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Role of medicinal plants and their chemical constituents in ameliorating the cause for non-alcoholic fatty liver disorder—A review

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), a silent epidemic, is one of the global threats linked with various concerns that can lead to chronic liver diseases. It is the most common liver disorder in Asian and Western countries, a continuum of ailments ranging from simple steatosis to steatohepatitis, cirrhosis, and liver carcinoma. Youngsters are lured with sugary beverages and other kinds of junk foods that may affect their metabolism due to their close association with obese, type 2 diabetes mellitus. The articles were collected from various online search engines, viz., Google Scholar, PubMed, and Science Direct. Keyword combinations undertaken for the searches were NAFLD, molecular mechanism or epidemiology, dietary factors, or herbal plants. The unmet criteria of the disease should be recognized as earlier as possible to meet the required demands to maintain a healthy lifestyle. However, there are no solid evident studies for the pathogenesis and progression of NAFLD. Insulin resistance and white adipose tissue are playing a vital role in the advancement of steatosis. Herbal plants have been widely utilized to overcome the allopathic side effects and bring a permanent solution for various diseases. The primary purpose of this study is to educate about phytoconstituent's role, such as flavonoid, saponin, polyphenol, terpenoid, and alkaloid, in ameliorating non-alcoholic steatohepatitis. Herbal plants are utilized as it is well said, "Nature is our best Physician," it is essential to understand the presence of phytomolecule and their secondary metabolites that may be useful in treating NAFLD-associated disorders.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is described as excessive fat accumulation in the liver cell without alcohol intake. It can also be caused due to viral hepatitis or drug-induced autoimmune disease (Marcuccilli and Chonchol, 2016). These secondary causes include medication side effects, specific endocrine conditions, and hepatitis C virus infection. The severity of the disease ranges from mild steatosis to non-alcoholic steatohepatitis (NASH), which can further progress to cirrhosis and hepatocellular carcinoma (HCC) (Lau and Wong, 2018). NAFLD can also be called metabolic-associated fatty liver disorder due to its close association with obese, type 2 diabetes mellitus (T2DM) reported as "Metabolic Syndrome" (MetS). The absence of appropriate and sensitive non-invasive testing for NAFLD makes accurate diagnosis difficult. When the level of a liver enzyme rises in overweight or obese people with no identified cause of liver disease, or when imaging studies suggest hepatic steatosis, it is commonly diagnosed on a presumptive basis (Salt, 2004).

The prevalence of NAFLD globally is estimated to be 25% (Mundi *et al*., 2020). NAFLD patients mostly remain asymptomatic, and they are diagnosed at the fibrosis or cirrhosis

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stage. People with central obesity are more likely to have NAFLD, including insulin resistance (IR) or T2DM, hypertension, excessive abdominal fat, and dyslipidemia. This group of chronic diseases is associated with an increased risk of cardiovascular disease and is referred to as the "MetS." Nearly 70% to 80% of patients have MetS or IR. Some patients experience vague right upper quadrant pain, high alanine aminotransferase (ALT), and hepatomegaly as risk factors for MetS (Hossain *et al*., 2016). It is also thought to be a hepatic symptom of MetS (Gottlieb and Canbay, 2019). If untreated, NAFLD progresses to hepatic inflammation and early fibrosis, indicating the onset of NASH. End-stage NAFLD symptoms include liver inflammation, fibrosis, cirrhosis, and increased risk of HCC (Eng and Estall, 2021). The present review is carried out by compiling literature from 1990 to 2021 concerning the traditional uses, phytochemistry, pharmacological activities, and toxicological aspects of various herbal plants and their role in treating NAFLD. Pieces of literature were collected from multiple online search engines, viz. Google Scholar, PubMed, Semantic Scholar, and Science Direct. Keyword combinations undertaken for the searches were NAFLD, molecular mechanism or epidemiology, dietary factors, or herbal plants.

Pathogenesis of NAFLD

In white adipose tissue (WAT), impaired insulin signaling raises lipolysis that generates fatty acid (FA). The results in substrate overload and further increased hepatic IR, with enhanced *de novo* lipogenesis as well as triglycerides (TG) accumulation (Buzzetti *et al*., 2016). Around 60% of FA for hepatic TG accumulation in NAFLD patients is derived from WAT-generated FA. 15% obtained from the diet and 25% from increased *de novo* lipogenesis, which is controlled through carbohydrate response element-binding protein and peroxisome proliferator-activated receptor δ (PPAR δ) (Buzzetti *et al*., 2014).

According to the two-hit theory, NAFLD consists of two stages of liver injury, such as intrahepatic lipid build-up and inflammatory development to NASH. During the first hepatic theory, fructose metabolism elevates intrahepatic lipid and *de novo* lipogenesis which inhibits mitochondrial β-oxidation of long-chain FAs. According to the second hit theory, fructose generates reactive oxygen species (ROS) that must be quenched by liver anti-oxidants and promotes protein fructosylation due to its five-membered furanose ring molecular instability. Many persons with NASH have vitamin deficiencies and a lack of anti-oxidant capacity to inhibit the formation of ROS, resulting in necroinflammation shown in Figure 1 (Lim *et al*., 2010).

HERBAL PLANTS IN NAFLD

Plants with active ingredients, pharmacological and toxicological effects, and their involvement in reducing the etiology of fatty liver disease are represented in Tables 1 and 3.

Phyllanthus niruri Linn.

Phyllanthus niruri is a herbal plant inhabited in Southeast Asian countries of the family Phyllanthaceae. It can treat numerous liver disorders, especially hepatitis and jaundice. Current studies show that it exhibits hepatoprotective properties on hepatitis-induced rats and is abundant in phenolic compounds and flavonoids, which is essential for a substantial anti-oxidant property. It will lower fat accumulation in the liver by lowering serum FA, decreasing IR, inhibiting *α-glucosidase,* cholesterol micellization, and *pancreatic lipase* that leads to a low amount of free fatty acid (FFA) and glucose which results in a *de novo* lipogenesis process with less fat accumulation in the liver. It minimizes hepatic fibrosis by reducing *Malondialdehyde* which is responsible for stimulating the hepatic stellate cell (Zarzour *et al*., 2017).

Phyllanthus niruri reveals its antiangiogenic effect against NAFLD. Additionally, it regulates *adipocytokine* secretion by improving insulin signaling inside the liver, which leads to lowering of fat accumulation as well as inflammation and down-regulation of [solute carrier family 10 (sodium/bile acid cotransporter) member 2] (SLC10A2), PPARγ and collagen alpha type I genes (Zarzour *et al*., 2018).

Phyllanthus emblica Linn.

The fruit of *P. emblica*, a member of the Phyllanthaceae family shows a variety of biological activities such as anti-inflammatory, anti-oxidative, anti-microbial, hypolipidemic, and hepatoprotective activities. It is also observed that the fruit exhibits a hepatoprotective effect exerted by ellagic acid, flavonoids, gallic acid, vitamin C, and it could be linked to anti-oxidant and anti-inflammatory activities (Kirschweng *et al*., 2018). Some observation shows that water extract of *P. emblica* (WEPE) minimizes adipose tissue weights of peritoneal and epididymal fat. This helps ameliorate steatosis in the liver of high-fat diet (HFD) induced rats, increase anti-oxidant enzyme activity and deplete lipid peroxidation. Thus, WEPE possibly shortens the further formation of NASH (Tung *et al*., 2018).

WEPE helps ameliorate steatosis in the liver of HFD induced rats by increasing PPAR-α in the liver. It is also observed that in the liver tissues, the WEPE fruit decreases the messenger ribonucleic acid (mRNA) of sterol regulatory element-binding protein -1c (SREBP-1c), and in peritoneal fat pads of HFD-induced rats, it enhances the mRNA of *adiponectin* (Huang *et al*., 2017).

Phyllanthus urinaria Linn.

Phyllanthus urinaria, a member of the Phyllanthaceae family is found to have minimized necroinflammation and hepatic steatosis but has never been tested in NASH patients. In NASH patients, it is better to enhance liver histology compared with placebo. It is also found to alleviate oxidative stress and liver fat in NASH patients. It also suppresses c-Jun N-terminal kinase (JNK), cytochrome P450-2E1 (CYP2E1), interleukin-6 (IL-6), nuclear factor-kappa B (NFκB), hepatic lipid peroxides, tumor necrosis factor-α (TNF-α). It decreases the transcriptional activity of cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT) and intensifies lipolytic CYP450 expression (Wong *et al*., 2013).

Allium sativum Linn.

Garlic is utilized as a medicinal plant in many cultures. It is a member of the Amaryllidaceae family and contains a variety of bioactive chemicals, including diallyl disulfide, S-allyl cysteine, S-methyl cysteine sulfoxide, allicin, ajoene, and SAC sulfoxide. It is also observed that regular garlic intake alleviates cancer and cardiovascular diseases. Several studies show that garlic consumption has a beneficial effect on obesity and IR, identified as a critical driver of NAFLD development. The impact of garlic on dyslipidemia (which is recognized as a significant risk factor of NAFLD) is due to increased *adiponectin* levels, reducing

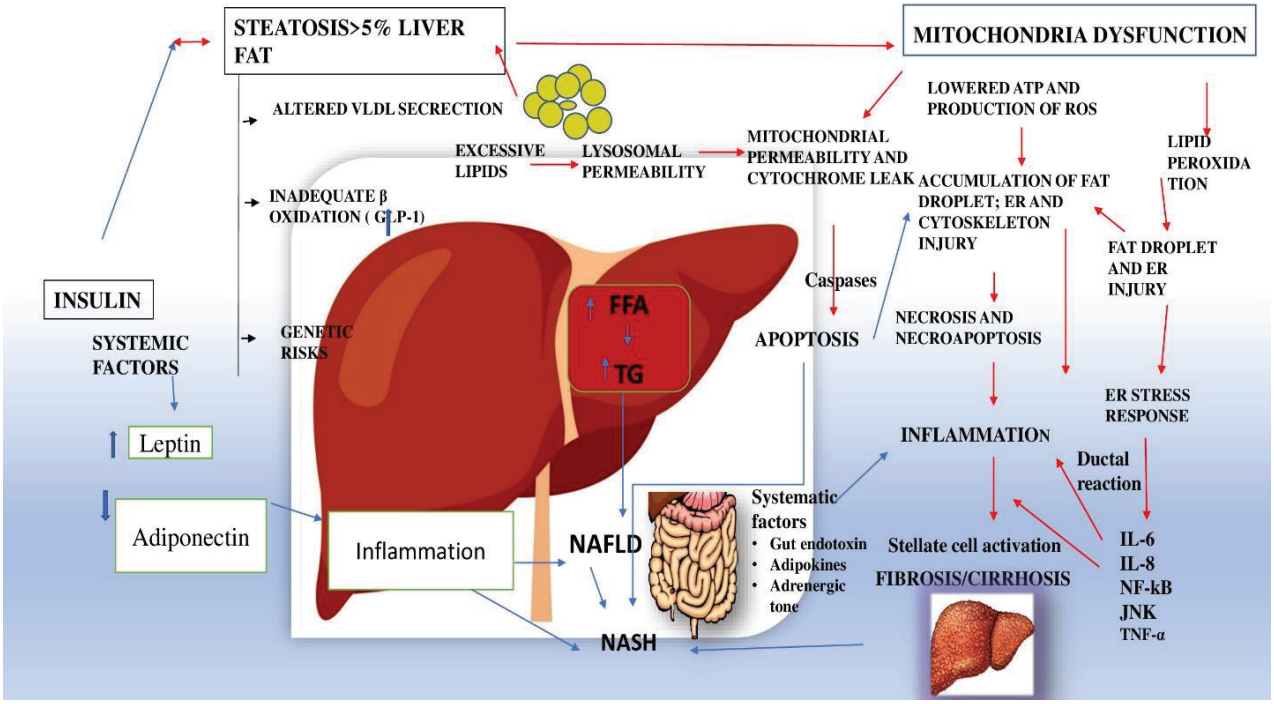


Figure 1. The figure represents, various factors such as FFA, TG, altered VLDL, inadequate β-oxidation, IR, adiponectin, leptin that plays a pivotal role in the cause of non-alcoholic fatty liver disorder (NAFLD), NASH and fibrosis/cirrhosis. NFκB block apoptosis induced by TNF alpha and mediates with the JNK for the suppression of the cascade leading to inflammation.

the enzyme activity involved in liver fat production, lowering intestinal absorption of TGs (Sangouni *et al*., 2020).

Myrica rubra (Lour.) Siebold & Zucc

Bayberry is a subtropical tree found in Southeast Asian countries that belongs to the Myricaceae family. It contains a lot of anthocyanins and phenolic acids such as sinapic, ferulic, caffeic acid, and salicylic acid. Their study suggested that specific pathological conditions such as inflammation, oxidative stress, liver steatosis has improved in experimental NASH. Bayberries are high in polyphenols, which function as an anti-inflammatory and anti-oxidant. It is having the capacity to deplete apoptosis in young individuals, lowers plasma biomarkers, and is characterized by oxidative stress and reduced inflammation. Thus, bayberry can prevent and treat the complications formed at the initial stage of NAFLD (Guo *et al*., 2014).

Curcuma longa Linn.

Curcuma longa, also known as turmeric, is a perennial herb in the family of Zingiberaceae. In Asian cuisine, turmeric is widely used as curry powder and traditionally used as a home remedy for various ailments. Curcumin exhibits a polyphenol structure and is used as renoprotective, anti-oxidant, anti-cancer, and immunomodulatory. It inhibits the synthesis of fatty liver and the development of some unsaturated fatty liver acids such as oleic acid, stearic acid, and linoleic acid; this might help ameliorate hepatic steatosis and inhabits FAs liver disease development. It also enhances oxidative stress levels and helps prevent NAFLD by reducing ROS production and preventing liver damage in steatohepatitis through decreasing cytosolic and nuclear translocation of high mobility group box 1 and NFκB as well as inducing PPAR-γ (Mansour-Ghanaei *et al*., 2019).

Curcumin also exhibits anti-neoplastic, anti-inflammatory, and anti-bacterial properties (Ghosh, 2019). According to the findings of their study, short-term curcumin supplementation enhances hepatic transaminase levels in NAFLD patients (Panahi *et al*., 2017). In NASH mice, it prevents the O-GlcNAcylation pathway, which leads to anti-oxidant responses (Lee *et al*., 2019). Intake of this supplementation improves the glycemic and lipid index (Rahmani *et al*., 2016).

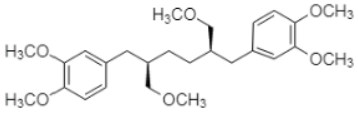
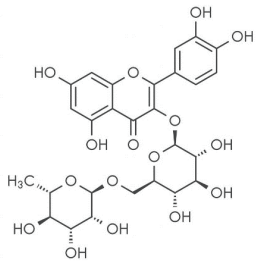
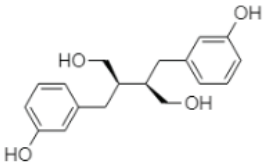
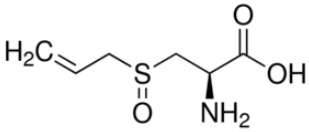
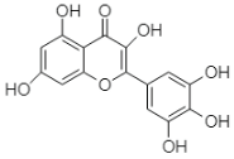
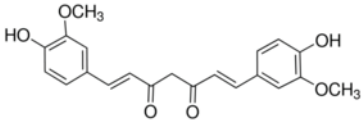
It is observed that curcumin can treat NAFLD mice induced with a high-fat high fructose diet by enhancing the metabolism of bile acids which is associated with nuclear erythroid 2-related factor 2 (Nrf2)/farnesoid X receptor (FXR)/Liver X receptor alpha pathway regulation and by preventing hepatic lipogenesis. It effectively restores the metabolic capability of the fatty liver by reversing the expression of CYP7A and CYP3A (Yan *et al*., 2018a, 2018b).

Silybum marianum (Linn.) Gaertn

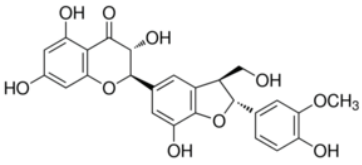
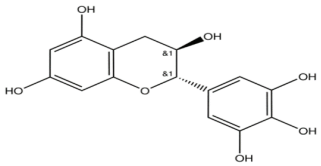
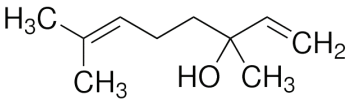
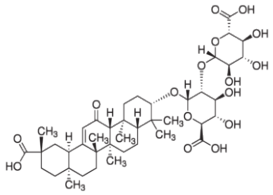
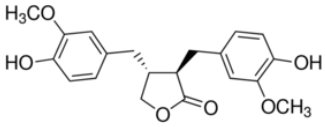
Silymarin is a milk thistle plant extract from the Asteraceaea family that has been used for centuries as a traditional herbal remedy for liver ailments. It contains isosilybin A and B, silydianin, silybins A and B, silychristin, and polyphenolic compounds, as well as six important flavonolignans. It also possesses anti-fibrotic, anti-inflammatory, and anti-oxidant properties (Kheong *et al*., 2017). It is found in Asia, Southern Europe, North and South America, North Africa, and South Australia (Camini and Costa, 2020).

The major biologically active component of *S. marianum* is silybin. It is not dose-dependent and can be used to treat NAFLD patients, notably NASH, compared to hepatoprotective drugs and antimetabolic disorders agents (Zhong *et al*., 2017). The

Table 1. Herbal plants and their active constituent.

S. no	Plants name	Chemical structure	Figure
1	*P. niruri* Linn.	 Phyllanthin	
2	*P. emblica* Linn.	 rutin Rutin	
3	*P. urinaria* Linn.	 Enterodiol	
4	*A. sativum* Linn.	 ± L -Alliin	
5	*M. rubra* (Lour.) Siebold & Zucc	 Myricetin	
6	*C. longa* Linn.	 Curcumin	

Continued

S. no	Plants name	Chemical structure	Figure
7	*S. marianum* (Linn.) Gaertn	 Silychristin	
8	*C. sinensis* (Linn.) Kuntze	 Gallocatechin	
9	*C. verum* J. Presl	 Linalool	
10	*G. glabra* Linn.	 Glycyrrhizic acid	
11	*L. usitatissimum* Linn.	 Matairesinol	

mechanism of action of silybin is followed by its act of interaction with various tissues. Silybin reacts through deactivating pro-inflammatory signals, which are acquired from activation of NFκB that is involved in the induction of the synthesis of the cytokines-like IL-1, IL-6, granulocyte-macrophage colony-stimulating factor, TNF-α (Federico *et al*., 2017).

Silymarin inhibits free radical injury and lipid peroxidation. It is also found that silymarin can block the release of TNF-α by removing hydroxyl radicals and maintaining the average superoxide dismutase level (Navarro *et al*., 2019).

It is also observed that silymarin is found to shrink inflammation, and treatment can minimize IR and deplete fasting insulin levels. In NAFLD patients, silybum + phospholipids + vitamin E complex is located to enhance liver enzymes plasma level, improve echography score of liver steatosis. NASH is associated with mitochondrial dysfunction. During the process of NASH, the excess of FFA intensifies in hydrogen peroxide (H2O2) mitochondrial production, which in return oxidize mitochondrial membranes and maintain the activity of uncoupling protein-2 and carnitine palmitoyl transferase-1 (Abenavoli and Bellentani, 2013). Some studies found that milk thistle extract exhibits a reducing trend in NASH and numerical reduction in the steatosis score when differentiated with the vehicle group (Pais and Amato, 2014).

Camellia sinensis (Linn.) Kuntze

Green tea (GT), a member of the Theaceae family, is the most commonly found in East Asia. It is derived from the leaves of *C. sinensis*, which are high in polyphenolic components such epigallocatechin gallate, catechin, and epigallocatechin 3 gallate (EGCG). It is used as a traditional medicine in diabetes, obesity, and cardiovascular diseases. It is also observed that catechins decline lipid peroxidation levels, oxidative stress (Mansour-Ghanaei *et al*., 2018).

GT minimizes the cholesterol level in the liver by lowering the fat absorption from the gastrointestinal tract and elevating the reabsorption of bile acid. It also regulates liver enzymes levels and reduces lipogenesis activity by preventing the expression of adipose lipogenic genes and hepatic genes

(Mahmoodi *et al*., 2020). It enhances the anti-oxidant activity and reduces the level of expression of TNF-α (Karolczak *et al*., 2020).

GT extract (GTE) is found to improve gene expression related to lipid oxidation. It also inhibits fatty liver accumulation through activation of adenosine monophosphate kinase (AMPK) and may also increase miR-34a, which is responsible for lowering PPAR- α expression with progression of steatosis. The hepatic lipid accumulation is prevented by increasing the hepatic miR-24, which further increases the insight target-a lipogenesis inhibitor. The primary polyphenol present in GT, EGCG, attunes the many miRNAs present in hepatocytes, which involves the modulation of insulin sensitivity, lipid metabolism, apoptosis, and inflammation. Changes in the expression of miR-122, miR-107, and miR-103 and the induction of plant polyphenols can shrink hepatic steatosis. A complete mapping of the pathway is required to reveal the involvement of miR34a and miR-194 in NAFLD (Torres *et al*., 2019).

EGCG has been utilized to lessen fat deposition in the liver in HFD fed in mice, which acts as a murine model of NAFLD in humans via specific pathways that include signal transduction, transcriptional, autophagy, and intracellular secondary message pathway (Ushiroda *et al*., 2019). The risk of NAFLD is ameliorated by the presence of anti-oxidants, lipid-lowering, anti-inflammatory effects, IR, and gut dysbiosis that are present in abundance in GT (Zhou *et al*., 2019).

Cinnamomum verum J. Presl

Cinnamon is a spice derived from the inner bark of the tree species *C. verum*, which belongs to the Lauraceae family and has anti-oxidant and insulin sensitizing characteristics. Some of the *in vivo* and *in vitro* studies estimated its effect on glucose metabolism by lowering post-prandial intestinal glucose absorption by preventing *α-glucosidase* and pancreatic *α-amylase*. It also enhances glycogen synthesis, potentiates insulin receptor activity and insulin release, and inhibits gluconeogenesis. Cinnamon plays a significant role in subsequent ROS and lipid peroxidation, which is considered as a known vital process in the development of NAFLD (Askari *et al*., 2014).

Chlorella vulgaris Beijerink

Chlorella vulgaris is a freshwater single-celled green eukaryotic microalga in the Chlorellaceae family that can be used as a supplement to treat NAFLD. Some studies state that it is rich in essential FAs and amino acids. It also consists of a reliable amount of fiber and intracellular phytochemicals such as tocopherols, carotenoids, and ubiquinone. This medication can also be used to prevent and manage hypertension, dyslipidemia, weight loss, and hyperglycemia. The supplementation of this can ameliorate IR and fasting serum glucose. In NAFLD patients, it is found to facilitate liver function and inflammatory biomarkers (Ebrahimi-Mameghani *et al*., 2017).

Glycyrrhiza glabra Linn.

Glycyrrhiza glabra, popularly known as licorice, is a Fabaceae-family herbaceous perennial legume native to Western Asia, North Africa, and Southern Europe. Glycycoumarin (GCM), a compound found in licorice, has been studied for its excellent bioavailability and high efficacy against alcoholic liver disease, non-alcoholic fatty liver, and acetaminophen-induced hepatotoxicity by activating the Nrf2 anti-oxidant system, inducing autophagy, activating AMPK-mediated energy homeostasis, inhibiting oncogenic kinase T lymphokine-activated killer cell. This shows the use of GCM as a hepatoprotective agent (Zhang *et al*., 2020).

GCM is found to inhibit hepatocyte lipoapoptosis. It is also found to activate impaired autophagy caused by lipid metabolic disorders. GCM reduces endoplasmic reticulum stress-mediated JNK and mitochondrial apoptotic pathway activation during autophagy activation (Zhang *et al*., 2016a, 2016b). Licorice root can also be used to treat bronchitis, stomach ulcers, viral infections, and sore throat. It is found in various countries like Italy, Russia, China, and Turkey. Glycyrrhizin exhibits anti-oxidant, immune-modulating activities, and anti-inflammatory properties (Hajiaghamohammadi *et al*., 2012).

Glycyrrhizin is considered to be a curative treatment of NASH accompanied by cholestasis. It aims for bile acid-mediated meta-inflammation and inhibits the FXR-NLRP3 inflammasome common pathway (Yan *et al*., 2018a, 2018b).

Diammonium glycyrrhizinate obtained from licorice roots is a glycyrrhizic acid considered a vital bioactive pentacyclic triterpenoid glycoside. It consists of anti-allergic, anti-viral, anti-tumor, and anti-oxidant properties. Diammonium glycyrrhizinate can be used to treat NAFLD since it can enhance the damage of the liver caused by anti-inflammatory activity in the liver (Li *et al*., 2018).

Linum usitatissimum Linn.

Flax, commonly known as common flax or linseed, is a flowering plant in the Linaceae family that is high in polyunsaturated fatty acids, especially linoleic acid, phytoestrogenic lignans, insoluble and soluble dietary fibers, anti-oxidants, and proteins. Many studies also found that flaxseeds can decrease the risk of MetS, dyslipidemia, and cardiovascular diseases. It is also found that flaxseed supplementation affects IR. A patient's flaxseed can minimize TNF-α and high sensitivity c reactive protein (Yari *et al*., 2016).

ROLE OF PHYTOCONSTITUENTS IN NAFLD

Flavonoids

Flavonoids are prevalent polyphenolic compounds present in nature. They are found to bind with glycosides more than aglycones regularly. Almost all flavonoids possess three rings, namely two aromatic rings and one heterocyclic ring. Based on variations in the C, ring flavonoids are divided into subclasses such as flavonols, flavanones flavones, anthocyanidins chalcones, and isoflavones. They have been proven to have beneficial effects on lipid metabolism, oxidative stress, IR, and inflammation which are considered the most critical pathophysiological pathways in NAFLD represented in Figure 2 and Table 2 (Van De Wier *et al*., 2017).

Saponins

These are glycoside aglycones of three common terpenoids found in terrestrial plants. Some saponins are antipyretic, anti-cancer, and anti-bacterial. The main active ingredients in *Polygala tenuifolia*, *Platycodon grandiflorus*, *Panax ginseng*, and *Glycyrrhiza uralensis* are saponins (Liu *et al*., 2015a, 2015b; Zhang *et al*., 2016a, 2016b). Saponin extract reversed the elevation in the expression levels of lipogenesis-related genes induced by fast-food diet (FFD), including MLX interacting protein-like and fatty acid synthase (FASN) in regular chow diet fed mice. The expression of FA oxidation-related genes, such as PPAR-α along with carnitine

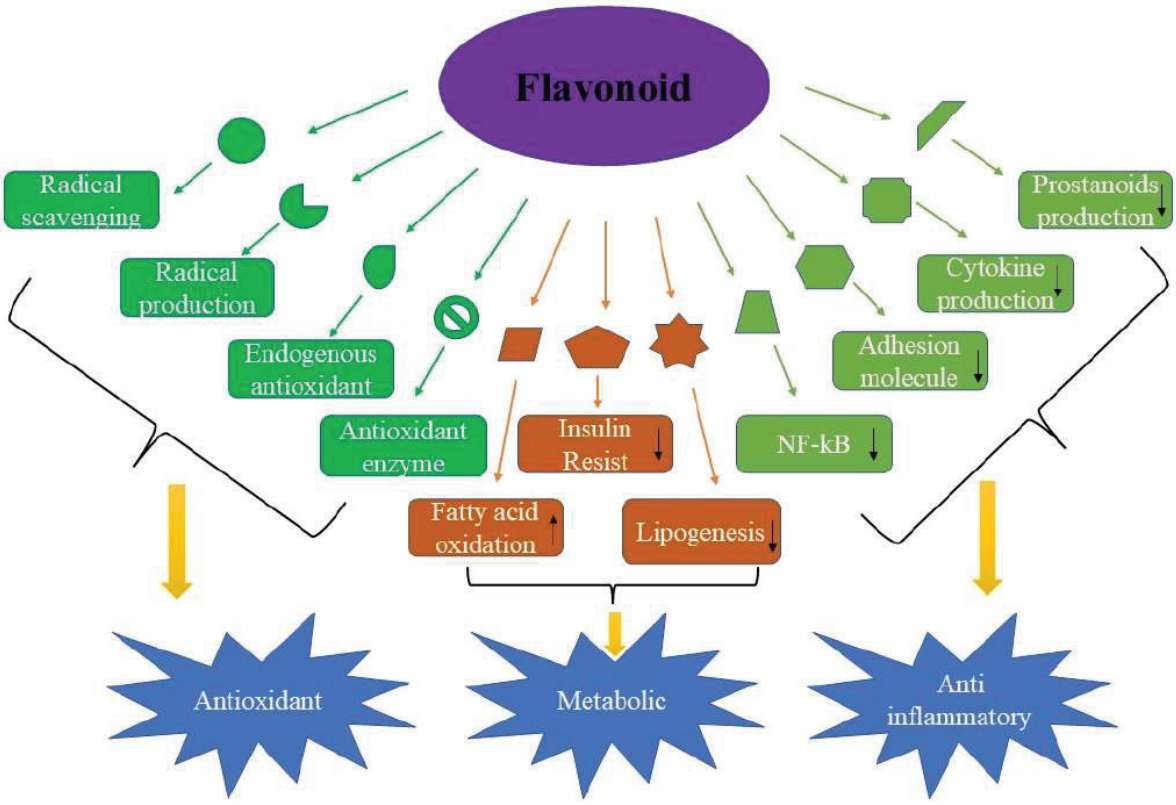


Figure 2. Flavonoids with different stages of action such as radical scavenging, endogenous antioxidant, increased FA oxidation, decreased production of cytokine, prostanoid, IR and lipogenesis for their role as anti-oxidant, metabolic and anti-inflammatory.

Table 2. Pathway and its function for flavonoids.

Natural	Pathway	Function
Flavonoid	PPARα	Stimulates PPARα to reduce steatosis by stimulation of β-oxidation
		PPAR-α inhibits NFκB to alleviate inflammation.
	NFκB	It prevents NFκB translocation to the nucleus but also the transcription of genes involved in the inflammatory response by inhibiting I κB phosphorylation and the IKK complex.
	Inducible NO synthase (iNOS)	Flavonoids inhibit NO production and in addition, it prevents the expression of inducible NO synthase (Yamamoto and Gaynor, 2001).

palmitoyltransferase-1, was increased in FFD mice, which improved saponin extract administration (Wang *et al*., 2021).

Dioscin is considered to be a natural steroidal saponin found in many herbs. It is found to show anti-fungal, anti-hyperlipidemic, and anti-tumor activity (Hsieh *et al*., 2013). When taken orally, it improves fat accumulation in the liver, lowers blood lipid levels, reduces TG deposition via FASN inhibition, promotes FA beta-oxidation, lowers liver cholesterol, regulates the mitogen-activated protein kinase (MAPK) signaling pathway and autophagy, and decrease oxidative stress and inflammation (Liu *et al*., 2015a, 2015b).

Alkaloids

This is a class of naturally occurring nitrogenous organic compounds. It has antifungal, antibacterial, antitumor, and analgesic properties (Kukula-Koch *et al*., 2016; Stegelmeier *et al*., 2015). It has also been shown to have a significant effect on NAFLD. Berberine an alkaloid is frequently used to treat inflammatory disorders and diarrhea in China (Zhang *et al*., 2013). Berberine helps combat metabolic problems such as diabetes and obesity (Zhang *et al*., 2010; Zhou *et al*., 2011). Berberine can be used as a cholesterol-lowering drug due to the distinct mechanism that distinguishes it from statins (Kong *et al*., 2004). When rats were administered an HFD that produced hepatic steatosis, berberine restored systemic alterations in gene expression. The lncRNA MRAK052686 and its associated gene Nrf2 are implicated in the pathogenesis of NAFLD in many modules of berberine-regulated genes (Yuan *et al*., 2015).

Terpenoids

Terpenoids are organic compounds with several hydrocarbon isoprene units and their oxygenated derivatives in their molecular formulae. Aldehydes, alcohols, carboxylic acids, esters, and ketones are examples of oxygenated products. It can be found in abundance in nature and are the primary constituent of various plant essences and pigment resins (Arendt *et al*., 2016). Terpenoids have a variety of physiological functions, including

Table 3. Pharmacological and toxicological effect of various herbal plants.

Plants	Toxicological effect	Pharmacological actions	Phytochemistry	Parts
P. niruri Linn.	After 14 days clinical signs of toxidromes (raising fur, draping, tremors, excitability, miosis, mydriasis, twitching, morbidity, and so on), as well as mortality were noted. This revealed no hematological side effects at either the low or high dose. As a result, acute toxicity of *P. niruri* aqueous leaf extract can be ruled out, and the LD50 of the aqueous leaf extract exceeds 5,000 mg/kg b. wt (Hashem *et al*., 2020).	The treatment of *P. niruri* leaf extract to diabetic hyperlipidemic rats resulted in significant reductions in plasma glucose, total lipids, cholesterol, TGs, low density lipoprotein cholesterol, and very low-density lipoprotein (VLDL)-cholesterol, as well as an increase in plasma High Density Lipoprotein (HDL)-cholesterol. *Phyllanthus niruri* has an effective dose of 1,000 mg/Kg (Hashem *et al*., 2020).	Rutin, Phyllanthin, Quercetin, quercetin3-O-alpha-L rhamnopyranoside, Astragalin, Limonene, p-cymene, Gallocatechin, Prenylated flavanone glycoside, nirurin (5,6,7, 4′- tetrahydroxy-8-(3-methylbut-2-enyl) flavanone-5-O-rutinoside), and quercetol (Bagalkotkar *et al*., 2006).	Aerial
P. emblica Linn.	Through acute exposure in rats, the standardized WEPE fruit with an LD50 > 5,000 mg/kg is regarded as non-toxic. In mice, a dose of 10 g/kg body weight of a 50% ethanol fruit extract causes no acute toxicity (Huang *et al*., 2015).	For 20 weeks, a WEPE fruit reduced body weight and epididymal fats. It also had a more significant effect on serum AST, hepatic steatosis, and oxidative stress. The water extract also reduced SREBP-1c mRNA in the liver while increasing adiponectin mRNA in the peritoneal fat (Huang *et al*., 2015).	Kaempferol-3-O-α-L-(6″-methyl)-rhamnopyranoside, Triactanol, kaempferol-3-O-α-L-(5″-ethyl)-rhamnopyranoside, Triacontanoic acid, β-amyrin ketone, BA, β-amyrin-3-palmitate, gallic acid, daucosterol, ursolic acid, lupeol acetate, oleanolic acid, quercetin and rutin (Li *et al*., 2015).	Aerial
P. urinaria Linn.	Both male and female patients aged 18 to 65 with positive hepatitis B surface antigen tolerate it well for 6 months. It is found that there is no difference in toxicological measures between the treatment and control groups; some participants in both of the groups suffered modest deleterious effects (Geethangili and Ding, 2018).	*Phyllanthus urinaria* has anti-steatohepatitis properties through anti-inflammatory activity viz. reduced TNF-α and IL-6 production via JNK and NFκB pathways), induction of FA oxidation (upregulation of CYP4a10 and C/EBP suppression), and antioxidant properties (reduced CYP2e1 expression) (Geethangili and Ding, 2018).	Lignans, 5-demothoxyniranthin, urinatetralin, D-bursehernin, enterodiol, urinaligran, (−)-syringaresinol tannins, flavonoids, phenolic acids, terpenoids (Geethangili and Ding, 2018).	Leaves
G. glabra Linn.	In the acute trial, mice were given a single dose (2 g/kg) orally. During a subchronic trial, mice were given extract at doses of 50, 100, 500, and 1,000 mg/kg for about 120 days. No significant differences were seen in blood pressure, hematological, and histology of mice. This indicated that it did not result in toxicity or mortality in mice (Kim *et al*., 2020).	In rats, glycyrrhizin has been shown to boost lipoprotein lipase expression, insulin sensitivity, and serum cholesterol levels (Eu *et al*., 2010; Lim *et al*., 2009).	Licoricidin, Glabridin, 31-O-Methylglabridin, Phaseollinisoflavan, Hispaglabridin A, Hispaglabridin B, Glabrene, Licoisoflavone Aα & Bα, Licoriconeα, Prunetin, Formononetin, Liquiritigenin, Liquiritin apioside, Licoisoflavanone, Licoflavoneb, 4'-7-Dihydryoxyflavoneb, Coumestan,5-O-Methylglycyrola, Herniarin, GCM A & B, Licuroside (Fenwick *et al*., 1990).	Root
A. sativum Linn.	Garlic infusions at high doses resulted in respiratory distress, weight loss, hair loss, and epidermal loss on the ventral side. The limbs had gone numb (Zhang *et al*., 2019).	In men, a higher intake of raw garlic was linked to a lower prevalence of NAFLD, but not in women. These findings imply that raw garlic consumption may protect against NAFLD (Zhang *et al*., 2019).	Ajoenes, thiosulfinates, vinyldithiins, sulphides, diallyl trisulfide, Alliin, S-propyl-cysteine-sulfoxide, allicin and S-methyl cysteine-sulfoxide (El-Saber Batiha *et al.*, 2020).	Bulb
C. longa Linn.	In acute or subchronic toxicity trials in guinea pigs, rats, monkeys, and dog's turmeric/alcoholic extract of turmeric/curcumin showed no harmful effects (even at large dosages) (Deshpande *et al*., 1998).	Over the course of 12 weeks, turmeric consumption reduced serum levels of glucose, leptin, insulin, and homeostatic model assessment of IR when compared to the placebo group. In comparison to the placebo group, there were no significant changes in weight, BMI, or liver enzymes (Navekar *et al*., 2017).	Curcumin, demethoxycurcumin, 1-hydroxy-1, 7-bis (4-hydroxy-3-methoxyphenyl)-(6E)-6-heptene-3, 1-(4- hydroxy-3, 5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-(1E, 6E)-1, 4-dione, 4-dien3-one; 3, 4-dihydroxyphenyl-1, 6-heptadiene-3, 5-dione and 1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one (Niranjan and Prakash, 2008).	Rhizome

Continued

Plants	Toxicological effect	Pharmacological actions	Phytochemistry	Parts
C. verum J. Presl	A 13-week repeat-dose oral toxicity research indicated that the body weights of rats were normal, kidney/liver weight and total cholesterol levels were elevated after receiving up to 2,000 mg/kg. A subsequent 8-week repeat-dose oral toxicity study disclosed that renal function increased remarkably, liver histology revealed distortions in hepatocytes, degenerative alterations in the glomerular and Bowman's capsules (Vijayakumar *et al*., 2021).	Cinnamic aldehyde (6.25–50 μM) significantly reduced NO, TNF-α, and prostaglandin E 2 levels and inhibited the protein expression of iNOS, COX-2, NFκB, and IκBα in lipopolysaccharide (LPS) stimulated mouse macrophages (Zhang *et al*., 2019).	Glycoside, Lignan, Lactone, Phenylpropanoid, and Terpenoids includes monoterpenes, diterpenes and sesquiterpenes which includes α-terpineol, β-bisabolene, α-bisabolol, linalool, camphene, β-pinene, camphor, geranyl acetate, curcumene, α-cadinol, α-calacorene, caryophyllene oxide, espatulenol, 15-hydroxy-α-cadinol, 1-(1,5-dimethyl-4-hexenyl)-4-methylbenzene, cedrane, (−)-isoledene, α-bulnesene, trans-caryophyllene, 16-O-β-d-glucopyranosyl-19-deoxycinncassiol G (Zhang *et al*., 2019).	Bark
L. usitatissimum Linn.	The acute and sub-chronic toxicities of flaxseed-derived maillard reaction product (MRP) revealed that the LD50 in rats was higher than 15.0 g/kg BW, but the ED50 of MRPs in the acute toxicology investigation was 12.3 g/kg BW. Consuming less than 0.75 g had no influence on weight, mortality, food intake, histology, gross pathology, hematology or serum biochemistry (Wei *et al*., 2019).	Dietary flaxseed oil reduced inflammation along with hepatic oxidative stress which helps to slow the progression of NAFLD. Flaxseed oil shows no effect on body weight change but significantly minimizes IL-6, TNF-α, and MCP-1 levels (Han *et al*., 2017).	Phytochemicals that are present in flaxseed are triterpenoid, steroids, glycosides, saponins, alkaloids, flavonoids, tannins, proteins, free amino acids, carbohydrates, and vitamin C. The phytoestrogen present are secoisolariciresinol and matairesinol (Yasmeen *et al*., 2018).	Seed
C. sinensis (Linn.) Kuntze	26-week old rats were employed and administered tea flower extract (TFE). During the 14-day period, female rats' average body weight increased from 191.2 ± 5.9 g to 216.1 ± 8.3 g, whereas male rats' average body weight increased from 192.8 ± 6.1 to 289.4 ± 12.3 g. The gross pathology findings revealed no visible lesions following the sacrifice on the 14th day. As a result, no indication of acute TFE toxicity in rats was discovered (Li *et al*., 2011).	GTE anti-inflammatory effects on gut barrier function, as well as prebiotic and antimicrobial effects on gut microbiology, help to limit the translocation of gut-derived endotoxins (e.g. LPSs) to the liver, where they would otherwise upregulate NFκB activation by Toll-like receptor-4 signaling (Hodges *et al*., 2020).	It consists mainly of total sugar (45.4%), polyphenols (13.6%), proteins (16.4%), water (9.1%), total ash (7.2%), caffeine (3.1%), saponins (0.9%), Floratheasaponins, Catechin, epicatechins, Gallocatechin, (−)-epicatechin gallate, amino acids (2.4%), epigallocatechin, (−)-epigallocatechin gallate (Gramza and Korczak, 2005).	Flower
M. rubra (Lour.) Siebold & Zucc	There were no clinical indications or deaths in the acute oral toxicity experiment at the bayberry kernel oil feeding dose level of 9.446 g/kg body weight. Furthermore, physical examinations revealed no noticeable treatment-related health changes in the 305 mice. All groups gained weight, and no significant differences were found (Xia *et al*., 2013).	By increasing plasma antioxidants and inhibiting the inflammatory apoptotic response, bayberry juice can protect against NAFLD during a 4-week period (Guo *et al*., 2014).	Myricetin, myricetin-3-O-rhamnoside, myricetin hexoside, quercetin, quercetin-3-O-rhamnoside, quercetin hexoside-gallate, quercetin-3-O-rutinoside, protocatechuic acid, p-hydroxybenzoic acid, caffeic acid, gallic acid, myricanone, kaempferol hexoside, myricanol, myricanene A & B, 16-methoxy acerogenin B, quercetin-3-O-glucoside, quercetin-3-O-glucoside, myricanone 5-O-α-Larabinofuranosyl-(1→6)-β-D-glucopyranoside, EGCG (Sun *et al*., 2013).	Fruit
S. marianum (Linn.) Gaertn	At doses up to 100 μM, silybin, silydianin, and silychristin were found to be safe and did not cause cytotoxicity in blood platelets. Oral ingestion of capsules containing 175 mg of milk thistle extract thrice a day (tid) for about 14 days exhibited no severe toxicity (Soleimani *et al*., 2019).	Silymarin suppresses the release of cytokines like TNF-α, adhesion molecules like E selectin, as well as the signaling pathways of NFκB, NO, and 5-lipoxygenase by exerting anti-inflammatory actions (Abenavoli *et al*., 2018).	Flavonolignans-Silymarin, Silybin, isosilybins (A and B), silydianin, silychristin, Silibinin-(2R,3R) -3,5,7-trihydroxy, [1,4] dioxin-6-yl] chroman-4-one silybin A and B [(2R,3R)-2-((2S,3S)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl)-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyra-n-4-one] (Abenavoli *et al*., 2018; Kirschweng, 2018).	Fruit

cough relief, expulsion of wind, induction of sweating, insecticide activity, and pain relief (analgesia) (Choi *et al*., 2013).

Betulinic Acid (BA) is a pentacyclic lupane type triterpene (3B-hydroxy-lup-20(29) en-28-oic acid). BA can be found in various foods, medicinal herbs, and plants, mainly birch bark. It is non-toxic in mice at concentrations of up to 500 mg/kg body weight, and the main mechanism for its hepatoprotective qualities is its anti-oxidants, which boost the body's redox system and lessen liver lipid peroxidation. By reducing hepatic steatosis via the calcium/calmodulin-dependent protein kinase-AMPK-SREBP1 signaling pathway, BA efficiently reduces intracellular lipid accumulation in liver cells, limiting fatty liver deposition. It has also altered the way MAPK pathways are controlled. BA therapy inhibits HFD-induced changes in nuclear SREBP 1c activity and hepatic TG accumulation (Quan *et al*., 2013).

Polyphenols

Polyphenols are considered as a diverse class of plant-derived compounds that consist of various water-soluble anti-oxidants reported as health-promoting agents. It can be suggested in the treatment of various metabolic disorders. Their bioactive compounds are abundant in fruits, vegetables, and beverages such as coffee, tea, red wine, and dark chocolate (Abenavoli *et al*., 2017).

Curcumin, the yellow pigment found in the *C. longa* plant is derived from curry and spices. Its anti-oxidant effects have been extensively researched in the context of liver metabolism (Pan *et al*., 2014). Curcumin protects the liver by suppressing the expression of NFκB target genes such as monocyte chemotactic protein 1 (MCP-1), cyclooxygenase-2 (COX-2), and intercellular cell adhesion molecule-1. According to Vizzutti *et al*. (2010), curcumin can reduce alpha-smooth muscle actin levels in NASH mice, along with the formation of ROS and tissue inhibitors of metalloproteinases-1 secreting activated hepatic stellate cells. Curcumin alleviates NAFLD by activating Nrf2, AMPK, and nuclear receptors, altering lipid metabolism and oxidative stress, and inhibiting NLRP3 inflammasome activation and gut microbiota, reducing inflammation and steatosis (Yan *et al*., 2020).

Resveratrol is a phytoalexin polyphenolic molecule that has been demonstrated to assist in the pathology of NAFLD (Bujanda *et al*., 2008). Some of the methods used to decrease inflammation include inhibition of pro-inflammatory mediator synthesis and release, modification of eicosanoids synthesis, prevention of kupffer cell adhesion molecules, and inhibition of COX-2, nitric oxide (NO) synthase via inhibitory effects on NFκB or activator protein-1 proteins (Alarcon De La Lastra and Villegas, 2005; Jang *et al*., 1997).

Chloroquine inhibits autophagy in acute myeloid leukemia-12 (AML-12) cells, which suggests that resveratrol's actions are likely linked to autophagy activation (Ji *et al*., 2015). According to the research, resveratrol has also been shown to diminish inflammatory liver damage in methionine-choline deficient diet-induced NASH mice in addition to IL-1, IL-6, ALT, aspartate aminotransferase (AST), and TNF-α levels in the blood that have been associated with autophagy (Shen *et al*., 2019). Furthermore, resveratrol has been shown to heal liver injury in experimental mice by activating autophagy and reducing NFκB activation (Li *et al*., 2014), implying that activation of autophagy could be used as an anti-inflammatory method to prevent NAFLD progression (Zhang *et al*., 2018)

CONCLUSION

The use of herbal medicine becomes vital for treating a variety of human ailments. The studies conducted with a deep understanding of the root cause of the disease have been applied widely to modify the ancient form of treatment to globally accepted medicines. The development of herbal medicine regarding its pathogenesis and pathway of the disease, i.e., for the NAFLD, has been widely studied and provided no prominent data with the background of the disease. There is no Food and Drug Administration approved medicines for NAFLD treatment. There is a wide rush in formulating and developing a drug either in allopathic medicine or the Indian system of medicine for the treatment of NAFLD. Herbal drugs will have a significant role in the future when the pathway of the disease is well studied with herbal plants. When compared to allopathic medicine, herbal medicine is cost-effective as it is readily available and needs only a thorough study for its scientific validation for proof of toxicity and efficacy.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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