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## VARIOUS TREATMENT MODALITIES OF NAFLD: A SYSTEMATIC REVIEW

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### Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is a prevalent hepatic condition characterized by excessive fat accumulation in the liver. With the rising global burden of NAFLD, various therapeutic approaches have emerged across different systems of medicine, including Ayurveda, Homeopathy, Allopathy, Siddha, and Unani. This comprehensive review article aims to provide an integrative analysis of the treatments available for NAFLD in these diverse systems, highlighting their unique principles, herbal formulations, dietary recommendations, and lifestyle modifications. In addition to these treatment strategies, various surgical interventions are also available to treat this fatal liver disease. We explore the existing scientific evidence, clinical efficacy, and safety profiles of these treatments. By synthesizing insights from multiple healing traditions, this review facilitates a holistic understanding of NAFLD management, fostering potential cross-disciplinary collaborations and personalized therapeutic strategies. The comparative evaluation of these treatments contributes to a broader perspective on addressing the complex issue of NAFLD, emphasizing the importance of individualized care in the management of this increasingly prevalent liver disorder.

**Keywords:** NAFLD, Ayurveda, Homeopathy, Allopathy, Siddha, Unani.

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### Introduction

Non-alcoholic fatty liver Disease (NAFLD) is the most common liver complaint worldwide and a leading cause of death worldwide [1,2]. The liver's accumulation of lipids, primarily triglycerides, can raise Non-alcoholic fatty liver Disease. A little quantum of fat/ lipids is generally present in the liver, but the issue arises when the lipid accumulation exceeds 5- 10% of the liver's total weight. But then in this case the accumulation of lipids in the liver isn't because of alcohol consumption, hence called Non-alcoholic fatty liver Disease.

NAFLD is defined as the presence of  $\geq 5$  of hepatic steatosis (HS), in the absence of contending liver complaint aetiologies, similar as habitual viral hepatitis, use of

specifics that induce steatosis similar as amiodarone or tamoxifen, and other habitual liver conditions, similar as autoimmune hepatitis, hemochromatosis, Wilson's disease, or significant alcohol consumption [3]. The global prevalence of NAFLD was estimated to be 32.4%. Prevalence and frequency of NAFLD are significantly advanced among men between 40 and 65 times more than among women [2, 5]. The frequency of NAFLD increases with age, type 2 diabetes, obesity, and hypertriglyceridemia [4].

According to research, a person may be more susceptible to acquire NAFLD if they have specific diseases or health conditions, certain genes, a particular diet, or certain digestive issues. Obesity, type II diabetes, and the metabolic syndrome, which includes dyslipidaemia and hypertension, are the main risk factors for NAFLD [8]. The reasons of NAFLD are still being researched by experts. According to research, having certain diseases or health problems, your genes, your nutrition, and your digestive system may increase your risk of developing NAFLD.

In most cases, NAFLD is symptomless. When it does, symptoms could consist of:

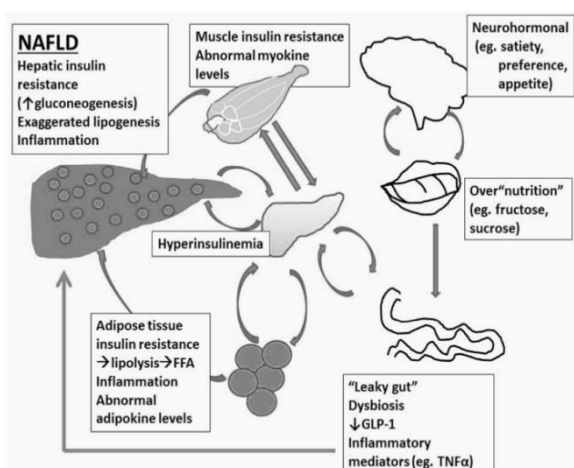
- Fatigue
- Upper right abdominal pain or discomfort

NASH and severe scarring (cirrhosis) symptoms and indicators may include

- Ascites

- Abdominal swelling,
- Enlarged blood vessels immediately below the skin's surface,
- Enlarged spleen, and red palms,
- Yellowing of the skin and eyes (jaundice) (Mayo clinic),
- GERD (Gastroesophageal Reflux Disease)[10],
- The prevalence of IBS symptoms, anxiety, and depression in NAFLD patients [9].

Overnutrition-Dysbiosis and hyperinsulinemia are the two primary processes implicated in the pathogenesis of NAFLD. Neurohormones are released from the brain whenever there is a sense of fullness, preference, or appetite. This encourages the person to eat more than is typically necessary, which results in the condition known as overnutrition. A disorder known as dysbiosis, or leaky gut, affects the intestinal tract or gut and is caused by excessive fructose and sucrose production. Dysbiosis is a condition in which the activity of beneficial bacteria in the large intestine, which aids in the absorption of vital nutrients into the blood, is out of balance.



**Figure 1: Schematic representation of pathophysiology of NAFLD**

Medical history, physical exam, blood tests & imaging tests are employed in the diagnosis of this condition.

#### Systems of Medicine Available For the Management of NAFLD

Presently there are no FDA approved drugs for treating Non-alcoholic fatty liver Disease (NAFLD). But to control the condition there are various medications followed in various systems.

#### Allopathy

Although no specific medications are currently approved for the treatment of NAFLD and its advanced forms, many potential medications have been thoroughly researched over the past few decades. These include statins and other lipid-lowering medications, anti-hypertensive medications, glucose-lowering medications (such as metformin, pioglitazone, GLP-1 receptor agonists, and SGLT-2 inhibitors), and additional potential medications,

such as obeticholic acid. Metformin is a biguanide that is broadly recommended as the initial pharmacotherapy in most patients with T2DM at the time of diagnosis [12, 13]. Since it aids in the glycaemic management of the condition, metformin is a great first-line treatment for T2DM. The paradoxical effects of metformin on hepatic glucose metabolism in non-diabetic subjects have also been demonstrated [13-15]. We can now better understand how metformin lowers blood sugar thanks to early clinical trials in T2DM patients that investigated the drug's mechanism of action [13, 16, 17].

T2DM is characterised by insulin resistance, which impairs insulin-stimulated glucose uptake and reduces insulin-stimulated HGP suppression [13, 18, 19]. However, increased gluconeogenesis is the main cause of higher rates of HGP and fasting hyperglycaemia in individuals with poorly managed T2DM [13, 19]. Although clinical trials in T2DM patients have demonstrated that metformin's major mechanism of action is inhibition of HGP without concurrent increases in plasma insulin concentrations [13, 20, 21]. Metformin is traditionally believed to work predominantly on the liver. Intestinal and peripheral glucose metabolisms have both been found to be impacted by metformin [13, 22, 23].

PPAR-Gamma Agonists Rosiglitazone and pioglitazone are two selective ligands of the peroxisome proliferator-activated receptor (PPAR)- $\gamma$  [24, 25]. Briefly, peroxisome proliferator-activated receptors (PPARs), constituted by three different isotypes (i.e.,  $\alpha$ ,  $\beta/\delta$  and  $\gamma$ ), are nuclear regulatory factors modulating key elements of glucose and fat metabolism [26]. In addition, they can also regulate inflammatory cell activation and fibrotic processes [26]. In this way, binding PPAR- $\gamma$ , and glitazones modulate insulin action, glucose, and lipid metabolism, as well as inflammation and adipose tissue biology [25, 26].

The PPAR- $\gamma$  has three isoforms [25, 26]. The PPAR-receptor-2 isoform, one of the three PPAR isoforms that are currently understood, is notably expressed in adipose tissue and is essential for the redistribution of intra-abdominal and subcutaneous adipose tissue through stimulating the accumulation of triglycerides in peripheral adipose tissue depots. [25,26]. PPAR- $\gamma$  is also expressed in Kupffer cells that are involved in the fibrosis processes [25,26]. In the context of cirrhosis, PPAR- $\gamma$  can reduce portal pressure, inflammation, angiogenesis, and portosystemic shunts [26]. Given these pre-clinical data [25, 26], several studies have been performed to test the potential beneficial effects of glitazones in NAFLD/NASH patients. For instance, in this context, a recent comprehensive analysis demonstrates that pioglitazone treatment in individuals with biopsy-confirmed NASH can have significant advantages on liver function, liver fat content, and resolution of NASH in both patients with and without T2DM [27]. Conversely, as compared to its beneficial effects on NASH, the effect of pioglitazone on liver fibrosis seems to be relatively modest [27].

### GLP-1 Receptor Agonists

According to the American Diabetes Association (2019) [25], glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a family of glucose-lowering medications that can cause significant weight reduction (on average 3-5 kg) and reduce insulin resistance. Human and mouse hepatocytes have been found to contain GLP-1 receptors, and activating these receptors may reduce hepatic steatosis by enhancing insulin signalling, decreasing hepatocyte lipotoxicity, and enhancing mitochondrial function [27,28]. These factors have led to the investigation of GLP-1RAs as a potential treatment for NASH.

### SGLT-2 Inhibitors

According to the American Diabetes Association in 2019 [25], sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a relatively new class of medications that lower blood sugar levels by increasing the amount of glucose that is absorbed by the kidneys, gut, heart, and kidneys. According to Raschi, E. et al. (2018), SGLT-2 is specifically expressed on the renal epithelial cells lining the S1 segment of the proximal convoluted tubule and encourages glycosuria. In this respect, insulin production is not necessary for the management of blood glucose homeostasis [24, 25]. Due to a combination of negative energy balance caused by increased glycosuria and substrate flipping towards lipids as a source of energy expenditure, experimental research employing animal NASH models revealed that SGLT-2 inhibitors have a beneficial effect on liver steatosis, inflammation, and fibrosis [29]. Due to these factors, SGLT-2 inhibitors have also been researched as a potential treatment for people with NASH.

### Ayurveda

Ayurveda, the name given to the traditional Indian medical system, is based on prehistoric literature that emphasises a "natural" and all-encompassing approach to physical and mental health. One of the oldest medical systems in the world, ayurvedic medicine is still used in India as a form of traditional medicine. Ayurvedic medicine includes products (mostly made from plants, but also occasionally from animals, metals, and minerals), nutrition, physical activity, and way of life.

The traditional Indian medical system known as Ayurveda has been practised for thousands of years and is still in use today. It has a strong philosophical and experimental foundation. It is a science of life with a comprehensive strategy for healthcare and personalised treatment. Physical, psychological, intellectual, ethical, and spiritual health are all considered to be a part of this acknowledged absolute medical system [30, 31].

Avipattikara Churna, Punarnava Mandoor, Sankha Bhasma, Tarunikusumakara Churna, Triphala Churna, Kutaki Churna are the few ayurvedic interventions available for treating NAFLD condition [32].

Whereas the majority of the constituents in Avipattikara Churna have the capabilities of Ama Pacana (removing toxins from the body), Mriduvirechaka (a moderate

laxative), and Lekhaniya (scraping away extra fats) [32]. It was discovered that the ingredients in Avipattikara Churna and Punarnava Mandura had hepatoprotective, antioxidant, and digestive effects. Improved digestion and metabolism were noticed within a few days of the start of the medication in a case study, per Sahu AK et al 2022, which likely improved biochemical parameters related to liver functions and lipid metabolism [32-35]. To facilitate the elimination of solid water from the colon, a daily laxative was also advised. Daily purging is another crucial component of management of Udara Roga (abdomen-related disorders) [32].

### Homeopathy

A medical method called homeopathy, commonly referred to as homeopathic medicine, was created in Germany more than 200 years ago. It is based on two uncommon theories:

The principle of "like cures like" states that a substance can treat a disease if it causes symptoms that are similar in healthy individuals. "Law of minimal dose": the concept that the efficacy of medication increases with decreasing dose. Frequently, no molecules of the original ingredient are left in many homeopathic products. Red onion, arnica (a mountain herb), poison ivy, belladonna (a deadly nightshade), and stinging nettle are a few examples of plants, minerals (such white arsenic), or animals (like crushed entire bees) that are used to make homeopathic remedies.

Homeopathic medicines are frequently produced as sugar pellets that are to be dissolved under the tongue, but they can also come in ointments, gels, drops, lotions, and pills. It is normal for different persons with the same ailment to receive different therapies since treatments are "individualised" or customised to each person. Homeopathy recognises clinical patterns of signs and symptoms that differ from those of traditional medicine and employs a separate diagnostic method to allocate therapies to specific persons (NCCIH).

1. **Chelidonium:** For Fatty Liver with Pain in Right Upper Abdomen the characteristics of the stools set Chelidonium apart from other species. Bryonia is mostly a gastro-hepatic treatment and causes right shoulder ache, giddiness, and slightly yellow skin and eyes. Hughes claims that real hepatitis is barely present. Chelidonium effects in the liver are extremely noticeable. The main symptom of this medication in hepatic diseases is a pain under the right shoulder blade's angle that may radiate to the chest, stomach, or hypochondrium. Other symptoms include liver swelling, chills, fever, jaundice, a yellow tongue, a bitter taste, and a craving for acids and sour foods like pickles and vinegar [36].
2. **Lycopodium:** For Fatty Liver with acidity Lycopodium has a significant impact on the liver. The area around the liver is delicate to the touch and has a tightening sensation, as though a cable were tied around the waist. Cirrhosis. Instead of being sharp and lancinating

like with *Chelidonium*, the pains are dull and painful—feeling fullness in the stomach following a little meal [37, 36].

3. **Phosphorus:** For Fatty Liver with Food Coming up after Eating Phosphorus is homoeopathic for fatty liver degeneration, manifesting as well-defined pain and jaundice. The stools are a white-grey colour. Phosphorus may also be necessary for cirrhosis and atrophy. Jaundice is a symptom of organic illnesses, and the treatment is effective for liver cancers. Additionally, *digitalis* has been suggested for acute yellow atrophy. Phosphorus may also be needed if pneumonia is accompanied by jaundice [38, 36].
4. **Nux Vomica:** For Fatty Liver with Pain in Abdomen after Eating Nux is the first treatment that comes to mind for liver ailments in those who have overindulged in alcoholic beverages, highly spiced food, quinine, or who have overused purgatives. The liver is painfully hard and enlarged, and it is sensitive to touch and garment pressure. The first treatment for liver cirrhosis. There may be colic [36, 39, 40].
5. **Bryonia:** For fatty liver with pain in the right hypochondriac region *Bryonia* is the first treatment that comes to mind when there are stitching pains in the right hypochondriac region, even though there are other options available. Other treatments, such as *Chelidonium* and *Kali carbonicum*. The hypochondriac region is painful under *Bryonia*; the liver is enlarged, clogged, and inflamed; laying on the right side, which minimises the motion of the parts when breathing, helps to alleviate the discomfort. One of the main treatments for jaundice brought on by an angry outburst [36,41,42].
6. **Podophyllum:** For fatty liver and jaundice *Podophyllum* is mostly used to treat liver conditions. It first causes a significant bile flow, then a great deal of torpor, followed by jaundice. When diarrhoea is prevalent, it is an indication of a torpid or chronically clogged liver. The cheeks and eyes are yellow, the liver is bloated and sensitive, and there is a terrible taste in the mouth. The bile may form gall stones, and the tongue is covered in a white or yellow coating [36, 43, 44,].
7. **Digitalis:** For fatty liver and jaundice caused by heart conditions *Digitalis* may be the cure for jaundice caused by heart conditions. There is neither bile retention nor duct obstruction; rather, the jaundice results from the liver's failure to extract the components from the blood that are necessary to create bile. Drowsiness, a bitter taste, discomfort, enlargement, and a bruised sensation are all currently present in the area of the liver [36, 41, 45].
8. **Myricacerifera:** *Myrica* is a crucial liver treatment. When compared to *Digitalis*, there is initially depression and then jaundice from improper bile synthesis in the liver, not from any obstruction. The eyes have a dingy, filthy, yellowish colour, the tongue

is coated in yellow, and there is a dull headache that is worst in the morning [36, 46].

9. **Ceanothus Americanus:** Patients with anaemia whose liver and spleen are to blame. Back and liver pain [47]. After dinner, there was a dull pain in the liver area. Sense of fullness in the liver area. Lying on the right side makes liver pain worse [36, 48].
10. **Chionanthus Virginica:** A well-known liver treatment. Jaundice, a swollen liver, constipation, and soreness. Jaundice in the hepatic region is painful and the menses have stopped [47]. Uncomfortable ache that travels from the right hypochondrium to the left iliac area. Feelings of unease near the liver and spleen. Liver hypochondrium. Hepatic obstructions in dangerous areas. Quick, weak pulse, bile-free stools, nearly black urine, and liver-region soreness are all symptoms. Cases of chronic jaundice. The same summertime jaundice [48].

### Siddha

The Siddha System of Medicine (SSM), which has been most dominant in the historical Tamil region, is the model for all other medical systems that have developed globally [49]. According to Tamil academics, Siddha medicine has a more than 5000-year history. This is one of the significant prehistoric medical practises used to treat human ailment since ancient times [60].

#### 1. Kadukkaimaathirai (KM)

Siddha doctors recommend *Kadukkaimaathirai* (KM), a polyherbal Siddha preparation, for anaemia, *sobai* (generalised edoema caused by liver disease), and *mahodharam* (ascites caused by liver disease) [51, 52]. It is recorded in the old Siddha literature [59].

*Terminalia chebula*, *Piper nigrum*, *Eclipta alba*, *Citrus limon*, and ferrous sulphate (made using traditional methods) are some of the primary ingredients in KM [52,59]. In earlier research, each plant in this combination has been shown to have a hepatoprotective impact on rats. It has been demonstrated that the fruit of *T. chebula* protects against *isoniazid*, *rifampicin*, and *pyrazinamide*-induced liver damage [53, 59]. *P. nigrum* has demonstrated a hepatoprotective effect in rats exposed to carbon tetrachloride and liver damage brought on by thioacetamide [54, 55, 59]. Ethanol extract of *C. limon* reduced the increased liver enzymes in rats with liver damage brought on by carbon tetrachloride (CCl<sub>4</sub>) [56, 59]. In rats with CCl<sub>4</sub>-induced hepatotoxicity, *E. alba* significantly improved the microsomal enzymes *aminopyrine N-demethylase*, *glucose 6-phosphatase*, *ALP*, and *lysosomal acid phosphatase*[57-59]. Studies using KM have demonstrated its hepatoprotective efficacy in rat models of CCl<sub>4</sub>-induced liver injury [52,59].Overall, the findings of this study show that KM significantly protected the rats' livers against the damage that ethanol-induced hepatotoxicity caused [59].

#### 2. Thiratchai Kudineer

The Thiratchai kudineer's main herbal ingredients include:

1. The wine vine, *Vitis vinifera* L.

2. Cardamom, *Elettaria cardamomum* L.
3. *Cuminum cyminum* L.
4. *Piper cubeba* L.
5. *Rosa x damascena* (Rose) Mill.
6. The wind gale, *Phyllanthus amarus*.

The medications can be prepared into a decoction by soaking them in hot or cold water for a few hours or overnight. The name of this is "ooralkiyazham". Sandhanaooral kiyazham decoction can be made by heating and decreasing the water. This is referred to as kodhikiyazham [74].

#### Unani

Unani system of medicine (USM) is part of the AYUSH System. AYUSH medicinal systems have evolved and it is blessed with plethora of having traditional values in it. USM is herbo-animo-mineral in origin which includes herbal constituents around 90% followed by animal constituents which ranges from 4-5% and lastly it has mineral constituents in range of 5-6% [71-73]. There is global growth in demand of herbal, complementary and traditional medicines.

#### Management of Non-Alcoholic Fatty Liver disease in Unani System of Medicine

##### IlajbilGhiza (Dietary Counselling)

Because one of the key contributing factors to fatty liver is irregular eating habits, nutrition is essential in managing the condition. Eating a balanced diet is essential because Su'mizajbarid can result from both hunger and excess. Food that is fried, oily, spicy, fatty, and poorly digestible should be avoided by the patient. For people with liver disease, it is best to suggest small bird a soup, chicken soup, pulses, sagodana kheer (*Metroxylan sago* gruel), Daliya (wheat gruel), Kishneez (*Coriandrum sativum*), Pudina (*Mentha piperita*), and other light, readily digestible foods.

##### Ilaj bit tadbeer (Regimenal Therapy)

Simple actions are the best method for managing Su'mizajBaridKabid. A quote from Jalinoos that was attributed to Alqamri in Ghinamuna reads, "Riyazat (exercise) in the form of swift run is strongly recommended as it reduces body mass." The hepatic region was massaged by RoghanAfsanteen, Sibr (*Aloe vera*), ZimadJalinoos, and ZimadSunbuluttib. Ilaj bid dawa (Pharmaco Therapy)

##### Ajil bid dawa (Pharmaco Therapy)

Depending on the pathogenic site, purgatives and diuretics may be used. If it is on the inferior surface i.e., on the concave side, purgatives and a modest form of muhallilat (an anti-inflammatory) are given. If it occurs on the superior surface of the liver (the convex side), diuretics are usually given. Fatty liver disease can be treated with a variety of unani single and compound pharmacopoeial drugs. Here are a few examples: A single unani medicine is often taken in the form of a decoction or powder: Anisoon (*Pimpinellaanisum*), Badiyan, Tukhm-e-Karafs (seeds of *Apium graveolens*), BeekhKasani (root of *Cichorium intybus*), Beekhlzkhar (root of

*Andropogenschoenanthus*), Sunbulut Tib (Nardostachysjatamansi), Mastagi (*Pistacia lentiscus*), ZaffranZaffran (Majoondabidulward, Dawaulkurkum, Sikanjabeenbazoori, Arqkasni, Arqmakoy, Arqbrinjasif, Aab-emurawaqain, Sharbat deenar, Sharbat bazoori, and others are examples of compound unani drugs[60-66].

#### Acupuncture

In acupuncture, certain spots on the skin are stimulated, typically with the insertion of needles. Acupuncture was initially founded on the theories of traditional Chinese medicine. Traditional acupuncturists view health in terms of a vital force or energy known as "Qi" (pronounced "chee") that travels along meridians to move between the organs. For health to be maintained, qi energy must flow through each of these meridians and organs in the proper quantity and quality. One way to change the flow of Qi is through the acupuncture points, which are situated along the meridians [67].

Due to its advantages of being inexpensive, having few side effects, and being easy to use, acupuncture has been used as a conventional way of traditional Chinese medicine to treat NAFLD in clinical practise. According to a clinical investigation, acupuncture has greater therapeutic effects on hepatic fat status, glycolipid metabolism, and insulin resistance than other treatments for NAFLD [68]. Through the inhibition of inflammation, the reduction of oxidative stress, and the promotion of lipid metabolism in liver cells, acupuncture was shown in several studies using NAFLD models to slow the progression of the disease [69, 70].

#### Bariatric surgery

Bariatric surgery may improve NASH and/or even fibrosis in patients who are morbidly obese and have NAFLD/NASH [75]. Patients with NAFLD/NASH may choose to have bariatric surgery or a weight loss procedure to lose weight. Dietary and exercise-based weight loss may be challenging to maintain. Long-term weight loss is made possible with bariatric surgery. Additionally, it aids in the enhancement of inflammatory and lipid metabolic pathways linked to the pathogenesis of NAFLD [76]. Currently, individuals with a BMI of 35 to 39.9 kg/m<sup>2</sup> who have any significant comorbidity, such as T2D, hypertension, NAFLD, or NASH, are advised to have bariatric surgery [77,78]. According to an analysis of 29 research, patients who underwent bariatric surgery exhibited a considerable improvement in their ALT, AST, Gamma-glutamyl transferase (GGT), and histology. Because bariatric surgery is an intrusive process, it has hazards like adjustable gastric banding (AGB) and dietary issues like postprandial hyperinsulinemic hypoglycaemia and other problems [80].

#### Gastric balloon placement

Weight loss and improvements in ALT and AST levels have been linked to the implantation of gastric balloons and the duodenal-jejunal bypass liner [81, 82]. In a study comparing the effects of an intragastric balloon and a placebo on liver histology [83] 18 patients were randomly

assigned to receive an intragastric balloon along with a healthy diet and exercise for six months, or just diet and exercise. Patients who underwent balloon installation saw a substantial improvement in NAS when compared to control patients (2 vs. 4,  $P=0.03$ ) and a significant drop in BMI when compared to placebo (1.52 versus 0.8,  $P=0.0008$ )[84]. The single fluid-filled intragastric balloon (IGB) induces meaningful weight loss and might be used in NASH treatment [85]. IGB enabled significant metabolic and histologic improvements in NASH in a prospective study. When used with a recommended diet and exercise routine, IGB seems secure and efficient for managing NASH [86]. IGB appears safe and effective for NASH management when combined with a prescribed diet and exercise program [86].

#### **The duodenal-jejunal by pass liner**

Significant DJBL (Duodenal-Jejunal Bypass Liner) treatment effects on NAFLD fibrosis and APRI score further support the idea that DJBL has protective benefits on liver-related morbidity and mortality in patients with obesity and T2DM[87].

#### **Conclusion**

NAFLD is the most common liver disease with gradual increase in its morbidity. There is no specific FDA approved drug available for the management of NAFLD. Traditional systems of medicine were reported to possess significant effect on the NAFLD. Selection of appropriate treatment method depends majorly upon the patient related factors and severity of the disease. Choosing the right treatment method for a given patient is the key to success in the management of NAFLD.

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#### **Conflict of Interest**

All the authors have no conflicts of interest to declare.

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Not Applicable

#### **Author Contribution**

P. Veeresh Babu – Idea and design of work, A. Sowmya – Collection of information and preparation of manuscript and P. Rahul – Collection of information and preparation of manuscript

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