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Review Article

TOWARD NONALCOHOLIC FATTY LIVER TREATMENT; A REVIEW ON HERBAL MEDICINE TREATMENT

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Abstract

This study, review the nonalcoholic fatty liver treatment with emphasis on herbal medicine treatment. The accumulation of the mass of triglycerides by 5% in the liver cells of those who are not alcoholic leads to a situation called nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver is known as the most common liver disorder in the world, such that its prevalence varies from 3% to 25% in different populations of the world per race, age, sex, place of residence and lifestyle. Numerous studies have been carried out on the NAFLD and its pathological mechanism and are still ongoing. In classification of the causes of fatty liver, two general groups can be noted: (i) an effective group with indirect effects such as hypothyroidism, pituitary hypoplasia, polycystic ovarian syndrome, and sleep apnea; (ii) The other group is directly involved in the development of this disease in individuals such as abdominal obesity, metabolic syndrome and type 2 diabetes. Most patients are asymptomatic and are diagnosed by disturbed liver tests. This disease is the most common cause of liver enzymes disorder after hepatitis and chronic liver disease. In more than three-fourths of patients during a clinical examination, the increased size of liver is visible, and the most common symptom is excessive fatigue, lethargy, and pain in the upper right abdomen. The patients may complain of persistent itching, jaundice or complications caused by the increased portal pressure. If the disease leads to liver cirrhosis, hepatomegaly is seen in most cases. In most cases, the patient only finds out about the fatty liver when a regular blood test (generally liver function tests) shows a problem. "Alanine aminotransferase" and "Aspartate aminotransferase" are the most important liver enzymes, and their increase of 1.5-2 times in the tests shows the involvement of liver with this disease. Due to the key role of lipid accumulation in NAFLD progression, inhibition of lipid accumulation is a major focus of anti-NAFLD drug development. A variety of anti-NAFLD agents are currently in preclinical development. Additionally, metformin, statins, and fibrates, are currently being tested as NAFLD treatments in clinical trials. This study aims to review medicinal herbs used to treat NAFLD around the world. The obtained results of the present review investigation demonstrated that 27 medicinal herbs were found that traditionally used to treat NAFLD around the world. The most parts of these plants are leaves, root, and flowers, respectively; whereas these medicinal herbs are most commonly used in countries of Asian and African such as Iran, Pakistan, India and South Africa, etc. The results demonstrated that medicinal herbs have universally used to treat NAFLD. Thus, we can consider them as alternative agents for treatment of NAFLD; nevertheless, more investigations are mandatory to elucidate the precise mechanisms and also toxicity of these plants in human subjects.

Keywords: fatty liver; plant medicine; treatment; traditional medicine

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Liver and its tasks

Liver is the largest gland in the body, which plays a role in metabolic activities of body such as digestion, and is responsible for more than 500 vital functions in the body. All blood of the digestive tract collected by the portal vein enters the liver and all the material absorbed from the gastrointestinal tract pass through the liver (1). The other tasks of the liver are the drug metabolism, toxin trapping, and purification of toxins by converting them into harmless materials (2). The participation in hematopoiesis (in the prenatal period), resistance to infections, rapid provision of energy when necessary, are among other liver functions (3). The liver stores the fat, vitamins (particularly vitamins A, D, E, K, B12), mineral salts (iron, folate, copper), and other nutrients. The highly specialized liver tissue regulates different and extensive biochemical reactions (4). The synthesis of albumin, globin, cholesterol, blood coagulation factors, and immune system factors, production of glucose from certain amino acids, glycerol and lactate, synthesis of phospholipids, lipoproteins and triglycerides are only some of the functions of this huge biochemical plant. It is obvious that any disturbance in the liver functioning causes a series of disorders that can cause irreversible damages to this organ followed by the whole body (5).

Nonalcoholic fatty liver

The accumulation of the mass of triglycerides by 5% in the liver cells of those who are not alcoholic leads to a situation called nonalcoholic fatty liver disease (NAFLD) (6). This disease that was first diagnosed by Ludwig et al. in 1980 has several stages, the first of which is liver fat or steatosis. At this stage, fat is accumulated in the liver cells, while there are no signs of inflammation or ulcers. In many patients, this situation does not lead to serious liver disease, but in some, it may become nonalcoholic steatohepatitis (7). The nonalcoholic steatohepatitis is a more serious condition, because it may lead to liver ulcer, and finally, it causes a chronic and irreversible disease called cirrhosis (8). The liver cirrhosis is a dangerous condition that does not have a visible symptom, but with the spread of disease, it causes liver fibrosis, and gradually there is a condition where the liver function is severely impaired and can be associated with the death of the patient (9-10).

It can be noted that in rare cases, this disease can lead to liver cancer. According to estimates, in patients involved with first stage of fatty liver, the likelihood of the disease turning to the liver cirrhosis in the next two decades of life is about 1-2%, but it is reported 5-11% for those who are passing the hepatic steatosis stage (11). This issue clearly notes the necessity for timely diagnosis and treatment of the disease. The disease is closely related to metabolic syndrome, which is a class of abnormalities including the increased abdominal fat, obesity and dyslipidemia or impaired fat metabolism, resistance to insulin, high blood pressure, and high triglyceride level (12). Many studies have shown that nonalcoholic fatty liver increases the risk of cardiovascular diseases, diabetes, and mortality caused by them (13).

Fatty liver is divided into three grades based on progress stages, which is defined based on ultrasound criteria: in grade 1 fatty liver (mild), the liver echogenicity increases slightly and the range of diaphragm and intrahepatic arteries are normal. This stage is in fact the first stage of disease development, which is often controlled easily by medicines. In grade 2 fatty liver (moderate), the liver echogenicity is increased moderately and the range of diaphragm and intrahepatic arteries are slightly faded (14). The conditions that cause false inflammation of fats in hepatocytes or fat accumulation in the interstitial spaces of liver organ gradually leads to this degree of disease. Grade 2 in the liver is a moderate to severe situation that require medical care and can sometimes be dangerous (15-16).

In grade 3 fatty liver (severe), the liver echogenicity is highly increased and the range of diaphragm and intrahepatic arteries and the posterior section of right lobe of liver are faded or are seen in small amounts. Grade 3 is in fact the most serious and advanced stage of the disease and is the state where the liver is exposed to a lot of fat accumulation. At this stage, the inflammation of the liver will occur (16-18). The inflammation in the liver makes the other parts of body come to the aid of liver and circulate the blood in the liver, but the liver is too weak to respond to this help (19). Moreover, at this stage, the arteries and veins are trying to pump nutrients and remove toxins, but the disease has reached a dangerous stage. At this stage, where the liver cirrhosis might occur, there is a very small chance for normal liver function (16-18).

Epidemiology

Nonalcoholic fatty liver is known as the most common liver disorder in the world, such that its prevalence varies from 3% to 25% in different populations of the world per race, age, sex, place of residence and lifestyle (20). The prevalence of this disease is highly increasing throughout the world due to being dependent on lifestyle of individuals (21). According to World Health Organization, lifestyle refers a combination of behavioral patterns and individual habits throughout life including nutrition, exercise, smoking, sleep and rest that is caused by the socialization process (22).

The statistics published in Asia indicate a prevalence of 5-18% of the disease (21), and also in accordance to the published statistics, the prevalence of nonalcoholic fatty liver in Iran varies from 2.9% to 30% in the general population, and it reaches 55.8% in patients with type 2 diabetes (23-24). This disease, which often is seen in the age range of 40-60, increases as the age enhance (25). The prevalence of this disease in men is twice as women, and as the age increases, the prevalence in women approaches men, and especially after menopause, the prevalence of fatty liver disease in women has an increasing trend (26). Unfortunately, due to the wrong lifestyle, many children and adolescents are obese, which could make them prone to fatty liver at an earlier age (27). There

is a relatively high statistical frequency of fatty liver in children; so in accordance to the studies, the prevalence of this disease in obese children in different communities is 42.6%-77.1% (28-29). If a person has fatty liver at an earlier age, the duration of disease increases, and along with this, the complications of fatty liver will also increase (29).

Pathophysiology

Numerous studies have been carried out on the NAFLD and its pathological mechanism and are still ongoing. In a group of studies, the role of vascular disorders in the occurrence of NAFLD is considered. The studies have shown that fatty liver is deprived of proper perfusion. Hence, a role is considered for cellular hypoxia in occurrence of NAFLD. According to this hypothesis, 4 stages are defined for occurrence of NAFLD, including steatosis (fat accumulation in hepatocytes), hepatocyte necrosis (caused by fat toxicity), fat release from hepatocytes (that causes inflammatory reaction), and venous obstruction that eventually causes cirrhosis. The above steps are very similar to histogenesis of artery atherosclerosis (30-34).

In another hypothesis, insulin resistance as the cause of steatosis and steatohepatitis and oxidative factors as the cause of inflammation and disease progression are the factors mentioned in "two-step theory", and they can be somehow attributed to the cause of disease. It is further explained that in obese people and those with diabetes, the insulin resistance increases the fatty acids in the liver cells, and this accumulation finally can lead to destruction of liver cells and leads to the fatty liver disease. In the condition that insulin resistance occurs, the pancreas is forced to produce additional pancreas (35-37). The excessive increase in insulin in the body is known as X syndrome, which can be seen in fatty liver disease (38). In the scientific literature review, there is a nutritional/genetic model that combines a two-stage theory with biological symptoms of other diseases and factors such as gene and nutrition and evaluates the effect of lifestyle and genetic changes for development of NAFLD pathology as effective factors in the development of this disease (20).

Causes and risk factors

In classification of the causes of fatty liver, two general groups can be noted: an effective group with indirect effects. Hypothyroidism, pituitary hypoplasia, polycystic ovarian syndrome, and sleep apnea are examples of this category; although they do not directly cause fatty liver, they can provide the situation for the disease and their control is effective in treatment of disease (20). The other group is directly involved in the development of this disease in individuals; abdominal obesity, metabolic syndrome and type 2 diabetes are more common in people with NAFLD, and their presence increases the likelihood of exacerbation of liver disease (39). In addition, the liver congenital diseases, high blood lipids, intestinal bypass surgery and fast weight loss, malabsorption of protein and calories, liver inflammatory diseases such as hepatitis C, poisoning with toxic substances such as carbon tetrachloride, trichloroethylene, phosphorus and fluridine, use of some medicines, such as tetracycline, valproic acid, amiodarone, and corticosteroids-containing compounds, care known as the causes and diseases associated with fatty liver. Pregnancy, due to the imbalance of hormones in this period as well as weight gain, is another cause of fatty liver disease (40).

Table 1. Some causes and risk factors of NAFLD (40)

Metabolic disorders	Compounds	Surgery	Drugs	Congenital diseases of the liver	Others
Diabetes	Phosphor	Removing a large portion of the small intestine	Metotrexate	Galactosemia	Overgrowth of intestinal bacteria
Obesity	Uranium compounds	Stomach shortening or jejunum	L-Asparaginase	Glycogen storage diseases	Severe anemia
Increase blood cholestrol	Thallium compounds		Bleomycin	Homocystinuria	Complete intravenous nutrition
Long Hunger	Chromate		Tetracycline	Wilson disease	Inflammatory bowel disease
	Antimoan		Amiodarone	Tyrosinemia	Lipodystrophy
			Estrogen		
			AIDS antiviral drugs		
			Hydrazine		
			Tamoxifen		

Complications

If the process of liver inflammation does not stop, cirrhosis can lead to events such as accumulation of water in the abdomen (ascites), inflammation of esophageal veins (esophageal varices) that can rupture and bleed, dizziness, drowsiness, and stuttering (liver encephalopathy), liver cancer, end-strage liver failure, which means cessation of liver function. In addition to direct destructive effects on the liver, this disease has a wide range of effects on other important organs of the body (41). The increased risk of chronic kidney diseases, cardiovascular diseases, type 2 diabetes, and colon cancer are among the most important side effects of the disease. Meanwhile, it has been shown in some studies that those with nonalcoholic fatty liver indicate a higher incidence of accumulation of atherosclerotic platelets. According to reports, the incidence of kidney diseases in those with fatty liver is 21-54%, while it varies from 3.7 to 24.2% in those without fatty liver. Besides, the likelihood of incidence of adenomatous polyps and colon cancer in those with fatty liver is reported 2-3 times, respectively (41).

Disease symptoms

Most patients are asymptomatic and are diagnosed by disturbed liver tests. This disease is the most common cause of liver enzymes disorder after hepatitis and chronic liver disease. In more than three-fourths of patients during a clinical examination, the increased size of liver is visible, and the most common symptom is excessive fatigue, lethargy, and pain in the upper right abdomen (42). The patients may complain of persistent itching, jaundice or complications caused by the increased portal pressure. If the disease leads to liver cirrhosis, hepatomegaly is seen in most cases. The other symptoms of cirrhosis including spider angioma, splenomegaly ascites, palmar erythema, and asterixis may also appear. In contrast, in rare cases, the course of disease is stopped or even returns to normal state without having any specific treatment for unknown reasons (42-43).

Diagnosis

In most cases, the patient only finds out about the fatty liver when a regular blood test (generally liver function tests) shows a problem. "Alanine aminotransferase" and "Aspartate aminotransferase" are the most important liver enzymes, and their increase of 1.5-2 times in the tests shows the involvement of liver with this disease (44-45). In laboratory tests, several factors can be the sign of insulin resistance, such as increase in Gamma-glutamyltransferase and serum Ferritin. Generally, an increase of about 50% in body iron storage along with other diagnostic symptoms can convince the physician to diagnose fatty liver disease (45). Moreover, the inflammatory biomarkers "TNFα" and "Interleukin 6" can also be referred as serum indicators in diagnosis of fatty liver (46). Meanwhile, in the suspected patients, direct and total Bilirubin, fasting blood sugar, and lipid profiles should be evaluated and monitored. The recent studies have shown that in patients with NAFLD, the plasma indicators of lipid peroxidation, inflammation, and endothelial dysfunction is higher compared to individuals without NAFLD (44). Ultrasound is one of the suitable and available diagnostic methods that is used to prove steatosis. The increased liver echogenicity known as "bright liver" that is seen in the liver affected area is properly visible in ultrasound. However, ultrasound does not play an important role in rejection of steatohepatitis or fibrosis and also has a low accuracy in obese patients (47). Among other diagnostic imaging methods, CT scan and MRI can be pointed out, which often have a higher sensitivity to ultrasound and are, of course, more expensive for the patient. However, none of these techniques can differentiate NASH from steatosis or fibrosis and also show the severity of the disease. What determines fatty liver diagnosis is liver biopsy, which properly shows the extent and severity of liver involvement (48-49). The access to disease progression and its prognosis can be achieved by this method. It is also possible to make decisions on the best treatment method using the results of this diagnostic method. Using this method and other techniques referred above, the fatty liver disease can be differentiated from diseases such as alcoholic hepatitis, viral hepatitis A, B, C, E, drug-induced hepatitis, autoimmune, ischemic, Wilson's disease, celiac disease, etc (48-49).

Treatment

Those with fatty liver, should first be examined for other diseases, and in case of having other diseases, a proper treatment should be initially conducted and until those diseases are not treated or controlled, the person is prone to fatty liver. In case of non-pharmacological treatment of the disease, it can be said that with control on underlying diseases such as weight loss, blood lipids, diabetes, or discontinuation of the causative drugs, the progression of this disease can be prevented, and in many cases, the reverse course can be followed that leads to treatment of this disease. Although weight loss is noted as the most desirable treatment method in many studies, it should not be overlooked that a sudden weigh loss followed by obesity-reducing surgeries can have an entirely reversible effect on the treatment of the disease (50). The use of a proper diet, including intake of low calorie and vitamin-containing foods, minerals, and required proteins can be a proper solution for body weight moderation (50-51). The control of underlying metabolic diseases, such as control

of diabetes and blood lipids in patients with fatty liver, has a beneficial role in improving the disease (52). In patients with irreversible cirrhosis due to NASH, "liver transplantation" could be the only appropriate treatment. However, diseases such as obesity, complications of diabetes, cardiovascular diseases, and fear of post-transplantation complications, might be the limitations for transplantation (53).

Due to the key role of lipid accumulation in NAFLD progression, inhibition of lipid accumulation is a major focus of anti-NAFLD drug development (54). A variety of anti-NAFLD agents are currently in preclinical development. Additionally, metformin, statins, and fibrates, are currently being tested as NAFLD treatments in clinical trials. However, these drugs have significant adverse side effects, including enhanced risk of infection and osteoporosis (55-56). Hence, novel treatment candidates with high efficacy and minimal side effects are urgently demanded for the treatment of NAFLD (57).

Table 2. Some drugs used in the NAFLD treatments

Antioxidants	Insulin-Sensitive Drugs	Blood lipid lowerers
Vit E	Metformin	statins
Vit C	Thiazolidinedione	Gemfibrozil
Betaein		Colic acids
N-acetyl Cysteine		
Superoxide dismutase		

Medicinal herbs for fatty liver treatment

The history of treatment of diseases with medicinal herbs is as long as the history of human life on Earth (58). From the very beginning, by virtue of experience and acquired knowledge, according to the requirements throughout the life on Earth, humans have treated themselves with medicinal herbs (58). Despite the fact that the progress in the production of industrial drugs somehow prevents the human beings from paying attention to one of the first and most accessible medical resources, the 20th century is called the return to nature and use of herbal medicines by many pharmaceutical scientists (59). The beneficial properties and limited adverse complications of herbs could be the reason to emphasize their therapeutic role in the treatment of various diseases. In the present literature review, by searching the databases of Web of Science, PubMed, Google scholar EMBASE, Scopus, using the combination of keywords such as "herbal medicines", "fatty liver", "medical treatment", "blood lipid reduction", we intended to find the articles related to fatty liver and the therapeutic effects of herbal medicines on nonalcoholic fatty liver, the results of which are shown in Table 3.

Table 3. Beneficial plants for NAFLD

Scientific name	Common name	Family	Part of use		Reference		
Spinacia oleracea L.	Spinach	Amaranthaceae	Leaves		60		
Crocus sativus	Saffron	Iridaceae	Flower		61-62		
Ficus carica	Fig	Moraceae	Fruit		63-64		
Malus domestica	Apple	Rosaceae	Fruit		65		
Cydonia oblonga Mill.	Quince	Rosaceae	Fruit		66		
Vitis vinifera L.	Currant	Vitaceae	Fruit		61		
Berberis vulgaris	Barberry	Berberidaceae	Fruit		67		
Corylus avellana	Hazelnut	Betulaceae	Leaves-nuts		68		
Apium graveolens	Celery	Apiaceae	Leaves-stem		69		
Cicer arietinum L.	Chickpea	Fabaceae	seeds		70-71		
C. zeylanicum	Cinnamon	Lauraceae	Bark - powder and dried flowers		72-73		
Rosa damascene.Mill	Iranian Damask Rose	Rosaceae	Flower		74		
Cucumis melo var.inodorus	Melon	Cucurbitaceae	Fruit		75		
Portulaca oleracea	Common Purslane	Portulacaceae	Leaves-Flower		76		
Nobilis Laurus	Bay Laurel (rand)	Lauraceae	Leaves		77		
Punica granatum	Pomegranate	Lythraceae	Fruit		78-79		

Beta vulgaris	Beets	Amaranthaceae	Leaves		80		
Citrus medica L.	Citron	Rutaceae	Fruit		81		
Daucus carota	Carrot	Apiaceae	Fruit		82		
Asparagus officinalis	Asparagus	Asparagaceae	Stem-Flower		83		
Cuminum cyminum	Cumin	Apiaceae	Seeds		84		
Nigella Sativa	Black seed	Ranunculaceae	Seeds		85		
Prunus dulcis	Almond	Rosaceae	Fruit		86-87		
Zingiber officinale	Ginger	Zingiberaceae	Rhizome		88		
Raphanus sativus L.	Radish	Brassicaceae	Root-leaves		89		
Allium sativum	Garlic	Amaryllidaceae	Root		90-91		
Cucurbita pepo L. Elaeagnus	Squash	Cucurbitaceae	Fruit		92		

The obtained results of the present review investigation demonstrated that 26 medicinal herbs were found that traditionally used to treat hypertension around the world. The most parts of these plants are leaves, root, and flowers, respectively; whereas these medicinal herbs are most commonly used in countries of Asian and African such as Iran, Pakistan, India and South Africa, etc. Table 3 shows the medicinal plants that traditionally used to treat hypertension around the world.

Traditional medicines can prevent NAFLD through a variety of mechanisms, including: (1) depressing lipogenesis through down-regulating sterol regulatory element-binding protein 1c (SREBP-1c); (2) increasing β-fatty acid (FA) oxidation by up-regulating peroxisome proliferator activated receptor α (PPARα); (3) increasing insulin sensitivity and depressing oxidative stress through increased antioxidant levels *via* nuclear factor-erythroid 2-related factor 2 (Nrf2); and (4) inhibiting activation of inflammatory pathways (93).
According to previous studies carried out on phytochemical examination of the most of the plants listed in the table above, we found that a major part of main compounds of these plants are polyphenols, flavonoids, terpenoids, alkaloids and tannins.

Polyphenols
Polyphenols as a heterogeneous class are derivatives of plants containing several water-soluble antioxidants, which are widely used in the treatment of many diseases, especially metabolic diseases. The studies show that polyphenols indicate their liver protective effects through increasing oxidation of fatty acids and modulation of insulin resistance, oxidative stress, and inflammation, which are the main pathogens associated with progress from a simple fat accumulation to development of nonalcoholic fatty liver (94-95). In addition, Abenavoli et al. (2017) showed that, generally, the antioxidant-rich foods, and especially polyphenols, along with lifestyle changes, can be considered as effective treatment of nonalcoholic fatty liver (96).

Among the polyphenol compounds, previous investigation showed that resveratrol can reduce liver fat accumulation via various mechanisms, such as reduced lipogenesis, improved fatty acid oxidation, reduction lipid peroxidation through stimulating the Nrf2-dependent antioxidative response in high fructose fed rats (97). Previous clinical trial study also showed that the level of liver enzyme with inflammatory cytokines was significantly improved in patients with NAFLD treated with resveratrol at the dose of 0.5 g for three months (98). Moreover, a number of the polyphenol compounds are present which such as curcumin, techin-3-gallate (99), salvianolic acid B (100), anthocyanidin (101), ellagic acid (102) and cyanidin-3-glucoside (103) which their beneficial effects have been observed in the treatment of NAFLD.

Flavonoids
Flavonoids are well-known as a group of phytonutrients, which found in a large number of fruits, vegetables, grains, bark, roots, stems, flowers, etc. Reviews have reported that flavonoids compounds have potential effects on the treatment of chronic diseases such as type 2 diabetes mellitus, cardiovascular and fatty liver diseases via immunomodulatory, anti- inflammatory, and antioxidant properties (104).
One of the most important flavonoid compounds is quercetin which has a broad spectrum of biological properties. Previous studies demonstrated that quercetin has potential effects on fatty accumulation, inflammation, fibrosis, nitrosative/oxidative stress, and insulin resistance related with non-alcoholic fatty liver diseases (105). Recently, *Pisonero-Vaquero et al (2015) and Mohan et al (2015) demonstrated that* quercetin reduces lipid accumulation in hepatocytes in obese mice probably via modolation of mitochondrial oxidative metabolism; indicating quercetin can considered as a beneficial dietary supplementary to decrease the obesity-induced hepatosteatosis (106).

Another compound which is present in a wide spectrum of plants is rutin. Previously it has been proven that (107) this compound is able to reduce adiposity, recover insulin sensitivity, as well as diminish cardiac remodeling and liver damage in rats with high-fat diet-fed (108). In line with previous study, Fu et al (2014) demonstrated that rutin successfully repressed palmitate-induced macrophage activation and decreased liver fat by repressing transcription of SREBP-1c and CD36 in the liver (109). In addition to this compounds, a number of flavonoids compounds such as pueraria (110), baicalein (111), luteolin (112), hydroxysafflor yellow A (113), genistein (114-115), silybin (116), isorhamnetin (117), iridin (118), naringin (119), shikonin (120), apigenin (121), kaempferol (122), myricetin (123), and pinocembrin (124), similarly exhibited noteworthy roles in the nafld treatment.

Terpenoids
The terpenoids, also well-known as isoprenoids, indicate a wide range of natural products especially in plant essence, and pigment resins derived from terpenes. These compounds exhibit extensive biological and medicinal applications such as anti-tumor, anti-diabetic, anti-inflammatory, antioxidant, antimicrobial, and analgesic effects (125).
Reviews have shown that many terpenoids compounds including betulinic acid, artemisinin, as well as ursolic acid gentiopicroside (126-127) represented important roles to treat the NAFLD. deMelo et al (2009) demonstrated that betulinic acid by affecting

the AMPK-SREBP signaling pathway (considerable decreases in hepatic AMPK phosphorylation, and improved activation of SREBP1) significantly decrease the hepatic lipid accumulation in mice (128).

Saponins

Saponins as an extensive phytochemical group have a triterpene or steroid aglycone and one or more sugar chains. Many biological activities such as antimicrobial, anti-cancer, and immune modulation have been attributed to these compounds. So far, the role of some saponins compounds such as dioscin, ginsenoside Rb1, ginsenoside Rg1 and trillin in the treatment of NAFLD (129). One of the main steroid saponins compounds which broadly exist in plants and herbs is dioscin. Reviews have demonstrated some medicinal applications including anti-tumor (130), anti-hyperlipidemic (131), and anti-microbial properties (132). Recently, Liu et al (2015) demonstrated that treatment of mice with dioscin without loss of appetite and increased physical activity resulted in weight loss, decreases blood lipid levels, reduce liver fat accumulation, liver cholesterol and triglyceride deposition by means of decreasing oxidative stress and inflammation and modulation the MAPK signaling pathway and autophagy (133).

Alkaloids

Alkaloids are class of phytochemicals that generally contain basic nitrogen atoms. Studies demonstrated the various pharmacological activities, such as antimicrobial, anti-inflammatory, analgesic, and anti-tumor effects (134). Reviews have shown that several alkaloids compounds such as berberine, sophocarpine (135), rutecarpine (136) and oxymatrine (137) exhibited potent roles in NAFLD treatment.

Berberine is isolated from the herb *Coptis chinensis* Franch. and widely used to treat diarrhea and other inflammatory diseases in China (138). Recent studies have proved a new therapeutic function of berberine in metabolic disorders, including obesity and diabetes (139). Berberine can be used as a cholesterol lowering drug, through a unique mechanism distinct from statins (140). These studies suggested a potential therapeutic activity of berberine for NAFLD. Liver gene expression profile analysis showed that high fat diet induced hepatic steatosis in rats led to global changes in gene expression, and treatment with berberine reversed this process. Several modules of berberine-regulated genes, including abundant long non-coding RNAs (lncRNAs), were identified by bioinformatics analysis. Among these berberine-regulated genes, we found that the lncRNA MRAK052686 and its associated gene Nrf2 are implicated in the pathogenesis of NAFLD. Hence, the study provides a new insight into the mechanism of the pharmacological action of berberine in the prevention and treatment of NAFLD. Other alkaloids such as sophocarpine, rutecarpine and oxymatrine (129) also play significant roles in protecting against NAFLD.

Other pure products have been showed to be effective in the treatment of NAFLD, including schisandrin B (141), honokiol (142), rhein (143), and emodin (144). TCM are worthy of further study. This review only summarizes a drop in the bucket, and more Chinese medicines that are useful for the treatment of NAFLD will come to light in the future.

Tannins are natural complex compounds, which are made of polyphenolic chemicals, and are abundant in the peel, leaves, and roots of most plants. Tannins, along with other important biological compounds, such as flavonoids, lead to destruction of free radicals and antioxidant effects, and are used in treatment of oxidative stress and hyperlipidemia (145-146). According to the results of the study by Fallah Hosseini et al., the compounds existing in food supplements and medicinal plants such as tannins, flavonoids, sterols, and other antioxidant compounds can affect the metabolism of lipids by influencing metabolic reactions of various tissues. The increase in metabolism of lipids can be proposed as one of the therapeutic routes for fatty liver (147).

The other effective herbal ingredients, the blood lipid lowering properties of which can be noted based on the studies, are alkaloids and terpenoids. Naczk, M et al. reported that major biological compounds including flavonoids, alkaloids, and terpenoids have positive effects on lowering the serum levels of liver enzymes as well as improved lipid profile (148).

CONCLUSION:

Fatty liver disease is one of the most important gastrointestinal diseases and largely depends on the lifestyle of individuals, diet, and type of activity. Multi-faceted therapies are considered for the disease, including medicinal and non-medicinal treatment. In the medicinal treatment, we also find two categories of chemical drugs and herbal medicines. In the present study, we found that the plants from different families have had beneficial effects on the treatment of fatty liver, which is important due to the common and extensive side-effects of chemical drugs, thereby intorudcing herbal sources as a proper alternative to chemical synthetic drugs. However, this can only be proven by further and comprehensive studies.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Competing Interests

The authors declare that they have no competing interests

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