

The Role of Natural Drug Silymarinin in Chronic Liver Disease Patients

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ABSTRACT

Background: Prediabetic patients and healthy overweight people also tend to suffer from NAFLD, but researchers have only scratched the surface of this condition. This study analyses the effect of hepatic steatosis on fibrosis and evaluates the key predictors of liver injury in prediabetes to see if the liver damage induced by prediabetes can be restored by adopting a Mediterranean diet and taking the nutraceuticalsilymarin.

Place and Duration: In the department of Medicine of KGN Teaching Hospital/Bannu Medical College, Bannu for the duration of one year from 1st June 2019 to 30th May 2020.

Methods: A total of 212 prediabetic individuals without a previous diagnosis of NAFLD and 126 healthy controls underwent a clinical evaluation, transient elastography evaluating liver stiffness (LS), and a controlled attenuation parameter (CAP). Subsequently, 212 patients at risk for developing diabetes participated in a prospective randomised interventional study, with 104 assigned to a Mediterranean diet alone and 108 assigned to a Mediterranean diet plus supplementation with silymarin (a flavonolignan complex isolated from *Silybum marianum* and *Morus alba*). Six months of treatment with 420 milligrams of silymarin twice daily. Participants underwent follow-up clinical and instrumental evaluations after the 6-month experiment period ended. Genotyping for patatin-like phospholipase domain containing 3 in prediabetic individuals (PNPLA3).

Results: To date, natural products and their derivatives have accounted for over 50% of the natural remedies used to treat liver disorders. Despite natural medicine's many benefits and low risk, clinicians should be aware of the potential for adverse reactions such as liver injury, interstitial pneumonia, and abrupt respiratory failure. This means that when using naturopathic regimens to treat liver disorders, we must do everything in our power to prevent and avoid the negative influence of these drugs as much as possible. Using real-world examples to stress the importance of preventing and managing adverse reactions to the natural agents, this article explores the current application and proposed improvements of natural medicine in the treatment of liver illnesses.

Conclusion: Silymarin has demonstrated effectiveness as a supportive treatment for the majority of liver diseases, including cirrhosis and alcohol-induced liver damage. Among patients with cirrhosis, silymarin therapy resulted in a substantial decrease in fatalities due to liver complications in clinical trials.

Keywords: Liver illness, Cautions, Adverse Reactions, Herbal Medicine, Natural Nutraceuticals.

INTRODUCTION

To cure human ailments, natural medicine practitioners typically rely on natural substances and their derivatives [1,2]. Medical sociology is also known as the study and practise of identifying and preventing human illness [3]. For thousands of years, this remedy has been utilised to cure a wide range of illnesses in humans [4-6]. Many conventional disease-prevention and -treatment strategies have complementary or alternative counterparts in natural medicine [7]. Herbs, nutrients, dietary supplements, etc. used in naturopathy must be found in nature and unaltered or little processed. Uninformed healthcare providers and the general people alike recognise the benefits of using natural remedies [8]. Natural medicine is partially governed by legislation, which is not the case for many other forms of complementary and alternative medicine. As a result, naturopathic doctors can practise legally in many parts of the Americas. Patients are increasingly drawn to them because of the personalised attention they receive, the affordable prices they offer, and the extended consultation times they provide. The use of nutraceuticals is a part of the naturopathic practise of medicine.

Toxins, infections, metabolic products, circulatory materials, and neoformations can all cause damage to the liver despite the organ's critical role in the body [9]. The liver is the largest of the digestive organs found within the body and is essential to a wide variety of functions. Liver illnesses have several possible origins, including viral hepatitis, alcoholism, and non-alcoholic fatty liver disease [10]. Many natural ingredients have been shown to have preventative and therapeutic effects on the liver, according to recent studies on functional diets such nutraceutics [11].

The practise of naturopathy, which emphasises the use of natural therapies to treat disease, is on the rise around the world. When dealing with liver issues, it is helpful to incorporate what is

known about the best diet and way of life into regular practice [12]. Treatment of the underlying cause of illness, as opposed to only the symptoms, is the focus of natural medicine. Naturopathy is guided by guiding concepts that include an emphasis on the body's innate healing abilities, a focus on the whole person, individualization, prevention, the avoidance of injury, and the physician's role as educator [13]. Most importantly, these drugs should only be administered by trained medical professionals (i.e., naturopathic doctors) who adhere to professional standards of care and have a strong moral compass. Even natural agents promoted as having hepatoprotective benefits can trigger severe adverse drug responses if these precautions aren't taken.

In place of conventional liver treatments, this article focuses on natural and herbal remedies, food, and nutraceuticals. This article takes a look at the current condition and proposed improvements of several natural medications used to treat liver illnesses. It also discusses the potential side effects of natural agents for liver disease and advises us to be cautious when using them.

Liver illness herbal remedies: Herbs have been utilised for ages to treat liver disorders in both traditional Oriental medicine and ancient Western medicine. Avicenna, one of the most well-known physicians of the ancient world, wrote what is now known as The Canon of Medicine, which is widely studied in the West. Many hepatoprotective herbs and compound medications, as well as some formulas with the effect of treating liver illnesses, were introduced by Avicenna in the Canon.

The effectiveness of Chinese herbal treatment has been repeatedly demonstrated in clinical settings over many centuries. Herbal combination formulations used in medical prescriptions have a lengthy history. Herbs included in a formula should be chosen with great care according to the principles of traditional Chinese medicine, with an emphasis on the idea of individualised

care [14]. Correlative clinical trials have now established the efficacy and safety of several herbal remedies in the treatment of liver diseases.

Herbal medicine for liver diseases: Several medicinal plants are worth mentioning in detail due to their impressive hepatoprotective and therapeutic benefits.

Natural medicines	Causes and how they work (or don't work)
Silymarin	Powerful antioxidant, anti-inflammatory, cell-permeability, and membrane-stabilizing qualities; support for liver regeneration; inhibition of collagen fibre deposition.
Long pepper	tumour development suppression; treatment for hepatitis, cancer, bronchitis, asthma, constipation, gonorrhoea, tongue paralysis, diarrhoea stomachache, spleen disorders, cough, and other gastrointestinal difficulties, cholera, chronic malaria, viral hepatitis
Holy Basil	anti-inflammatory properties; hepatoprotective effects (especially when combined with silymarin)
	Immunomodulatory, anti-stress, anti-diabetic, hepatoprotective, hypolipidemic, painkilling, fever-reducing, and a host of other beneficial effects

Silymarin: Silymarin (*Silybum marianum*) is extracted from the milk thistle plant, which is indigenous to Asia and Southern Europe. *Silybum marianum*'s use as a hepatoprotective medication in Europe dates back two millennia [15]. The drug has been used to treat a wide range of liver and biliary conditions. The ancient Greeks and Romans were the first people to use milk thistle as a treatment for ailments ranging from liver issues to snake bites. Then, in the Middle Ages, people started recommending milk thistle to treat hepatitis and other liver conditions. Toxin-induced liver problems and cirrhosis, as well as chronic liver illnesses, are now endorsed by the German Commission E, the country's equivalent to the FDA.



Fig.1. Leaves and blooming flower of silymarin

Despite the plant's long history of use in the treatment of liver problems, silymarin, the active constituent in milk thistle, was not found in milk thistle seed extract until 1968. Although silymarin has been shown to act as an antioxidant, an anti-inflammatory, a regulator of cell-walls and membranes, a stimulant of liver regeneration, and a virus and cancer fighter, the exact mechanism by which it achieves these effects is still unclear. The leaves of this plant have been used in salads, while the fruit has historically been roasted and used as a coffee replacement. In addition to its health benefits, it is a common food additive.

MATERIAL AND METHODS

Before beginning treatment, 212 patients with prediabetes (HbA1c 5.7-6.4 percent, or 39-46 mmol/mol) were compared to 126 healthy controls with a BMI between 25 and 29. All patients had a clinical evaluation, transient elastography to determine liver stiffness (LS), and a controlled attenuation parameter (CAP). At the time of enrolment, patients underwent biochemical tests of blood samples and provided basic demographic data including age, sex, and body mass index. Patients with prediabetes who matched the inclusion criteria had not been treated for diabetes for longer than 12 weeks, either with drugs or lifestyle changes. Excessive alcohol

consumption (defined as more than 3 drinks per day), obesity (BMI 30 kg/m²), and the inability to obtain valid TE measurements were also exclusionary, as were negative hepatitis C virus (HCV) or hepatitis B virus (HBV) serology, coexisting autoimmune hepatitis, hemochromatosis, cholestatic liver disease, drug-induced damage, and the presence of focal hepatic lesions Triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels were all measured using enzyme-based techniques. Research on glycosylated haemoglobin was conducted using high pressure chromatography (HbA1c). In the department of Medicine of KGN Teaching Hospital/Bannu Medical College, Bannu, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were tested enzymatically, and plasma glucose levels were quantified.

RESULTS

Clinical effects of Silymarin

Cirrhosis of the liver or alcoholic liver disease: Fatty liver disease, which is caused by an accumulation of fat in the liver, is a common reason for liver ailment (FLD). An alcoholic fatty liver is the precursor to more advanced forms of liver damage caused by alcohol abuse (AFLD). The results of silymarin on people with alcoholic liver disease and/or liver cirrhosis are summarised in Table 1. Cirrhosis of the liver was the focus of six of these clinical trials (mainly alcohol-related). Two further studies investigated the effects of silymarin on clinical outcomes including mortality, and two randomised controlled trials made survival a main clinical objective. The findings of these studies on the effects of silymarin on mortality are shown in Table 2. Patients with cirrhosis were evaluated in a double-blind, prospective, randomised research to determine the efficacy of silymarin (a formulation derived from Eurosil 85) on survival. For at least 730days (median observation length, 1247 days), 87 of the 170 cirrhotic patients were given silymarin 420 mg/day whereas the other 83 were given a placebo. 47 alcoholics and 40 non-alcoholics were among these patients (45 alcoholics and 38 non-alcoholics). Liver illness was the cause of death for 32 of the placebo group's 39 people, but only 16 of the silymarin group's 28. The results showed that the silymarin group had a significantly higher 121 days survival rate than the placebo group ($P = 0.036$). Treatment reduced mortality in alcoholic cirrhotic patients ($P = 0.01$) and in those with less severe cirrhosis (class A disease by Child-Turcotte criteria; $P = 0.03$), as determined by subgroup analysis. Patients who were given either a placebo or an oral silymarin formulation derived from Eurosil 85 had their survival rates compared over a 730days period. When compared to the placebo group, the death rate for those on silymarin was 14.6%. (non-statistically significant for the time frame of this study). Mortality rates were similar between the two groups overall ($P = 0.06$); but, when comparing only the 29/75 people who had been diagnosed with hepatitis C, it was found that none of the 13 patients in the silymarin group died, while 4/16 patients in the placebo group did. The odds ratio for liver-related death in the silymarin versus placebo groups was calculated to be 0.53 based on an analysis of clinical data utilising silymarin from five separate studies (i.e., 47 percent risk reduction; 95 percent confidence

ranges 0.33-0.86). Participants who took silymarin had a 4.9% lower annualised mortality rate from liver-related causes compared to patients who took a placebo, who had a 9.3% higher death rate. Patients treated with silymarin were less likely to require hospitalisation due to liver-related disorders in one of the trials included in this meta-analysis, compared to patients treated with placebo (10.0 percent vs. 16.3 percent; $P < 0.01$). Trials in patients with alcoholic and/or viral liver disease found that milk thistle

significantly reduced liver-related mortality when compared to placebo or no intervention in all trials examined, but this effect was lost when the analysis was limited to high quality studies. A deeper understanding of silymarin's role in liver-related mortality necessitates additional research. There was a substantial improvement in liver function after 4 weeks of treatment with silymarin versus a placebo for 97 individuals with moderate, acute, and subacute liver impairment from alcohol intake.

Table 1. Medical studies involving silymarin and people who have alcoholic liver disease or cirrhosis

No of patients	Condition	Treatment(n)	Duration in days	Silymarin outcomes
100	Abnormalities in the liver (78 percent with daily alcohol use)	420 mg of silymarin each day (47) Placebo (50)	30	Enhanced liver histology, ALT, AST, and other liver function parameters
120	ALD (50% with cirrhosis)	420 mg of silymarin each day (57) Placebo (50)	91	Essentially no effect
36	ALD	Silymarin 17 Placebo (19)	182	Patients with ALD and cirrhosis, including those with mild severity illness as measured by ALT, AST, bilirubin, and procollagen production, experienced the greatest improvement in survival over four years.
59	ALD (72% with cirrhosis)	Daily Dose: 280mg Silymarin (25) Placebo (34)	456	There was no change in liver function, disease progression, or mortality.
62	insulin-treated T2DM with alcoholic cirrhosis	The recommended starting dose of silymarin is 60 mg daily (30)	365	Reduction in fasting blood sugar, HbA1c, and MDA; reduction in daily insulin demand; normalisation of alanine aminotransferases AST and ALT
200	ALD with cirrhosis	Daily dosing of 450 milligrams of silymarin (103) Placebo (97)	730	Small to no effect on the development or outcome of liver disease
50	Liver cirrhosis due to alcohol-related liver disease	Daily dosing of 450 milligrams of silymarin (24) Placebo (25)	182	Molecular Damage and Type III Procollagen Amino-Terminal Propeptide

Abbreviations: HbA1c, glycosylated haemoglobin; MDA, methylenedioxymphetamine; GSH, glutathione; Not Available, or NA Silymarin was created using the Eurosil 85 technology to treat type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) (T2DM).

Table 2. Research into the effects of silymarin on cirrhosis patients' survival rates.

dosage of silymarin (mg/day)	characteristics of the patient/disease	N	Treatment duration in days	Silymarin (% patients)	Placebo (% patients)
420	Factors in the development of alcoholic and non-alcoholic cirrhosis of the liver 92/78	180	28	22.4	40.3
420	Cirrhosis and alcoholic hepatitis, 58 cases	116	3	1.8	5.2
280	The effects of alcohol on the liver (24/29 patients with biopsy results had cirrhosis).	72	16	15.3	14.2
450	A, 37.9 percent /24.7 percent; B, 51.5% /62.9 percent; C, 6.8 percent /7.2 percent; alcoholic cirrhosis; Silymarin/placebo	201	25	10.9	19.4

Long pepper: Long pepper is another plant widely used in both Ayurveda and Chinese medicine (Fructus Piperis Longi; Figure Figure2). Hepatotoxicity, inflammation, diabetes, obesity, depression, and cancer are just some of the many diseases that can be treated with this inexpensive and easily accessible plant (23). Antioxidant activities improve, leading to a modulation of liver function.



Fig. 2. Fruits of long pepper

Because of its ability to reduce transglutaminase activities, Fructus Piperis Longi extract has been shown to be effective in treating liver diseases, including jaundice, which is caused by an

excess of bilirubin (total, direct, and indirect). Results from in vitro studies showed that the long pepper ethanol extract was more effective than the control against hepatitis B virus [16]. This plant was tested for its ability to protect rodent livers from CCl4-induced acute, chronic, and permanent damage. No deaths have ever been linked to using the plant as a cooking spice, and even at extremely high quantities, there have been no known side effects.

Holy Basil: In TCM, Ayurveda, Greek, Roman, Siddha, and Unani, the plant *Ocimum sanctum* L. (Labiatae), also called "Tulsi" in Hindi and "Holy Basil" in English, has been acknowledged as a significant hepatoprotective agent. Green veggies like this are a staple of the excellent Thai cuisine and are frequently stir-fried with rice, shrimp, or pig [17]. This plant's phytochemicals have been associated with a number of medicinal effects, including analgesia, diabetes prevention, anti-inflammatory, antipyretic, antistress, hepatoprotection, hypolipidemia, immunomodulation, and even anti-neoplasia [18]. According to certain research, holy basil and silymarin exhibit synergistic hepatoprotective action when administered in conjunction to treat liver problems [26]. The use of this plant as a chemopreventive or radioprotective agent in humans has not been linked to any significant side effects [19].

Treatment of liver disease by diet and nutrition: Treatment of liver diseases with vitamin and mineral-rich whole foods has been found to be effective. There are a number of benefits to liver health that have been linked to diets high in natural foods, particularly plant-based diets [20]. as a result, they are widely used in many countries for the treatment of liver problems. Numerous mechanisms have been identified by which naturopathic medicine protects the liver, including anti-oxidative action.



Fig.3. Holy basil as a green vegetable

Table.3. This table provides details on the use of some herbs for the treatment of liver conditions.

Organic vegetation	Consequences and Possible Mechanisms
Coffee	The possibility of lowering the danger of developing cirrhosis, hepatocellular carcinoma, and other liver problems
	decreasing mortality, liver scarring, and hepatocellular carcinoma
Apple	To reduce oxidative stress in rats treated with tamoxifen
	To counteract the death of cells caused by CCl ₄ , this compound possesses antioxidant properties and the ability to upregulate nuclear factor.
Resveratrol	has antioxidant, anticancer, and tumor-fighting effects.

Coffee: Coffee is consumed all around the world and is the most widely consumed beverage. Coffee consumption has been linked to improved serum liver function test results and a decreased risk of cirrhosis and hepatocellular cancer in a number of case-controlled and epidemiological studies. The drink's antioxidant, anti-carcinogenic, and anti-fibrotic properties are all likely involved. Almost all types of liver disease can be prevented or slowed by drinking more than two cups of coffee daily [21]. There is, however, no concrete proof that either increasing coffee consumption by an existing coffee drinker or initiating coffee drinking by a coffee abstainer can benefit liver disease. Caffeine is a stimulant molecule that increases alertness and cognition; regular coffee drinkers may develop signs of clinical dependency, withdrawal, tolerance, or intoxication similar to those of substance abusers [22].

Fruits: Apples and citrus fruits, two of the most widely consumed plant foods, have been demonstrated to have protective effects against multiple chronic diseases. Apples and mandarins, too, contain a lot of healthy antioxidants. Dietary supplementation with dried apple and mandarin orange has been shown to protect against tamoxifen-induced liver damage in rats. CCl₄-induced hepatocyte apoptosis was blocked by an apple pomace aqueous extract, which was shown to be hepatoprotective in a separate study [23]. On the other hand, it's not easy to steer clear of the allergens that cause the most common allergic reactions: fruits. Some people experience an oral allergy syndrome when they eat certain fruits (apples, citrus, peaches, etc.)

Plant phytoalexin: Mulberries, red grapes, peanuts, soy, knotweed, and sickle pod are just a few of the many plants that are

able to contain natural resveratrol because plants manufacture it in response to damage. Resveratrol has been proven to protect against non-alcoholic fatty liver disease, enhance lipid metabolism, and suppress the production of liver inflammatory markers. In addition, it stimulates sirtuins, which may help many species live longer [24].

The paucity of effective hepatoprotective medications in current allopathic therapy can be countered by consuming more vegetables, particularly green leafy ones. Also, certain natural compounds provide protection against liver disease.

DISCUSSION

The combination of various active components in the natural composition results in a broad variety of therapeutic effects. The best course of action in the current era of allopathic medicine is to employ a number of strategies to address the heterogeneity of liver cancer cells, which is the primary cause of therapy failure. Many of the active ingredients in a naturopathic medicine, such as those protective against liver disease because of its antioxidant, anti-inflammatory, antiviral, and anticancer effects. Pro-apoptosis, reduction of proliferation, and cell cycle arrest are all hallmarks of these active components; all three are intimately connected to the mechanisms of anti-cancer effects.

In contrast to other kinds of alternative medicine, naturopathy is somewhat governed by law. For a very long time, scientists in the West have argued about whether or not natural medicines should be included in conventional medicine. Concerns about natural medication safety for treating liver disorders have been raised. The use of a combination of two or more medications has been shown to be more effective in treating sickness, but the choice of each herb within the formula must adhere precisely to the principles of Chinese herbal therapy.

The "Sho-saiko-to Event" in Japan could have been prevented if practitioners of traditional Chinese medicine had adhered to its core principles [25]. Western doctors in Japan administered Chinese medication without following the tenets of traditional Chinese medicine theory, leading to this tragic outcome.

Fever-inducing disorders have been treated with this Chinese herbal medicine for around three thousand years. There are no reports of widespread pulmonary adverse effects unlike what occurred in China. The fundamental message is that a comprehensive understanding of the disease and the individual patient's needs is essential for effective diagnosis and treatment. One patient had been on this formula nonstop for three years, consuming a whopping 7.5 kg of the medicine in total. If the decoction is taken regularly and in large amounts, it might be fatal.

The effectiveness of medications and the severity of their potential adverse effects can be impacted by a number of factors. Elderly patients, those receiving interferon concurrently with Sho-saiko-to, and those taking the drug for longer periods of time are at a higher risk of adverse events, according to the literature. The fact that long-term, consistent administration of this decoction has been linked to cases of acute hepatitis should serve as a reminder that even herbs promoted as having hepatoprotective benefits might cause adverse drug reactions. Despite the fact that herbs have positive medicinal effects, extreme caution is required while dealing with any potential adverse reactions.

This Kampo formula needs to be dynamically modified, in addition to the time period and consumption amount. By switching from potent ginseng to dangsen (*Codonopsis pilosula*), potentially serious side effects can be avoided. Another herb in the mixture, banxia (*Rhizoma pinelliae*), is toxic to the digestive system and inhibits the brain's respiratory control centre and peripheral nerves. When treating a patient with traditional Chinese medicine, Fruit from the Chinese magnoliavine and dried ginger are commonly used in place of ginseng, jujube, and fresh ginger for the treatment of cough, while pollen is used instead of banxia for the treatment of thirst. As a result, it is crucial to adapt the Sho-saiko-to formula to each individual patient by changing the proportions of the individual herbs.

CONCLUSION

Silymarin has demonstrated effectiveness as a supportive treatment for the majority of liver diseases, including cirrhosis and alcohol-induced liver damage. Among patients with cirrhosis, silymarin therapy resulted in a substantial decrease in fatalities due to liver complications in clinical trials. Specifically, the antioxidant activity of silymarin is thought to be the mechanism through which it delivers these therapeutic effects. By neutralising free radicals responsible for lipid peroxidation and modulating enzyme pathways linked to cellular damage that ultimately results in fibrosis and cirrhosis, it functions as an antioxidant. To treat liver disorders holistically, use a treatment like natural medicine. Research and clinical use of naturopathic treatments for liver illness are expanding at a rapid pace. However, understanding the underlying mechanics of function and safety is still difficult, if not impossible. Natural compounds have a wide variety of therapeutic applications due to their unique properties, such as antioxidant, anti-inflammatory, antiviral, and antitoxic properties. Patients typically respond positively to the use of natural substances to treat liver illnesses due to the wide range of therapeutic effects and few side effects. Furthermore, natural medication should be tried first in the treatment of liver disorders, rather than allopathic therapy, for the benefit of patients' safety. Despite the fact that natural medications have positive therapeutic effects, they require extreme caution when dealing with any adverse reactions. The best method to avoid these side effects is to make sure these drugs are only administered by trained medical professionals. In addition, naturopathic practitioners must have strong moral principles and a strong feeling of duty. As practitioners of natural medicine, naturopaths are bound by and expected to uphold a set of guiding principles. It is imperative that patients adhere to their physician's instructions when using natural medications for the treatment of liver problems. There are unanswered questions about the system's security. Natural medicines, on the one hand, are inexpensive and widely available, yet they are sometimes misunderstood as being completely safe to use. However, there is a deficiency in authorities charged with monitoring the practise of natural medicine. These are the primary factors that cause people to take natural medications excessively for extended periods of time and experience negative side effects. Both the physician and the patient need to exercise caution when handling medications. There is a specific purpose, route of administration, and recommended dosage for every medication. Excessive dosing beyond the recommended amount may almost probably cause unwanted effects. Natural remedies and everyday foods can't be misused either.

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