Print ISSN: 2958-3675 | Online ISSN: 2958-3683
International Journal of Medical and Pharmaceutical Research
Available Online at https://ijmpr.in/
ORCiD ID: 0000-0002-3849-6959
Volume 4, Issue 1; 2023; Page No. 01-07
Review Article Open Access

Management of Non-Alcoholic Fatty Liver disease with Unani medicine: A Review

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ABSTRACT
The prevalence of non-alcoholic fatty liver disease (NAFLD), a common chronic liver condition, is high in developed nations. One of the main contributors to chronic liver disease and cryptogenic cirrhosis has been identified as NAFLD. A greater risk of developing NAFLD exists in those with obesity, insulin resistance, diabetes mellitus, hyperlipidemia, and hypertension. The connected key pathological processes, such as insulin resistance, abnormal lipid metabolism, oxidative stress, inflammation, apoptosis, and fibrosis, are linked to the development of NAFLD. From basic steatosis to non-alcoholic steatohepatitis, NAFLD can evolve (NASH). For the treatment of NAFLD, the herbal medicine has had significant positive effects on the reduction of inflammation and steatosis. It has been discovered that these effects involved the various lipid metabolism and inflammatory regulation pathways. In this study, we focus particularly on the use of herbal medicine for treating fatty liver disease and provide an overview of the research on NAFLD, herbal medicine research, and the idea and function of unani medicine in treating fatty liver disease.

Keywords: *Cryptogenic cirrhosis, Obesity, Hyperlipidaemia, Insulin resistance, Apoptosis*

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INTRODUCTION

Large vacuoles of triglyceride fat build up in the liver cells, causing fatty liver, commonly known as fatty liver disease (FLD), which is reversible (i.e. abnormal retention of lipids within a cell). Fatty liver, which affects people with excessive alcohol use and obesity worldwide and has a variety of causes, might be regarded as a single disease (with or without effects of insulin resistance). Additional illnesses that affect fat metabolism are linked to the disorder [1]. Alcoholic FLD and non-alcoholic FLD both exhibit microvesicular and macro vesicular fatty alterations at various phases, making it difficult to discriminate between them morphologically. Alcoholic Steatosis or Non-Alcoholic Fatty Liver Disease (NAFLD), and the more severe variants as Alcoholic Steatohepatitis (part of alcoholic liver disease) and Non-Alcoholic Steatohepatitis, may be used to describe fatty liver when the contribution of alcohol is taken into account (NASH). Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders in the world, and its advanced stage manifests as hepatic fibrosis and inflammation. Cirrhosis, liver cancer, and liver failure can all develop as a result of NASH [2, 3].

Due to the increased prevalence of obesity in both children and adults, non-alcoholic fatty liver disease (NAFLD) is now a significant public health concern. The hepatic component of metabolic syndrome is thought to be represented by NAFLD, which is characterised by hepatic steatosis (the presence of fat in the liver parenchyma without inflammation) in the absence of excessive alcohol use (less than 21 units for men and 14 units for women) [6]. NAFLD is a spectrum of diseases that includes simple steatosis, steatohepatitis, fibrosis, and cirrhosis (fat in the liver parenchyma accompanied by inflammation, hepatocyte ballooning, and lobular inflammation) [2]. Simple steatosis (SS) seldom develops to severe disease, whereas non-alcoholic steatohepatitis (NASH) progresses to fibrosis and cirrhosis in 20% of patients over the course of 15 years [5].

PATHOGENESIS

The "many organs-multiple hits" theory, which demonstrates crosstalk between the liver and several organs, including the gut, white/brown adipose tissue, skeletal muscle, and central nervous system, suggests that a number of mechanisms contribute to NAFLD pathogenesis [6]. Changes in the composition of the gut microbiota and changes in

intestinal lipid signalling can cause intestinal damage and toxic microbiota products, which may facilitate the entry of pathogen-associated molecular proteins (PAMPs) or damage-associated molecular proteins (DAMPs) into the liver through the portal vein. The intricate link between the liver and intestine suggested by Vannim in 2009 is represented by the gut-liver axis, which is crucial in the development of NAFLD [7, 8].

The host's bile acid metabolism, which is strongly associated to NAFLD pathogenesis, may change as a result of gut dysbiosis, which may also change the gut microbiota's capacity for metabolism [9]. The intestinal flora is necessary for the conversion of bile acids and functions as signalling molecules in extra hepatic and hepatic tissues to control the metabolic pathways for lipids and carbohydrates as well as energy homeostasis [10]. The bile acid metabolism and farnesoid X receptor (FXR)/endogenous takeda G-protein-coupled receptor 5 (TGR5) signal transduction pathways, which are crucial in regulating the de novo synthesis of fat in the liver and the transport of triglycerides, can therefore control the occurrence and development of NAFLD. In addition, numerous studies have shown that the gut microbiota plays a significant role in obesity and insulin resistance (IR), which are linked to the development of NAFLD [11]. Although these modifications can be reversed by transplanting normal flora to obese individuals, Firmicutes and Actinomycetes are substantially more prevalent in obese patients than Bacteroides [12, 13]. Additionally, research indicated that intestinal flora transplantation in conjunction with gut dysbiosis repair could improve metabolic syndrome and insulin sensitivity [14].

EPIDEMIOLOGY

The global pooled prevalence of NAFLD is now estimated to be 24% due to the pandemic spread of obesity, mainly in western nations [15]. It is noteworthy that 8% – 19% of NAFLD patients in Asia are reported to be lean or non-obese [16]. In the US, NAFLD is now the second most common reason for liver transplantation [17]. It is estimated that 16% of normal weight people without metabolic risk factors have NAFLD [18], compared to 43-60% of diabetic patients [19,20], 91% of obese patients after bariatric surgery [21], and up to 90% of patients with hyperlipidemia [22]. Additionally, the prevalence of NAFLD rises with age, from less than 20% in those under 20 to more than 40% in those over 60 [23]. While the progressive NASH is resistant to treatment, the non-progressive stage of NAFLD is asymptomatic and pharmacologically treatable. When treating NAFLD, the majority of commercially available medications, such as vitamin E, only reduce hepatic steatosis and inflammation while having minimal effect on the increasing fibrosis [24,25].

Numerous clinical trials assessing various current NASH medication candidates have fallen short of their primary objectives or have shown only modest therapeutic efficacy, such as obeticholic acid [26]. There are still a number of medications being developed for NASH, including nuclear receptor agonists (obeticholic acid, GFT505, elafibranor), insulin sensitizers (glitazones, pioglitazone, metformin), and glucagon-like peptide-1 receptor agonists [27-29]. Promising anti-NASH treatments can take up to three years to be registered, and up until recently, the U.S. Food and Drug Administration (FDA) has not authorised any medications to treat NASH. Only bariatric surgical treatment or non-pharmacological weight loss strategies such a healthy lifestyle, nutrition, and/or physical activity are currently effective [30, 31]. Therefore, there is an unmet medical need for the creation of drugs to treat NAFLD, particularly the incurable NASH.

Concept of fatty liver in Unani system of Medicine

The synthesis of Akhlaat is regarded to be the centre of all metabolic processes in the body according to the Unani medical system, hence liver disorders are treated urgently. As a result, there is no explicit description of fatty liver disease in the classical Unani writings, though Unani scholars have identified various illnesses that fit the modern criteria of fatty liver disease. In cases of fatty liver, the liver enlargement is typically not painful and is accompanied by symptoms such as flatulence, dyspepsia, and indigestion. These definitions and descriptions of Warm-e-Kabid Balghami correspond to those of fatty liver. In one way or another, every Unani scholar has mentioned Warm-e-Kabid Balghami in their treatises. They have defined it as a non-painful enlargement of the liver caused by the accumulation of Phelgm (Balgham), and they have noted that Balgham's (Phelgm's) Mizaj (temperament) is cold and wet. In a similar vein, Fat (Shahm's) temperament Unani physicians described the morphology of the liver as enlarged and loose, which is the characteristic of phlegm (Balgham), and the accumulation of phlegm in the body also causes indigestion, flatulence, anorexia, and other symptoms. However, phlegm accumulation does not cause any pain or other signs of inflammation in the liver. Obesity, hyperlipidemia, and other significant causes of fatty liver are all included in unani literature as the primary causes of phlegm (Balgham) formation in the body. In unani texts, it is stated that phlegm is formed from fat, also known as shahm (balgham).

MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER IN UNANI SYSTEM OF MEDICINE

The complete protocol for management is described below.

Ilajbil Ghiza (Dietotherapy)

In managing fatty liver, nutrition is crucial because irregular eating patterns are one of the main contributing reasons. It is advised to eat a balanced diet because Su'mizajbarid can be caused by both famine and overeating. The patient should stay away from fried, oily, hot, fatty, and poorly digested food. Small bird soup, chicken soup, pulses, sagodana kheer (Metroxylan sago gruel), Daliya (wheat gruel), Kishneez (Coriandrum sativum), Pudina (Mentha piperita), and other light, easily digestible foods should be recommended for liver sufferers.

Ilaj bit tadbeer (Regimenal Therapy)

The easiest way to manage Su'mizaj Barid Kabid is with easy steps. Alqamri in Ghinamuna cited Jalinoos as saying that "Riyazat (exercise) in the form of brisk running is highly advised as it reduces body mass." Roghan Afsanteen, Sibr (Aloe vera), Zimad Jalinoos, and Zimad Sunbuluttib performed a dalk (massage) on the hepatic region.

Ilaj bid dawa (Pharmaco Therapy)

Ajil bid dawa (Pharmaco Therapy) Purgatives and diuretics may be utilised depending on the pathological site. Purgatives and mild muhallilat (an anti-inflammatory) are administered if it is on the concave side (inferior surface). Diuretics are frequently administered if it is on the convex side (superior surface) of the liver.

There are numerous unani single and compound pharmacopeal medications that can treat fatty liver disease. These are a few of them: • Decoction or powder is the typical form in which a single unani drug is administered: Anisoon (Pimpenellaanisum), Badiyan, Tukhm-e-Karafs (seeds of Apium graveolens), BeekhKasani (root of Cichorium intybus), BeekhIzkhar (root of Andropogenschoenanthus), Sunbulut Tib (Nardostachysjatamansi), Mastagi (Pistacia Lentiscus), Zaffran (Majoondabidulward, Dawaulkurkum, Sikanjabeenbazoori, Arqkasni, Arqmakoy, Arqbrinjasif, Aab-e-murawaqain, Sharbat deenar, Sharbat bazoori, and others are examples of compound unani drugs. AfsanteenQurs, jalinoos, Jawarish [32–39].

Clinical Application of Herbal Medicine on NAFLD

Clinical trials could validate the experimental advantages of herbal medicine use in NAFLD patients in a clinical context. The use of herbal medicine therapy has improved NAFLD clinical trials. Herbal medicine appeared to have a better impact on the normalisation of AST and the disappearance of radiological steatosis in the treatment of NAFLD patients in randomised controlled trials that compared herbal medicine alone or in combination with other interventions or pharmaceutical agents [40]. For instance, daily resveratrol ingestion combined with lifestyle modification for a period of 12 weeks produced better results than lifestyle modification alone. In the meantime, resveratrol administration resulted in lower levels of ALT, AST, LDLC, TC, and TNF-alpha in NAFLD patients [41]. For the purpose of validating the effectiveness of herbal medicine in treating NAFLD, the establishment of random control trials for herbal medicine is crucial and vital. We summarised the clinical studies on herbal remedies that have been shown to have beneficial effects on the biochemical and physiological characteristics of NAFLD (including herbal formulas, crude extracts, and pure bioactive compounds from medicinal plants) [42].

Herbal Formula against NAFLD

For treating patients with NAFLD, the herbal formula is created using the selection of suitable medicinal plants and the dosage of each herb. The use of herbal medicine as a therapy for NAFLD was investigated by the meta-analysis of 62 randomised controlled studies. It stated that an average of ten species were used in each formulation of 246 Chinese herbs that have been clinically used for NAFLD. It was discovered that herbal remedies work well for treating NAFLD, and Crataegi Fructus (Shan-Zha) was the most often utilised remedy among 17,670 patients, being used 321 times (Shi et al., 2012). The Nigella Sativa, Zataria Multiflora, Trachyspermumammi, and Pistacia lentiscus components of the Dava Albalgham have demonstrated anti-inflammatory, anti-atherogenic, and antioxidant properties. Dava AL-balgham has been used in a double-blind, randomised trial for 76 patients with fatty liver disease. Patients with fatty livers who received treatment for three months saw an improvement in their serum level of liver enzymes [43].

Single Herb against NAFLD

Salvia miltiorrhiza Bunge (Danshen) was tested in eight randomised controlled trials involving 800 patients, and the meta-analysis was done to corroborate its efficacy and safety. In patients with NAFLD, it was found that Salvia miltiorrhiza Bunge had beneficial effects on ALT, AST, TC and TG, LDL, and the liver/spleen computed tomography ratio. Salvia miltiorrhiza Bunge must still undergo higher-quality future randomised clinical trials to determine whether it is safe and effective for treating NAFLD [44].

Pure Natural Compound against NAFLD

The natural polyphenol curcumin, which comes from the turmeric plant Curcuma longa L., has lipid-modifying, anti-inflammatory, and antioxidant activities. In 87 NAFLD patients, Panahi et al. reported a randomised, placebo-controlled trial of curcumin. They came to the conclusion that daily curcumin supplementation for 8 weeks reduced liver

lipid accumulation as well as the levels of AST and ALT in NAFLD patients without any issues with tolerance [45, 46]. In persons with type 2 diabetes mellitus who are non-insulin dependent, cinnamon demonstrated improvement in serum glucose and lipid levels. To determine whether cinnamon has an insulin sensitizer effect in NAFLD patients, additional research including 50 patients with the disease was conducted. In NAFLD patients, the results demonstrated that daily intake of cinnamon (1.5 g) for 12 weeks had favourable effects on lipid profiles, insulin resistance, liver enzymes, and high-sensitivity C-reactive protein [47,48]. Strong antioxidant properties in ginger help to lower the peroxidation of lipids. To determine if Ginger has any impact on the liver biomarkers (ALT, AST, and g-glutamyl transpeptidase) and fatty liver score in fibro-scan, the Early Phase I clinical trial of Ginger in the treatment of NAFLD in patients with type 2 diabetes mellitus is currently underway [49]. 64 NASH patients participated in the Silymarin clinical trial study, and after 8 weeks of treatment, the NASH patients' hepatic enzyme levels clearly decreased [50].

DISCUSSION

With encouraging outcomes, a vast range of natural substances, entire extracts, and herb formulas have been extensively studied against various NAFLD diseases [51]. Numerous studies have been conducted on polyphenols, including resveratrol, quercetin (found in green tea and soy isoflavones), silymarin (obtained from Sylbum marianum), silybin, and rutin, which have been proven to be beneficial in treating NAFLD [52,53].

The main pathogenic processes in the progression of NAFLD that were mediated by herbal medicine were insulin resistance, fibrosis, oxidative stress, inflammation, and apoptosis [54].The amelioration or reduction of fat mass, insulin resistance, serum levels of FFA, AST, and ALT, hepatic lipid accumulation and fibrosis, as well as hepatic oxidative stress, inflammatory response, and apoptosis, were all mentioned as satisfactory improvements of NAFLD disease outcomes and endpoints. As a result, we reviewed the application and function of herbal medicine in NAFLD. The use of herbal medicine therapy has demonstrated promising anti-inflammatory, antioxidant, and anti-apoptotic capabilities that may have positive impacts on slowing the progression of NAFLD's inflammatory condition. Baicalin, for example, exerted anti-inflammatory and anti-oxidant activities that can reduce hepatic fat buildup, suppress induced hepatic inflammation, and prevent liver fibrosis by blocking hepatocyte death [55]. Their activity was always implicated in several routes to ameliorate NAFLD.

By enhancing PPARg and modifying lipid metabolism, Gegenqinlian decoction influences NAFLD [56]. Alisma orientalis is resistant to the upregulation of hepatic lipid export caused by de novo lipogenesis. In addition, it altered inflammatory and fibrotic mediators, oxidative stress cytokines, and lipo-apoptosis and liver injury panels [57]. Resveratrol can be viewed as a pharmacological SIRT1 activator that affects hepatic steatosis by increasing the transcription of genes linked to lipids, oxidative stress, and inflammation while reducing ER stress through the autophagic process [58–60]. It has also been demonstrated that herbal remedies used in conjunction with other therapies had a significantly more positive outcome than either strategy used alone. For instance, combining calorie-restriction therapy and lingguizhugan decoction could increase the lowering of fasting blood cholesterol levels [61, 62].

CONCLUSION

Among the many pathological features of NAFLD, which is a chronic liver disease, are steatosis, lipotoxicity, oxidative stress, ER stress, and insulin resistance. Herbal products are increasingly being investigated through carefully planned controlled trials that offer proof of their positive benefits in liver disease. The majority of outcomes are still equivocal due to the variety of complex clinical trial conditions for drug dosing methods and patient choice. Unani medicine provides tried-and-true, efficient, and secure cures. Unani medicine places a big emphasis on the liver and the disorders that affect it. As the organ responsible for the body's metabolic processes and the formation of humours, the Unani doctors believe that maintaining the liver's regular function is essential to regaining health. It is clear from the present review that unani doctors are highly versed in the morphology and pathophysiology of fatty liver disease. Therefore, additional clinical trials of some well-known herbal remedies for the treatment of NAFLD ought to be carefully examined or reexamined, as they might offer more compelling human data.

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