuminoids	Ginger, Ginger plant (Ganjali 2017)
Resveratrol	Stilbenes	Grapes, Blueberries, Peanuts, Berries (Brown 2010, Charytoniuk 2016)

Pterostilbene	Stilbenes	Blueberries (Paul 2010)
Piceatannol	Stilbenes	Passion fruit, Grapes (Lee 2019)
Ellagic acid	Phenolic acids	Nuts, Pomegranates, Berries (Kang 2016)
Ferulic acid	Phenolic acids	Grains, Coffee, Peanuts, Nuts (Kumar 2014)
Cholorogenic acid	Phenolic acids	Coffee, Beans, Potato, Apple, Prunes (Nabavi 2019)

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