Review Article

Harnessing the potential of Plants and their bioactive compounds in NAFLD (Non- Alcoholic Fatty Liver Disease) – A Systematic Review.

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ABSTRACT

Fatty liver disease (FLD), referred to as non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD), is a severe health problem that affects a large number of individuals worldwide, particularly one in every three in India. The main cause of FLD is lipid accumulation in the liver, which is accompanied by oxidative stress and inflammation. This study examines non-alcoholic fatty liver treatment with a focus on herbal medicine treatment. Non-alcoholic fatty liver disease (NAFLD) occurs when triglyceride mass accumulates by 5% in the liver cells of non-alcoholics. It is the most frequently encountered liver disorder in the world. Numerous studies on NAFLD and its pathological mechanism are ongoing. Natural compounds play an important role in the development of new medications and active ingredients. Plants compounds are used to treat various liver conditions. However, in severe cases, using just one medicinal plant is insufficient. These plants contain powerful medicinal compounds such as alkaloids, glycosides, saponins, flavonoids, antioxidants, and terpenes that have hepatoprotective effects. The purpose of this study is to conduct a global review of medicinal herbs used to treat NAFLD. The outcomes of the current review investigation revealed that 39 plants are traditionally used to treat NAFLD around the world. However, more study is required to understand the specific mechanisms and toxic effects of these plants in humans, for considering them as an alternative agent in the management of NALFD.

Keywords: NAFLD, hepatitis, lipid accumulation, medicinal plants, phytochemicals

1. INTRODUCTION

The liver is the vital and largest gland in the body and plays a major part in many metabolic activities of the body such as digestion, clotting factors, formation of hormones, serum proteins, cholesterol, bile, enzymes, maintain homeostasis, detoxification of the toxic substances (certain drugs, alcohol) and metabolism of the various components (carbohydrates, proteins and lipids) [1]. Weakening of the liver causes serious health issues. Many biochemical reactions of the body are regulated by highly specialized liver tissue [2]. This massive biochemical plant performs a variety of functions, including the synthesis of albumin, globin, cholesterol, blood coagulation factors, and immune system factors, the production of glucose from specific amino acids, glycerol, and lactate, and the synthesis of phospholipids, lipoproteins, and triglycerides. It is evident that any disturbance in the function of the liver causes a series of ailments that can cause irreversible damages to liver, even to Whole body [3].

Epidemiology, Prevalence and Management of NAFLD

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide, affects nearly 30% of adults in the general population and approximately 70% of those with obesity and type 2 diabetes (T2DM) and is already among the top indications for liver transplantation in most of the developed countries. In the last decade, it has become

evident that NAFLD is a multi-systemic disease, which is associated not only with adverse hepatic outcomes but also with relevant extra-hepatic complications, such as T2DM, cardiovascular disease (CVD), chronic kidney disease (CKD) and specific extra-hepatic cancers. In 2020, a panel of international experts has proposed the change of the terminology from NAFLD to metabolic associated fatty liver disease (MAFLD), as well as an update in the definition of fatty liver disease. Specifically, the diagnosis of MAFLD can be supported by the presence of hepatic steatosis, as detected by serum biomarker scores, imaging methods or histology, in individuals with overweight/ obesity, T2DM or multiple metabolic alterations. Given these premises, fatty liver disease is gaining more and more attention in both clinical and basic research [4].

Non-alcoholic fatty liver disease (NAFLD) is a condition where 5% of triglycerides accumulate in liver cells without inflammation or ulcers. It has stages, including liver fat accumulation, non-alcoholic steatohepatitis, and cirrhosis. The disease can lead to liver ulcers and severe liver function impairment, potentially causing death. Ludwig first diagnosed NAFLD in 1980 [5].

Non-alcoholic fatty liver disease can sometimes lead to liver cancer. According to estimates, in patients with the first stage of fatty liver, the likelihood of the disease progressing to liver cirrhosis in the next two decades of life is about 1-2%, whereas it is reported 5-11% for those who have passed the hepatic steatosis stage. It is closely associated with metabolic syndrome, which includes abdominal fat, obesity, dyslipidemia, insulin resistance, high blood pressure, and elevated triglyceride levels. According to the World Health Organization, the global prevalence of this disease is increasing as a result of individual lifestyles such as nutrition, exercise, smoking, sleep, and rest, which are influenced by socialization. Over the past few decades, the prevalence of NAFLD has significantly increased worldwide, along with the rise in type 2 diabetes and obesity. However, due to a variety of genetic and sociodemographic factors, there are notable regional variations in the rates of rise in the incidence of NAFLD, as well as in the severity of NAFLD, NASH, and the associated problems among different ethnic groups. According to a recent comprehensive study, the prevalence of NAFLD has risen by more than 50% worldwide over the past three decades, from 25.3% in 1990–2006 to 38.0% in 2016–2019.World Health Organisation also reported that the prevalence of fatty liver disease is much higher in men than in women. Studies consistently show that men are more likely than women to be diagnosed with non-alcoholic fatty liver disease (NAFLD), which means that men are more likely than women to develop fatty liver disease. If current trends continue, the prevalence of NAFLD is expected to rise drastically across many global areas by 2030 [6.

Causes

Fatty liver disease (FLD) is caused by two types of conditions: indirect (hypothyroidism, polycystic ovarian syndrome, pituitary hypoplasia and sleep apnea) and direct (abdominal obesity, type 2 diabetes, metabolic syndrome). Other risk factors include congenital liver diseases, high Cholesterol levels, rapid weight loss, intestinal bypass surgery, protein and calorie malabsorption, inflammatory liver diseases, toxic substances, and certain medications. Pregnancy can also exacerbate fatty liver disease by causing hormonal imbalances and weight gain. Managing these conditions can aid in the treatment of the disease [7].

Symptoms and Diagnosis

Majority of patients have no symptoms, and based on abnormal liver tests, it is being diagnosed. Following hepatitis and chronic liver disease, this is the most familiar cause of abnormalities in liver enzyme. More than three-quarters of patients show an increase in liver size during a clinical examination, with the most frequent symptom being excessive fatigue, pain in the upper right abdomen and lethargy. Patients may report tenacious itching, jaundice, and complications caused by high portal vein pressure. Hepatomegaly is most commonly seen as the disease progresses to liver cirrhosis. Other signs of liver cirrhosis include ascites, spider angioma, palmar erythema, splenomegaly, and asterixis. Rather, in extremely rare instances, the disease's progression is halted or even reversed

without any specific treatment, for unknown reasons. Ultrasound (USG) is one of the most appropriate and readily available investigative methods for determining steatosis [7].

The non-alcoholic fatty liver disease (NAFLD) activity is graded using a histological scoring method called the NASH (Non-alcoholic Steatohepatitis) score. Steatosis, lobular inflammation, and hepatocyte ballooning scores are added to determine the final score. The range of the score is 0 to 8.

Interpretation of scoring

0–2: Typically regarded as not indicative of NASH

3–4: May be regarded as borderline, positive, or non-diagnostic for NASH.

5–8: Typically seen as a NASH diagnosis

- A diagnosis of NASH should be made first, then the NAS is used to grade activity.
- The NAS score is correlated with a diagnosis of NASH, but it's not a reliable way to establish the presence or absence of NASH.

The risk of NASH in individuals who are morbidly obese is predicted by the NASH clinical score system. There are grades for no NASH, mild NASH, moderate NASH, and severe NASH on the NSFIB Non-alcoholic Steatohepatitis (NASH)-Fibro Test.

Treatment

The person with fatty liver must first be evaluated for other co-morbidities, and if other diseases exist, proper treatment should be initiated; unless those infections are treated or controlled, the person is at risk of developing fatty liver. Regarding non-pharmacological treatment, it can be said that the disease's onset can be avoided and, in many cases, the disease can be treated by controlling its underlying causes, such as diabetes, blood lipids, weight loss, or stopping the substances that cause it. It is crucial to remember that rapid weight loss followed by surgeries to reduce obesity can have a totally reversible effect on the treatment of disease, even though numerous studies have found that weight loss is the most desirable treatment approach. A well-balanced diet that includes less calorie and vitamin-rich foods and essential minerals and proteins can be an effective weight-management strategy. Controlling underlying metabolic diseases in fatty liver patients, such as diabetes and blood lipids, can help to improve the condition. In patients with irreversible liver cirrhosis caused by NASH, "transplantation of liver" may be the only appropriate treatment option. Obesity, diabetes complications, cardiovascular disease, and concerns about post-transplant complications are all potential barriers to transplantation.

Because lipid accumulation is so important in the progression of NAFLD, anti-NAFLD drug development is heavily focused on inhibiting it. Numerous anti-NAFLD drugs are presently in preclinical development. Metformin, fibrates and statins are all being tested as NAFLD treatments in clinical trials. Though, these medications come with serious side effects, such as an increased risk of osteoporosis and infection. Thus, novel treatment candidates with high efficiency and minimal side effects are immediately needed for the treatment of NAFLD [8].

Plants in the management of fatty liver

The usage of medicinal plants to treat diseases antecede as far as human history. Humans have used medicinal herbs to treat themselves since the beginning, based on their experience and acquired knowledge, as well as the needs of their lives on Earth.

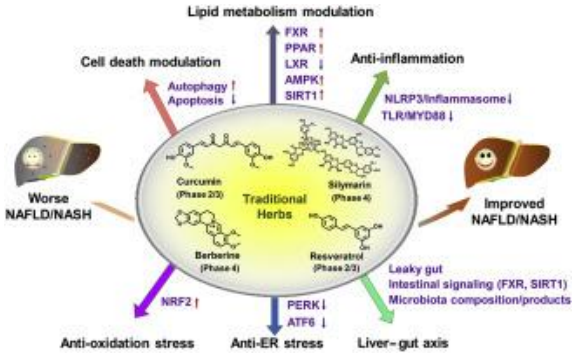

Figure1: Medicinal plants in the management of NAFLD

Despite the fact that advances in industrial drug production have prevented humans from focusing on the oldest and most accessible resources, many pharmaceutical scientists see the 20th century as a return to nature and the use of

herbal medicines. The beneficial properties of herbs, as well as the low risk of side effects, may highlight their role in the treatment of numerous diseases.

This review article tries to compile reported articles on the therapeutic effects of herbal medicines on non-alcoholic fatty liver that are available in various scientific journals and may be useful to scientists, scholars working in the field of pharmacology and health professionals, therapeutics to develop evidence-based alternative medicine for the management of fatty liver in humans and animals. This piece of work also demonstrates the significance in plants in the quest to reveal their potential effects on treating NAFLD and the accountable bioactive components.

Table 1: Therapeutic effects of bioactive compounds from medicinal plants in the management of Non-Alcoholic Fatty Liver Disease (NAFLD)

Scientific name	Bioactive Component/ Extract	Study Model	Main effects	Reference
Allium cepa (Onion)	Whole extract	SD rats	Alleviating steatosis, ballooning, and lobular and portal inflammation	9
Allium sativum (Garlic)	Allicin	C57BL/6 mice	Reduces steatosis, inflammation, and gut dysbiosis	10
Apium graveolens (Celery)	Whole seed Extract	HFD rats	Showed ameliorative impacts against NALFD progression	11
Asparagus officinalis (Asparagus)	Root extract	HFD rats	Reduces the blood lipid level	12
Berberis vulgaris (Barberry)	Whole Extract (Capsules)	Human Patients	Reduces liver enzyme level and lipid levels in blood serum	13
Beta vulgaris (Beets)	Whole extract	Human Patients	Reduced the liver enzyme level and HDL, LDL level	14
C. zeylanicum (Cinnamon)	Whole extract (Capsules)	Human Patients	Ameliorates the hepatic enzyme and LDL level	15
Camellia sinensis (Green tea)	Catechins	HepG2 cells C57BL/6 mice	Reduces lipid accumulation, increasing gene expression related to catabolism of TG and fatty acid	16
	Phenols Flavonoids	Wistar rats	Improving hyperlipidaemia and oxidative stress	17
Camellia sinensis (Black tea)	Polyphenol	3T3-L1 pre-adipocytes C57BL/6N mice	Reduces lipid accumulation, oxidative stress, and inflammation and improving the intestinal environment	18
Cassia obtusifolia (Chinese senna)	Whole Extract	Wistar rats	Reduces histopathological changes, dyslipidemia, and lipid peroxidation in the liver	19
Cicer arietinum (Chickpea)	Whole seed Extract	HepG2 cells HFD rats	Improved lipid profile and hepatic enzymes	20,21
Citrus medica L. (Citron)	Flavonoids	HFD rats	Suppressed both systemic and intrahepatic inflammation	22
Coffea arabica (Coffee)	Caffeic acid	AML 12 C57BL/6 mice	Reduces steatosis endoplasmic reticulum stress and increasing autophagy	23
	Trigonelline	AML 12 HepG2 cells C57BL/6J mice	Reduces steatosis and lipotoxicity and promoting autophagy	24
	Pulp extract	Wistar rats	Reduces steatosis, insulin resistance, and oxidative damage	25
	Seed extract	C57BL/6J Mice	Improving liver fat oxidation, energy metabolism, intestinal cholesterol efflux, and gut permeability	26
	Caffeine	C57BL/6J mice	Alleviating steatosis	27
	Caffeine	SD rats	Increasing the susceptibility of NAFLD	28
Crocus sativus (Saffron)	Crocin	Wistar rats	Alleviating histopathological changes, dyslipidemia and inflammation	29
Cucumis melo var. (Melon)	Whole fruit extract	Syrian golden hamsters	Exhibits antidyslipidemic and antiglycemic activity along with the	30

			antiadipogenic activity	
Cuminum cyminum (Cumin)	Seed extract	HFD rats	Ameliorates dyslipidemia, oxidative stress and hepatic damage	31
Curcuma longa (Turmeric)	Curcumin	C57BL/6 mice	Regulating exogenous xenobiotic metabolism and bile acids	32
		PBM cells C57BL/6 mice	Preventing oxidative damage, inflammation and intrahepatic CD4+ cell accumulation	33
		AML12 cells C57BL/6J mice	Reduces lipid accumulation, oxidative damage and inflammation	34
Cydonia oblonga Mill. (Quince)	Whole leaf Extract	Cell cultures	Lower liver enzyme levels and reduces Lipid peroxidation	35
Daucus carota (Carrot)	Fruit extract	Wistar rats	Improves DHA levels in liver and decreases production of MUFA	36
Fallopia multiflora (Polygonum)	Stilbenes Anthraquinones	L02 cell Wistar rats	Improving mitochondrial β oxidation and dyslipidemia	37
Ficus carica (Fig)	Nano extract	STZ-induced diabetic rats	Ameliorates the lipid levels in blood serum	38
Hovenia dulcis (Oriental raisin tree)	Whole Extract	SD rats	Alleviating steatosis and inflammation	39
Malus domestica (Apple)	Polyphenols	HepG2 cells	Improved Hepatic IR	40
Nigella Sativa (Black seed)	Seed extract	Human Patients	Reduces inflammatory biomarkers	41
Nobilis Laurus (Bay)	Whole leaf extract	Hep G2 cells	Exhibits anti-dyslipidemic and anti-hyperglycemic activity and reduces inflammation	42
Olea europaea (Olive)	Nano extract	STZ-induced diabetic rats	Ameliorates the lipid levels in blood serum	43
Panax ginseng (Ginseng)	Ginsenosides	L02 cells	Reduces steatosis, oxidative stress, and mitochondrial dysfunction	44
Platycodon Grandiflorum (Pomelo)	Platycodin D	SD rats	Inhibiting inflammation and endotoxic process	40
Portulaca oleracea (Common Purslane)	Whole extract (Capsules)	Human Patients	Improved lipid profile and liver enzyme Profile	45
Prunus avium (Sweet cherry)	Anthocyanins	HepG2 cells LO2 cells	Activating autophagy	46
Punica granatum (Pomegranate)	Peel Extract	Human Patients	Reduced hepatic steatosis	47
Rhodiola rosea (Rose Root)	Salidroside	L02 cell	Alleviating inflammation, steatosis and induces autophagy	48
	Silybin	FaO cells	Reducing fat accumulation and mitochondrial damage	49
	Silybin	C57BL/6J mice	Regulating lipid metabolism	50
Rosa damascene (Iranian Damask Rose)	Whole extract (Capsules)	Human Patients	Ameliorates the Hepatic enzymes and LDL, slight increase in HDL	51
Solanum lycopersicum (Tomato)	Lycopene	SD rats	Reducing gut dysbiosis	52
	Lycopene	SD rats Wistar rats	Alleviating liver injury, lipid accumulation, fat infiltration, and oxidative stress	53
Spinacia oleracea (Spinach)	Whole Extract	Wistar rats	Ameliorates the gut microbiota and dyslipidemia	54
Taraxacum coreanum (Dandelion)	Whole Extract	SD rats	Improving body composition, glucose metabolism, ethanol degradation, and gut dysbiosis	55
Vitis vinifera L (Grape)	Resveratrol	HepG2 cells	Inhibiting lipogenesis and proliferation	56
	Resveratrol	HepG2 cells SD rats	Inhibiting oxidative damage and lipid accumulation	57
	Resveratrol	HepG2 cells, C57BL/6 mice	Reducing the expression of SREBP-1c and FAS genes	58
	Polymerized Anthocyanin	C57BL/6J mice	Improving liver function, dyslipidemia, and hepatic steatosis	59
	Rutin	RAW 246.7 cells, *HepG2* cells,	Inhibits oxidative damages, lipogenesis, and	60

		C57BL/6 mice	autophagy	
Zingiber officinale (Ginger)	Rhizome extract	Human Patients	Improves HDL level	61

Conclusion

Fatty liver disease (FLD) is one of the most prevalent gastro-intestinal diseases, and its severity is largely determined by an individual's lifestyle, diet, and level of activity. The use of synthetic medicine (allopathic) can have serious side effects on the liver and is expensive. As a result, medicinal plants (bioactive constituents) are used to treat liver conditions with few complications and at a very low cost. This review article focuses on hepatoprotective plants. Plants contain a wide range of constituents, such as alkaloids, glycosides, terpenes, phenols, flavonoids, and saponins, which are used to treat a various liver disease. Extracts from medicinal plants lay the groundwork for the discovery of new compounds (drugs). In accordance to the present review, we found that the plants from various families have had beneficial effects in managing fatty liver disease. Amongst the plants and its bioactive components reviewed, silymarin, resveratrol, ginsenosides, salidroside, curcumin showed better effects in the treatment of NAFLD. However, this can only be proven by further and extensive studies.

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Contribution

All authors contributed equally to content discussion, writing and reviewing the manuscript.

Conflict of interest

The authors declare no competing interests.

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