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Hepatoprotective Effects of a Polyherbal and Apitherapeutic Mixture (HEPBAL) in Patients with NAFLD and Viral Hepatitis

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Abstract: *Ginger, turmeric, black seed, artichoke leaves, Azerbaijani thistle honey, and beebread have a hepatoprotective effect; therefore, they show effective results separately in case of alcohol-dependent and non-alcoholic Liver obesity, hepatitis and toxic liver damage. We studied how it can affect liver enzymes and hepatocytes in this group of patients. We took all these natural plants and bee products in the optimal dose required by the body and prepared a paste called Hepbal, so that everyday people could eat comfortably as a food supplement, as well as see the therapeutic and prophylactic results.*

HEPBAL paste for liver Ingredients: *Flaxseed, Ginger, Seed of thistle, Powder of Yellow Ginger, black cumin, and honey. Benefits: Herbal paste prepared based on well-tested recipes improves the function of the liver and gallbladder. As a hepatoprotection, it affects the recovery of liver cells in liver diseases (hepatitis and cirrhosis), spleen disease, bile duct infections, gallstones in gallbladders, inflammatory bowel disease, colitis and cholecystitis. It helps to remove toxic substances while taking medicine (antibiotics, chemotherapy, painkillers, etc.).*
Side effects: Individual sensitivity to the contents of the product. Usage: In acute process 1 teaspoon, during chronic diseases 1 dessertspoon twice a day before eating. Results: 48 women and 54 men with the third level of fatty liver dystrophy decreased to the second level (fibrosis did not occur). During the treatment of 114 patients who had hepatitis C virus, I used HEPBAL paste as a protector for the liver. After the analysis, 24 patients, who had liver cirrhosis ALT and AST in the blood reduced twice. Another 81 patients from 90 who had virus had disappeared in blood analyses and in the exogenous factor of liver and GGT in the blood get normal.

Introduction

Herbal products have become increasingly popular, especially among those with chronic diseases. Milk thistle honey has been used for hundreds of years by herbalists and physicians alike to treat a wide range of liver pathology, including fatty liver disease, hepatitis, cirrhosis, and to protect the liver from environmental toxins. Today, millions of people consume milk thistle to support healthy liver function. Researchers have focused their efforts towards studying silymarin, a mixture of flavonolignans extracted from milk thistle, as well as the most active ingredient of this extract, silybin. Silymarin and silybin have become some of the most prescribed natural compounds, and the use of the two names is often interchangeable. However, each has a different clinical purpose, but there are no definitive results in terms of clinical efficacy. Currently, there is no regulation of herbal products such as milk thistle in the United States as they are not considered drugs and are not under the supervision of the US Food and Drug Administration. Like most herbal products, the FDA does not approve or recommend the usage of milk thistle as a treatment for any medical condition.

Recent studies have focused on the role of milk thistle in treating nonalcoholic fatty liver disease, a common hepatic manifestation of metabolic syndrome. The prevalence of NAFLD in western countries is approximately 20% to 30%. Currently, there is no consensus approach when it comes to the treatment of NAFLD. Most clinicians approach the disease by emphasizing lifestyle modification, including diet, weight loss, and limiting alcohol intake. However, studies suggest milk thistle can exert beneficial effects in patients with NAFLD. Data indicate that silymarin treatment correlated with a reduction in insulin resistance and a significant decrease in fasting insulin levels. Patients treated with 600mg/day of silymarin for 12 months demonstrated lower fasting insulin levels. A separate clinical trial evaluated the effectiveness of silymarin compared to metformin and pioglitazone in NAFLD patients. Research showed that patients treated with silymarin had significantly lower transaminase levels compared to those treated with metformin or pioglitazone. In a sample of 25 patients, treated for four months with 200 mg silymarin three times a day before meals, there was a significant reduction in blood glucose levels (from 156 +/- 46 mg/dl to 133 +/- 39 mg/dl), compared to an increase in the placebo-treated group. In the same period, their HbA1c levels also dropped by an average of 1 point. The same group of patients also demonstrated significantly reduced levels of total cholesterol, triglycerides, and LDL. Another study aimed to evaluate the efficacy of combined treatment, which includes vitamin E, silybin, and phospholipids, demonstrated that this complex improves liver damage, especially plasma markers of liver fibrosis, as well as insulin resistance.

Nonalcoholic Fatty Liver Disease (NAFLD) is known to be the most prevalent hepatic disorder that is characterized by excessive hepatic fat accumulation, in absence of remarkable alcohol consumption. It affected people around the world in range of 25–30% in developed and 6–35% in developing

countries. Although many aspects of NAFLD pathogenesis are not yet fully understood, metabolic disturbances such as excessive fat accumulation and insulin resistance play an important role in the pathogenesis of NAFLD. In modern medicine, adherence to lifestyle and dietary modification is a first strategy for NAFLD management or/and prevention of disease progression to cirrhosis and hepatocellular carcinoma. However, many patients fail to comply with the lifestyle modification. Owing to the growing prevalence of NAFLD and paucity of beneficial remedy, a surge of interest to detect novel effective therapy for alleviating or preventing progression of this disease with minimal side effect is required.

In the last decades, growing evidence has shown that investigators are interested in finding effective natural alternatives therapy in the treatment of numerous diseases. Although vary medical plants were used as traditional and self-care, there is lacked sufficient information in efficacy and their possible side-effects on diseases and this issue made it one of the important problems faced by doctors.

Ginger supplementation resulted in a significant reduction in alanine aminotransferase, γ-glutamyl transferase, inflammatory cytokines, as well as the insulin resistance index and hepatic steatosis grade in comparison to the placebo. We did not find any significant effect of taking ginger supplements on hepatic fibrosis and aspartate aminotransferase.

Ginger is the root of *Zingiber officinale* and is one of the most used spices in many countries. Ginger contains active ingredients such as gingerol, shogaol, zingerone and β-bisabolene. In ancient medical practice, ginger was used for treatment of various disorders such as rheumatoid arthritis, neurodegenerative diseases, inflammation and asthma. Previous studies have shown that ginger and its active compounds can exhibit anti-diabetes, anti-cancer and anti-inflammatory properties. It has been shown that ginger extract can exhibit antioxidant activity and reduce the levels of pro-inflammatory biomarkers. Moreover, recent studies on patients with Type II diabetes and hyperlipidemia have shown that ginger can reduce insulin resistance and serum triglyceride concentration(1).

Turmeric (Curcuma longa) is a perennial herb belonging to the ginger family (Zingiberaceae). The main biological activity of turmeric is related to curcumin which has commonly used as curry powder in Asian cuisine. Curcumin has a polyphenol structure and has been traditionally used as a household treatment for various diseases. Several studies suggested that curcumin has antimicrobial, antiinflammatory, antioxidant , immunomodulatory, renoprotective, anti-cancer, hepatoprotective, phypoglycaemic pr operties which are acts through signaling pathways and regulating gene expression.

Although a large body of evidence *in vitro* and animal studies have supported hepatoprotective activity of curcumin, results from single human study have remained inconclusive. Therefore, the present review was aimed at providing a summary and conclusive result for effect of curcumin/turmeric on NAFLD in compare with placebo in adult participants(2).

After 3 months of *N. sativa* treatment, the mean HCV RNA levels (PCR) (147028.2 ± 475225.6) significantly decreased relative to their baseline levels (380808.7± 610937, P = 0.001). All cirrhotic patients (compensated and decompensated) showed no change or improvement in their Child-Pugh score,

patients presented with variable Child-Pugh score, yet the proportions' numbers were small for a valid statistical test. There was a significant increase in total protein and albumin levels after treatment. However, there was no significant change in liver enzymes (AST and ALT), bilirubin, or INR. Renal function did not show a significant change from baseline. TAC showed a significant increase after treatment (1.612 ± 0.56) relative to the baseline values (1.35 ± 0.05, P = 0.001, Figure Figure1B).1B). Hematological functions varied significantly after 3 months of *N. sativa* treatment. There was a significant increase in RBCs (P = 0.001) and platelets (P = 0.004) and a significant decrease (P = 0.013) in white blood cells.

The liver tissue samples of the 0.2 mL/kg CCl_4 group exhibited remarkable damage. Irregularities were observed in the parenchymal structure, and the classic lobular structure could not be distinguished. In addition, sinusoidal dilation (++), congestion (+), inflammation (++), intense degeneration (+++), vacuolisation, nodular types of cellular damage (+++), pycnotic nuclei of necrotic cells with eosinophilic cytoplasm (+++) and hypertrophic cell structures (+++) were observed. In the recovery group, sinusoidal dilation (+), inflammation (+), congestion (+) and cellular damage (+) were observed. Sinusoidal dilation (+) and congestion (+) were examined in the curative group(3).

The nutritional requirements of honeybees, *Apis mellifera*, are met by the collection of pollen, nectar, and water. Nectar is the primary source of carbohydrates, while pollen provides proteins, lipids, vitamins and minerals. Bee bread (BB) is a fermented mixture of plant pollen, honey, and bee saliva that worker bees use as food for larvae, and for young bees to produce royal jelly. Pollen collected by bees is mixed with a small amount of honey and saliva and packed into the cells of the honeycomb where it undergoes a chemical change to form a product called bee bread. This mixture undergoes different chemical processes due to the action of distinct enzymes from glandular secretions, microorganisms, moisture and temperature (35–36 °C chamber temperature offspring), allowing the transformation, improvement and preservation of the stored pollen, which is called bee bread after two weeks of initial storage.

Despite the role of BB as the main source of protein for bees, its functional properties have been correlated, as well as its flavonoid content, with the BB's floral origin. BB has demonstrated in vitro antibacterial, antioxidant, and antitumor properties. For the last activity, ethanolic extracts were screened against tumor cell lines (human glioblastoma cell line U87MG) and the normal human astroglia cell line SVGp12 (CRL-08621) using in vitro assays.

The BB composition varies according to the origin of the pollen but is mainly composed of water, proteins, carbohydrates, lipids, inorganic elements and various other minor components such as decanoic acid, gamma globulin, nucleic acids, vitamins B and C, pantothenic acid, biopterin, neopterin, acetylcholine, and reproductive hormones, among others.

The quality information available on the literature for beebread remains limited, with few reports on the phenolic composition of this mixture. Some phenolic compounds were previously identified in BB samples from Poland, Russia, Latvia and Georgia. Other reports on BB samples from Spain and Poland mentioned only total phenolics

measured by the Folin-Ciocalteu colorimetric assay and did not provide detailed characterization in terms of individual phenolic compounds.

In the present study, five BB samples, collected from *Apis mellifera* hives located in different apiaries near Guba, in the northeast region of Azerbaijan, and one sample of commercial BB were characterized by HPLC-DAD-ESI/MS in terms of their phenolic profile. Furthermore, the samples were screened against different human tumor cell lines, as well as against non-tumor liver cells(4).

Methods

PubMed, Scopus, Web of Science and Google Scholar were systematically searched until December 2017. We included randomized controlled trials (RCTs) which examined the effect of curcumin/turmeric supplementation on NAFLD in adult participants. Main outcome was alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Potential risks of bias (ROB) were assessed by using Cochrane ROB tool.

Thirty patients with hepatitis C virus (HCV) infection, who were not eligible for IFN/ribavirin therapy, were included in the present study. Inclusion criteria included: patients with HCV with or without cirrhosis, who had a contraindication to IFN-α therapy, or had refused or had a financial constraint to IFN-α therapy. Exclusion criteria included: patients on IFN-α therapy, infection with hepatitis B or hepatitis I virus, hepatocellular carcinoma, other malignancies, major severe illness, or treatment non-compliance. Various parameters, including clinical parameters, complete blood count, liver function, renal function, plasma glucose, total antioxidant capacity (TAC), and polymerase chain reaction, were all assessed at baseline and at the end of the study. Clinical assessments included: hepato and/or splenomegaly, jaundice, palmar erythema, flapping tremors, spider naevi, lower-limb edema, and ascites. *N. sativa* was administered for three successive months at a dose of (450 mg three times daily). Clinical response and incidence of adverse drug reactions were assessed initially, periodically, and at the end of the study.

N. sativa administration significantly improved HCV viral load (380808.7 ± 610937 *vs* 147028.2 ± 475225.6, $P = 0.001$) and TAC (1.35 ± 0.5 *vs* 1.612 ± 0.56, $P = 0.001$). After *N. sativa* administration, the following laboratory parameters improved: total protein (7.1 ± 0.7 *vs* 7.5 ± 0.8, $P = 0.001$), albumin (3.5 ± 0.87 *vs* 3.69 ± 0.91, $P = 0.008$), red blood cell count (4.13 ± 0.9 *vs* 4.3 ± 0.9, $P = 0.001$), and platelet count (167.7 ± 91.2 *vs* 198.5 ± 103, $P = 0.004$). Fasting blood glucose (104.03 ± 43.42 *vs* 92.1 ± 31.34, $P = 0.001$) and postprandial blood glucose (143.67 ± 72.56 *vs* 112.1 ± 42.9, $P = 0.001$) were significantly decreased in both diabetic and non-diabetic HCV patients. Patients with lower-limb edema decreased significantly from baseline compared with after treatment [16 (53.30%) *vs* 7 (23.30%), $P = 0.004$]. Adverse drug reactions were unremarkable except for a few cases of epigastric pain and hypoglycemia that did not affect patient compliance(5, 6).

Results and Discussion

Mixture with bee products and herbs
Used in Liver Support Therapy.

Ingredients:
Turmeric root,

Ginger root,
Artichoke leaves,
Nigella seed,
Bee Bread,
Thistle honey.

Turmeric Curcuma longa
We have known for centuries the use of curcumin in turmeric to cleanse the liver.
As is known, turmeric regenerates liver cells.
Turmeric helps in removing toxins from the liver.

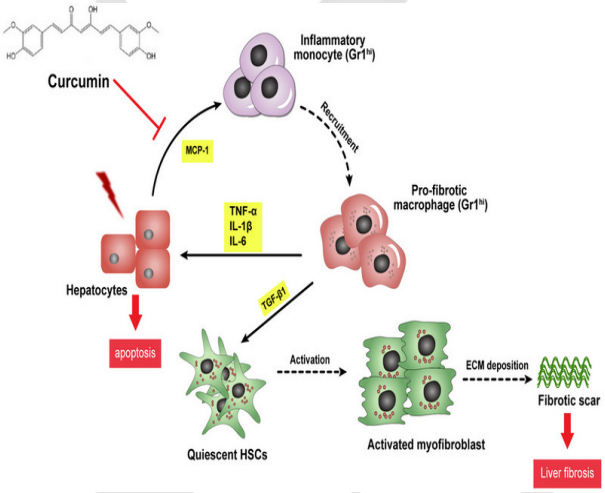

Figure 1.

As Avicenna said:
Consuming turmeric is beneficial for the liver and facilitates digestion.
(The Book of Healing)

Nigella Sativa
Black seed protects the liver from some toxic heavy metals.
Studies have clearly revealed that the black seed solution protects the liver on mice against a toxic substance called carbon tetrachloride.
In addition, it has been stated that toxic substances have less effect on the tissue of the liver(7).

Cynara scolymus
Artichoke has been used for over 2000 years to treat liver and gall bladder ailments, jaundice, in which "eyes and skin turn yellow".
It has been shown that the components found in artichokes, called flavonolignan (also known as cynarin), protect liver cells against alcohol, acetaminophen (Tylenol), and the highly toxic tapeworm fungus(8).

Bee bread
It is a bee product that can be easily dissolved by the body.
It reduces liver enzymes.
Natural Lactic Acid Bacteria and Bifidobacteria in it give it a natural probiotic feature.
Zingiber officinale
Thanks to the antioxidants it contains, ginger reduces triglyceride values and thus helps to reduce liver fat.
It can reduce ALT, AST and GGT levels during steatohepatitis and hepatitis B. Results were available within 12 weeks.
It is effective in basic therapy in non-alcoholic fatty liver disease(4).

Thistle honey
Although thistle honey is an interesting type of honey, it is a very rare honey.
It is common in Azerbaijani districts.
Milk thistle honey, whose active ingredient is Silymarin, creates a synergistic effect with other herbs.
It is easier to absorb the body and its agonist effect with other herbs, like other strained honey.

Effects of Hepbal paste on ALT- one of the liver enzymes

Table 1.

Different groups of liver patients	***Users of Hepbal paste***	***Patients***

Chronic Hepatitis B	31 U/I	62 U/I
Non-alcoholic Steatohepatitis	40 U/I	99 U/I
Alcoholic Hepatitis	113 U/I	208 U/I
Liver Cirrhosis	100 U/I	164 U/I

Number of patients for the study: 44 patients
Period of the study: 8 weeks
The daily dose: 15 kg / mg * 3 times.

Effects on the liver size in case of Steatohepatitis

Table 2

Patients with Liver Lubrication	***Users of Hepbal paste***	***Patients***
Nonalcoholic Steatohepatitis	143 mm grade I	169 mm grade II
Alcoholic Steatohepatitis	155 mm grade II	195 mm grade III

Number of patients for the study: 33 NASH and 36 ASH
Period of the study: 12 weeks
Daily dose: 20 kg / mg * 3 times.

We could get results on these diseases using Hepbal paste:
Hepatitis B, Hepatitis C, NASH, ASH, Cirrhosis.

Other effects of the Hepbal mixture:
Antioxidant effect on toxic hepatitis damaged by long-term chemical therapies
Results due to liver cirrhosis and the lactobacilli which are intestinal disorders (diarrhea-constipation)
Regulation of loss of appetite due to containing flavonoids and minerals

Contraindications:
Active stomach ulcer (bleeding)
Acute intestinal infection
Lower Gastrointestinal bleeding diseases
Organ failure due to Diabetes Mellitus

Using Hepbal paste with medicines:
When it was used with Tenofovir (for Hepatitis B), it took away the side effects of the drug.
It was used with Sofosbuvir, Ledipasvir, Daclatasvir (for Hepatitis C) and positive effects were experienced on ALT and AST.
It caused diarrhea when it was used with Ursodeoxycholic acid.

Goals related to Hepbal paste:
We started research on other liver diseases and cancer with the Japanese scientists.
To start production abroad
To start research together with several countries to highlight the cooperation of Phytotherapy and Apitherapy.
Researching the unknown effects and side effects of bee products to reach conclusions.

Hepbal paste:
It can be considered possible to be used in pregnancy, except for intestinal infections.
Children over 1 year old can use it.
Chronic patients can use it alongside drugs.

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