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Role of Nutraceuticals on Hepatoprotectivity

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and Type 2 diabetes (T2D) are major public health challenges worldwide, associated with metabolic derangement and unhealthy life style behaviours demanding efficient nonpharmacological strategies. Together, however, these effects have not been studied in controlled trials, and specifically a no-added-sugar WFPB diet combined with eTRE. have not been studied in controlled investigations. So far, it seems that WFPB diets improve HbA1c, insulin resistance, glycemic control, and cardiometabolic risk through their ability to decrease oxidative stress, dietary acid load, and deleterious lipid accumulation in muscle and liver (whereas) eTRE helps enhance insulin sensitivity and metabolic flexibility by aligning food intake with circadian biology. These are approaches that may be additive in terms of visceral fat and beneficial gut microbiota reduction but can prove difficult to follow in everyday life. NAFLD affects about 25% of adults and is even more prevalent in individuals with diabetes or obesity; it can progress to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and increased cardiovascular mortality. With no approved pharmacological treatments, lifestyle change remains central to NAFLD management. Nutraceuticals such as silymarin, vitamins E and D, omega-3 fatty acids, berberine, carnitine, resveratrol, polyphenols, anthocyanins, betaine, astaxanthin, probiotics, fruits, vegetables , species , herbal plants and curcumin have shown promise in improving hepatic fat and metabolic parameters due to antioxidant, anti-inflammatory, and lipid-modulating effects, although evidence from high quality long term randomized trials have always been both scanty and inconsistent. In summary, the present results testimonial the WFPB diets, eTREs, weight loss and selective nutritional use in a context of comprehensive lifestyle interventions while highlighting the requirement for well-designed trials for long-term safety, compliance and clinical efficacy.

Keywords: (NAFLD), Type 2 diabetes, insulin resistance, antioxidant, anti-inflammatory, lipid-modulating effects.

INTRODUCTION

The Liver is the largest glandular organ in the body, which regulates the physicochemical properties.

. It is one of the most important organ in our body, which regulate the metabolic pathway, and it also helps in detoxification of the body. It metabolises carbohydrates, lipids, alcohol, various kinds of medications, and it also filter the pot pollutants. [1]

It performs over 150 vital activities, many of which play an important role in metabolic regulation. Particularly the liver, is a primary organ for the regulation of glycol Lipid metabolism, gluconeogenesis, glycogenolysis, glycogenesis, synthesis of apolipoproteins, cholesterol and triglycerides and secretion of l d l cholesterol via the biliary system .The liver is phone off the significant organ, which help in body's homeostasis preservation. [2]

The substances which contain anti-inflammatory interpolative Antioxidant antibiotic anti neoplastic properties help in maintenance of liver. Nowadays the liver is begin to not to perform its expected function due to its metabolic range, Immune mediated ,carcinogenic ,infectious and some kind of toxic substances Nutraceuticals are the substances which help in treatment of many psychological diseases. [3]

Neutracicals include dietary supplements such as nutrients, herbal products, cereals, milk, derivatives, drinks and soups. A very aged Indian Ayurvedic system of medicine used plant based medication for treatment of various diseases, including liver illnesses. By the estimation of world has organization, the people around four billion people in the world are estimated to use plant based, its supplements. The present review has done to accomplished plant based medication that have been accessed in vivo and invitro models. [4]

MATERIALS AND METHODS:

SUBSTANCES USED FOR HEPATOPROTECTIVITY

1.VITAMIN D:

25-hydroxyvitamin D3, commonly named vitamin D, is a fat-soluble vitamin that is synthesized in the skin upon the conversion of 7-Dehydro cholesterol to the active form of vitamin D by ultraviolet light .Its biological role include maintaining mineral metabolism modulation immune response, And including insulin secretion and cell differentiation .The vitamin exerts Other metabolic action, among which are anti-inflammatory and anti fibrotic properties that might be relevant for NAFLD Patient, Vitamin D deficiency has been associated With insulin resistance and increase diabetes and Mets Risk in variation studies .Therefor, D deficiency is strongly linked to NAFLD, And this deficiency have been found in as much as 25% of Patient with Mets in several reports.Low level of vitamin D have Also been associate with a higher histological severity of NASH In a Study that include subjects with chronic elevation of liver enzymes and ultrasound detector hepatic steasosis ,later confirmed by liver [5].

Clinical trials ,However, have yield mixed result. For instance, sharifietal. Conduct a double-blind, Placebo-controlled study using 50,000 Iu Vitamin D3 every 14 days for 4Months in 53 patients and noted no Significant difference in liver function tests, HOMA-IR, or steasosis grades. Like wise, no Clinically significant changes in liver Histology, biochemistry, insulin resistance, or adipocytokine Profile were observed in another high doses vitamin D3 administration study. Considered the small number of study participants and short term studies, this result should be interpreted with caution. Large scale randomizer controlling trails are needed to substrate. where vitamin D supplementation may affect yeah NAFLD Disease progression. [6]

2.VITAMIN E

Treatment of HIGH-DOSE VITAMIN E Liver damage from high doses of vitamin E, especially the biologically active form that blocks inflammation and liver scarring, is becoming increasingly worrisome. An effective dose, therefore, is approximately 40 times the RDA (800 IU/day), but taking about 20 times the RDA of vitamin D (400 IU/day) has been associated with increased risk of all-cause mortality. As a result, clinicians frequently choose lower and safer doses, which may also be less effective, or administer vitamin E with other agents that might be similarly beneficial in NAFLD treatment.[7]

The membrane-bound nutritional antioxidant, alpha-tocopherol, inhibits three critical steps in memorial- lipid peroxidation. Free radicals have been implicated in liver disease as a cause of oxidative damage. Although the cellular damage that occurs in liver disease is known to be multifactorial, it seems probable that free radicals are involved both in initiation and perpetuation of this damage. For example, abnormal bile acid levels and elevation of heavy metals including copper and iron stimulate the generation of free radicals in the liver.

Oxidative stress is one of the main factors in hepatic injury; as one of the two-hit hypotheses, it is a crucial link developing from simple steatosis to steatohepatitis. Elevated ROS generation may stimulate lipid peroxidation, leading to the inflammatory and fibrotic activation of stellate cells. Lipid peroxidation is also augmented in NAFLD and may promote the same proinflammatory responses as well as tissue destruction. Oxidative and antioxidant status in NAFLD Several studies have reported on the oxidative/antioxidant profile of patients with NAFLD.[8]

3.VITAMIN C

Ascorbate (Vitamin C) is a vital water-soluble intracellular antioxidant. It is capable as well of regenerating the active form of alpha-tocopherol by reducing the tocopherol radical. Patients with liver disease It's already well known that humans suffering from advanced liver disease have a low hepatic vitamin C level, in part because they don't produce vitamin C as cats and dogs do. The vitamin C concentration has not been reported in dogs and cats with liver diseases. While vitamin C may be beneficial in hepatic diseases, it can also serve as a pro-oxidant when there are concentrations of supplementation with vitamin c should be avoided in dogs prone to copper associated hepatotoxicity.

Several studies of vitamin C status in NAFLD have been cross-sectional. Some studies have identified that the daily intake of vitamin C in affected individuals was significantly lower than non-affected ones, whereas others showed no significant difference regarding dietary and plasma levels of vitamin C among cases with NAFLD compared to ones without it. These discrepancies could be due to the observation that several of the studies only used an estimated dietary intake and not a directly measured plasma concentration. Only two randomized controlled trials (RCTs) have assessed the effect of vitamin C supplementation so far, in NAFLD.[9]

4.CARNITINE

L-carnitine is a key compound in the transport of fatty acids into mitochondria and to its metabolic activity, acting as a stabilizer for cell membrane and also having the capability to lower serum lipids.[10] It also helps to stabilize energy homeostasis in tissues possessing high rates of fatty acid oxidation and possesses the capacity to regulate inflammatory processes. Treatment of L-carnitine has a beneficial effect in obesity, type 2 diabetes and liver cirrhosis.

L-Carnitine is a vitamin-like substance synthesized in the body and found in the liver, brain, heart, and other tissues. Therefore, liver disease can cause carnitine depletion. L-carnitine transports fatty acids into mitochondrial matrix for beta-oxidation, where long-chain acyl fragments are cleaved by CPT2 to generate acetyl CoA which in turn enters TCA cycle to produce energy. Carnitine deficiency can lead to both hepatocyte triglyceride accumulation and the accumulation of toxic acetyl-CoA metabolites that disrupt rial function. Clinically, deficiency increases ammonia, hypoglycemia and fatty liver are observed. Armstrong showed in one study that the supplementation of L-carnitine prevented hepatic triacylglycerol accumulation during rapid weight loss in obese cats. Another trial demonstrated that obese cats consuming L-carnitine while undergoing a weight loss protocol were able to tolerate it safely. L-carnitine deficiency also has been implicated in the pathogenesis of idiopathic feline hepatic lipidosis, although Jacobs documented variable concentrations.

5.OMEGA-3 FATTY ACIDS

Omega 3 fatty acids are very important for the body to grow and develop as they play many different types of roles in many different body's systems or organs. Omega 3's are needed to grow and work properly; therefore, a balanced diet should theoretically provide enough sources of omega 3 fats; however, due to a decrease in the quality of most people's diets and the processing of foods, combined with increased physical demands, many more people now look to supplement their diets with additional omega 3 fatty acids.[11]

In multiple meta analyses of RCTs conducted on subjects taking omega 3s as a supplement, the data showed that omega 3 fatty acids (DHA, EPA) significantly decrease the amount of AST and GGT levels present in the blood.

The effects of omega 3s as evidenced by these studies, when combined with their well-documented anti-inflammatory properties and ability to lower triglycerides, may prove beneficial as nutraceuticals in the clinical management of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) patients.[12]

A further look into the results of four RCTs conducted with a population of children (263) taking EPA and DHA supplements for extended periods found that, on average, children taking either one of the omega 3 supplements had significantly lower levels of AST, ALT and ultrasound measured hepatic steatosis (by 25%) with no reported adverse side effects.

Polyunsaturated fatty acids (PUFAs) classified as omega-3 fatty acids must be consumed from food sources and not synthesized by the human body. Among these fatty acids docosahexaenoic acid (DHA) and the eicosatetraenoic acid (EPA) are the two primary omega-3 PUFA types available. Fish oils are recognized as the most effective source for omega-3 PUFA. Evidence suggests that increasing fish intake by consuming two servings weekly reduces the risk of developing cardiovascular disease. In addition to reducing the risk of cardiovascular disease,[13] omega-3 PUFA are known to stimulate oxidization of triglycerides and fatty acids instead of allowing triglycerides to accumulate or for lipogenesis to occur due to their ingestion. Omega-3 PUFA may assist in restoring hepatocyte activity associated with peroxisome proliferator-activated receptor alpha (PPAR-α) by reducing levels of certain lipogenic enzymes.

6.SILYMARIN

Silymarin, which is prepared from the milk thistle plant, is a flavonoid polyphenol that includes silybin, isosilibinin, silicristin and other related compounds. In the liver it diminishes inflammation and fibrogenesis, facilitates regeneration and inhibits Kupffer cell generation of leukotrienes, which are involved in hepatic stellate-cell activation. Silymarin was reportedly found to have membrane-stabilizing and antioxidant properties, presenting the potential adjunct therapy of inflammatory liver diseases such as cirrhosis, hepatitis, alcoholic fatty liver disease and NAFLD.[14]

7. POLYPHENOLS

polyphenols are really important! They are a family of compounds that naturally occur in plants and have many health benefits. Polyphenols are antioxidants, which means they help the body prevent oxidative stress and inflammation. They've been associated

with several health benefits, including improved heart health, enhanced brain function and a lower risk of certain chronic diseases, such as diabetes and cancer.

Fruits (like berries, grapes, apples) Vegetables (such as onions and shallots) Nuts Cocoa Coffee Tea Red wine Green tea Olive oil Onions Garlic Etc.[15]

8.ANTHOCYANINS

Anthocyanins are water-soluble biologically active components of the flavonoids. Anthocyanin containing diets have been demonstrated to reduce hyperlipidaemia, oxidative stress and liver steatosis in the experimental models of NASH. Patients with borderline non-viral hepatitis who drank a beverage enriched with high acylated anthocyanins, principle purple pigment of sweet potato, had a significant decrease in liver function tests such as (gamma-glutamyl transpeptidase)GGT. [16] More recently, in a double-blind placebo-controlled trial of 74 patients with NAFLD, the daily consumption of 320.

9.BERBERINE

Berberine hydrochloride is a quaternary ammonium salt of the benzyl iso quinoline alkaloid ($C_{20}H_{18}NO_4^+$; average molar mass 336.3612 g/mol; It is derived from different medicinal plants, mainly being the Berberis spp., and its known lipid-lowering and insulin-sensitizing effects in humans 68. It has also been reported that an early short-term supplementation (2–4 months) with 500 mg/day may improve indirect markers of hepatic steatosis as the Hepatic Steatosis Index and Hazuda, AUC for TG [17] or Lipid Accumulation Product (LAP) 69.

10.BETAINE

Betaine is a nutrient found in many foods. In the liver it gives a methyl group to homocysteine, turning it into methionine. This lowers homocysteine levels and raises methionine levels. One trial tested betaine pills on people with fatty liver disease. Betaine did not improve liver tests or tissue compared with dummy pills.

Fatty liver disease is a big problem for health systems worldwide. Most people with fatty liver do not get severe liver damage but have higher risk of heart disease. Treating fatty liver should use a global plan, not just focus on insulin.[18]

11.ASTAXANTHIN

A potential nutraceutical alternative to vitamin E, which could overcome the difficulty of balancing liver-protective “benefit” versus possible cardiotoxicity is represented by astaxanthin ($C_{40}H_{52}O_4$; 61 IUPAC name: (6S)-6-hydroxy-3-{(1E,3E,5E,7E,9E,11E,13E,15E,17Z)-18 [(4S) – 4-hydroxy-2,6, 6 -trimethylcyclohexyl]-3,7,12,16-tetramethyloctadeca-1,3,5-,7-,9-,11-,13–15–17-nonaenyl}-2,4 — dimethylcyclohexa-2 Astaxanthin : a marine carotenoid that produces purple-red hues.[19]

12.CURCUMIN

turmeric curcumin longer L is a popular spice in Asia especially in India in the HPV X protein transgenic mice curcumin longer leads to less visceral fat [20] in a particular clinical study of 100 Asian patients with metabolic single as shown a statistically significant improvement in the degree of hepatics steatosis assessed by liver ultrasound with a daily administration of 400 MG when the same clinical trials conducted on 102 iranian Patients supplementation with phytosome curcumin 500MG for eight weeks leads to a significant reduction in transaminase level curcumin also fights against liver cancer also involves the enhanced degradation of hypoxia induced Vector encouragement also promotes opposite of the Hep 3B cell [21] cartoon oil is better than curcumin curcumin oil passed hepatoprotective and sesquiterpenoi Might it’s main bio active ingredient.

13.PROBIOTICS

There is a strong link in between the one that commonly known as the liver gut access the gut supplies plate to the portal system and the intestinal blood content activates liver function while the liver secrets bile and influences intestinal functions If there is any alteration In homeostasis many results to the inflammation of the gastrointestinal tract which further leads to the inflammatory conditions of the liver which may further leads to the development of NAFLD for this probiotic are potentially and energizing therapeutic strategy.

By taking probiotic strains promising results are observed preliminarily ascites shows the treatment with L. bulgaris or s. Thermophiles This is the level of alamine amino transferase on the gamma glutamyl transferase 80.

Found that significant improvement in severity of fatty liver and a significant decrease in body mass index of children with NAFLD treated for four months with bilido bacteria lactobacillus and s. Thermophiles Strains similar results were obtained with the association L. Acidophilus And b.lactius for 8 weeks In adult patients with NAFLD these data suggest that probiotics couldn't reduce liver fat and thus prevents progression of NAFLD at the end of the treatment significant improvement of transaminase and cholesterol amine compared to the control group.[22]

FRUITS

1.Plum

Unripe plums have various polyphenols such as epicatechin and gallocatechin gallate. Immature plum extracts have been shown to possess anticancer activities in HepG2 cells by inducing apoptosis, activating caspases-8, -10 and3, and leading to DNA fragmentation . We also found that immature plum extract inhibited the growth of HepG2 cells in other experiments. The antimetastatic property is thought to be associated with activation of Nrf2 pathway. Studies in rats have also found that pretreatment with immature plum extract attenuated SCC-R-acetylesterase inhibitors. Similarly, rat studies showed that pre-treatment with immature plum extract attenuated the carcinogenetic effects of benzopyrene through induction of detoxification enzymes.[23]

2.Pomegranate

Pomegranate is a rich source of antioxidants and polyphenols. Its bioactive components have also demonstrated the suppression of diethylnitrosamine-induced hepatocarcinogenesis in rats by inhibiting inflammation through the NF-κB pathway. These results provide evidence for the antitumorigenic property of pomegranate.[24]

3.Black Current

Black currant is more rich in anthocyanins in which have both antioxidant and anti inflammatory properties. In vitro studies on HepG2 cells shows that anthocyanin rich fraction of black currant inhibited cell proliferation . In an animal rat model of liver cancer administration of dietary black currant skin in extracts (100 or 500 mg per kg in 22 weeks) repressed Gamma glutanyl transpeptidase .The study provides significant evidence for which can inhibit the inflammation of NF-KB signally by repression and decreases in oxidative stress through activating the NrF2 to pathway.

In two Stage liver cancer rat model conducted by diethyl nitrosome and which is promoted by phenobarbital BCSE also reduced the incidence number size and multiplicity.

In dose dependent fashion, the BCSE reduced the incidence, number, size and multiplicity of preneoplastic hepatic nodules. Additional findings indicated that it is due to induction or apoptosis may result anti-cancer activit .[25].

4.Grapes

Grapes in products of were recognized healthy dietary components against many pathophysiological processes silbene anthocyamines and procyimidins Which are abundant in grape skin seed and red wine which posts anti-inflammatory antioxidant From grape to people isolated DPP four and TPC cell culture weapon have strong chemo preventive properties asdepletef By an invitro human DNA topoisomera assay In liver cancer enriched with blood vessels and angiogencsia play key role in cancer metastus and relapse Researchers also suggested a possible anti carcinogenic use against the HCL From great extract from winery waste from seed extract we can treat in egg to cell and use DNA damage P53 upregulation and significant decrease of total PARP expression [26].

VEGETABLES

The available epidemiologic data suggest that the more dense the consumption of vegetables, especially cruciferous vegetables, tomatoes and legumes, [the] lower the cancer risk even for digestive-tract cancers. This is also supported by a recent meta-analysis which reveals that the consumption of more vegetables was associated with a lower risk of liver cancer (RR = 0.78, 95% CI = 0.62–0.99) [27].

1.CRUCIFEROUS VEGETABLES

Their preventive effects are mainly due to the high levels of glucosinolates and their metabolites, isothiocyanates. Radishes (Raphanus sativus L.) in particular are abundant in glucosinolates, isothiocyanates, and polyphenols . 4-Methylsulfanyl-3-butenyl

glucosinolate (glucoraphasatin) is one of the predominant glucosinolates present in radish, One of the most widely accepted underlying mechanisms for vegetables of the cruciferous family on anti-cancer is thought to relate to their ability to induce Phase II detoxification enzymes such as NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione-S-transferase and phenolsulfotransferases, that enhance removal of reactive metabolites of prototypic carcinogens . A large body of literature has demonstrated that GSL anti-tumorigenic effects are predominantly mediated via these protective pathways [28]. Nevertheless, isothiocyanates there is evidence that the isothiocyanates generated from glucosinolates are the most anti-carcinogenic compounds.

E.g., in precision-cut rat liver slices, bothed glucoraphasatin and its isothiocyanate from radish sprouts increased significantly those hepatic Phase II detoxification enzymes that metabolize chemical carcinogens like mycotoxins, heterocyclic amines and poly cyclic aromatic hydro carbons but did not alter cytochrome P450 enzymes (including the CYP1 family). Although it has been shown that sulforaphane (SUL), a major isothiocyanate in broccoli, enhances the expression of CYP1A1 in time- and concentration-dependent manners in both Hepa 1c1c7 and HepG2 cells. Since SUL has strong reactivity, it is quickly metabolized in human body to N-acetyl-L-cysteine (NAC) conjugate of SUL due to the attachment of NAC group having even stronger anti-hepatoma activity and more powerful induction of phase II enzyme quinone reductase .Sinigrin, another major aliphatic glucoraphanin in cruciferous vegetables, is metabolized to allyl isothiocyanate (AITC). Both AITC and synthetic NAC-AITC dose-dependently inhibit the proliferation of the Hepa1c1c7 murine hepatoma cells probably through elevation activity and gene expression of quinone reductase . In addition, these compounds reduced adhesion, invasion and migration of cancer cells via inhibition in the transcriptional activity of MMP-2 and MMP-9 in SK-Hep-1 human hepatoma cells . Rutabaga (Brassica napobrassica), commonly consumed in northern Europe and North America has also been found to have striking anticancer benefits. Rutabaga extracts including eight-day-old sprouts selectively inhibited the proliferation and induced apoptosis in HepG2 (liver cancer) cells with much milder effects on normal Chinese hamster ovary cells [29].

2.TOMATO

Tomato is an unsaturated carotenoid, and its level is from 11.6 to 14 mg/kg. Lycopene was proved to modulate cell proliferation, differentiation and apoptosis and is a potential candidate for the prevention of hepatocellular carcinoma (HCC) prevention. In mice treated with N-nitrosamines lycopene pretreatment significantly diminished the carcinogenic effects by decreasing oxidative stress and lowed chromosomal and membrane alterations . Furthermore, lycopene treatment markedly suppressed anti-apoptotic genes and enhanced the expression of caspases-3 and -9, along with p53 to promote apoptosis in N-nitrosamine-treated animals [30].

Significantly, the N-nitrosodiethylamine (NDEA)-induced tumour incidence, tumour multiplicity and tumour burden were significantly reduced by lycopene pretreatment in mice to 42.05 percent, 3.42 and1.39 respectively for liver tissues when compared with those of NDEA + ethanol-treated control mice which are 100 percent, >6 and about 4 approximately respectively along with improved survival rates. Histopathological examination also showed less aggressive tumour nodules. Together, these results demonstrate that lycopene acts as an anti-mutagen in the initiation stage of chemically induced hepatocarcinogenesis and lycopene is not the only active compound: tomatine (a glycol alkaloid that exists in much greater concentration in green compared to red tomatoes) also shows antitumor activity. In vivo research indicates that tomatine has antitumor activities different from lycopene, such as antigen-specific cellular immunity and direct inhibition of tumour cell membranes. A commercial tomato glycoalkaloid mixture (10:1 α-tomatine versus dehydrotomatine) exhibited cytotoxic activity against the HepG2 cell line in a dose-dependent manner, faster then doxorubicin. These findings suggest that eating green tomatoes (which contain more tomatine) may have an extra antitumor benefit [31].

3.ASPARAGUS

Asparagus SPP (Asparagus officinalis L.) is a popular edible plant which is used in soups, salads and other types of foods. Several studies have reported different pharmacological effects, such as anti-inflammatory (4), antimutagenic (5), and cytotoxic activities. These bioeffects are mainly due to its polysaccharides, steroidal saponins and flavonoids. Furthermore, asparagus polysaccharide can be effectively used for the treatment of breast cancer, leukemia and lung carcinoma. Recent studies indicated that these polysaccharides could preferentially inhibit the growth of HepG2 (IC_{50}: 5.7 mg/mL) and Hep3B (IC_{50}: 9.39 mg/mL) liver cancer cells with significantly lower toxicity against normal human hepatocytes (7702 cell lines; IC_{50} = 20.92 mg/mL). Mechanistic findings indicate that asparagus polysaccharides mediate G2/M cell cycle arrest and induce apoptosis via regulation of Bax, Bcl-2, and caspase-3.

In addition, asparagus polysaccharide has been characterized as an ideal embolic agent in transcatheter arterial chemoembolization (TACE), a minimally invasive treatment for patients with unresectable HCC. In combination with TACE, asparagus polysaccharide strongly suppressed the growth of liver tumours and prolonged the survival of rats without obvious toxicity.

Of the steroidal saponins in A. officinalis, asparanin A has been found to have wide-ranging antitumor activity against oesophageal, gastric and lung carcinoma cells, particularly leukemia cells. Asparanin A inhibited the proliferation of HepG2 cells in a time- and dose-dependent manner (IC50(6.20) = ± 0.56 μmol/L), inducing cell cycle G_2/M phase arrest through downregulation of Cdk1, Cdk4 and cyclin A, and upregulation of p21^WAF1/Cip1. Additionally, it promoted apoptosis through both intrinsic and extrinsic pathways in HepG2 cells [32].

4.FRENCH BEAN

Antiproliferative activity of the aqueous extracts from beans (Phaseolus vulgaris L.) was found in a study on extracts from above-ground parts of French bean. The extracts, at concentrations of 400 and 800 mg/Ml expressed marked antioxidant activity and inhibited the cell growth of HepG2 by 57% and 74%, respectively . 24 components, including 12 triterpenoids and seven flavonoids were isolated from P. vulgaris seed coat and some of them showed antiproliferative effects with IC_{50} values between 32.1 ± 6.3-779.3 ± 37.4 Legumes are also high in lectins, which serve as the major storage protein and have attracted considerable attention for their therapeutic applications such as antitumor, antibacterial, and anti-HIV effects. A 64 kDa hemagglutinin in dimeric form, was purified from the dried beans of P. vulgaris (1.1 g per 100 g seeds) arresting moderately HepG2 cells growth (IC_{50} ≈ 100 Mm) but not WRL-68 normal liver cells . Following work by this group resulted in the purification of a novel lectin, BTKL derived from the seeds of P. vulgaris that exhibited potent selective cytotoxicity against HepG2 cells (IC_{50} = 7.9 ± 0.5 Mm). Mechanisms of BTKL Antitumor Activity The mechanisms by which BTKL exerts antitumor activity might be induction of apoptosis and necrosis, increase of nitric oxide generation via induction of Inos, and induction of pro-inflammatory cytokines release, such as IL-1β, IL-2, TNF-α and IFN-γ . Another research also stated that a hemagglutinin from P. vulgaris had much higher antiproliferative activity against HepG2 cells than concanavalin A [33].

SPICES USED FOR HEPATOPROTECTIVE

1.SAFFRON

Saffron is a part of a flower ,which is stigmas of the flower .they were collected from the plant CROCUS SATIVA . It have medicinal properties such as reduces tumour ,oxidative damage and also said to have anti inflammatory properties in the liver tissues.[34]

2.GARLIC

There is a compelling epidemiological evidence that high intake of garlic can protect against various cancers. Garlic has various organosulfur compounds (OSCs) such as alliin, allicin, diallyl disulfide (DADS), diallyl sulfide (DAS), allyl mercaptan, and S-allylcysteine that are known to have anti-tumour effects (Figure 2). In experimental models, treatment with garlic powder reduced N-nitrosodimethylamine–induced liver DNA damage by 35%–60% in rats as detected by the comet assay; this action was mostly correlated to high alliin concentration of these samples Subsequently, researchers investigate the anticancer activities of certain garlic-originated OSCs in HepG2 cells treated with chemical mutagens. Except for allyl mercaptan, the OSPs tested all markedly suppressed DNA damage induced by aflatoxin B1, according to their results. On the other hand, allyl mercaptan specifically decreases those DNA breaks induced by dimethylnitrosamine. Diallyl disulfide was found to be effective in preventing induction of genotoxic damage by benzo(α)pyrene. In addition, all tested OSCs suppressed DNA damage by direct-acting agents such as H_2O_2 and methyl methanesulfonate. The antitumor activity of aged-garlic extract in rats was evaluated by a research team. It reduced hepatic nodules preneoplastic induced by diethylnitrosamine in the mouse and acted on liver cell proliferation . As immunological function is frequently compromised in patients with advanced cancer, a study of the product's immune-modulatory impact was done to 30 patients with late-stage digestive system cancers (84% liver cancer). In these patients, the activity of natural killer cells was increased with aged garlic extract treatment as demonstrated by the results [35].

3.TURMERIC

Turmeric (Curcumin longa L.), which is extensively used in Asia, has a good hepatoprotective activity. Curcuma longa extracts ameliorates the visceral adiposity, caudal fat ratio and disease progress in HBX transgenic mice‹ hinting its protective effect against HBV-related hepatocellular carcinoma. CUR is its major bioactive pigment with antioxidant, anti-inflammatory, and anticancer activities. Curcumin also inhibited chemically induced hepatocarcinogenesis in vivo, as evidenced by reduction of hyperplastic nodules, markers of liver injury, and body weight loss, 85 partially by increasing the degradation of HIF and facilitating Hep3B apoptosis . The most abundant plasma form of curcumin following oral administration, that is, curcumin glucuronide had poorer anticancer efficacy against HepG2 cells . Treatment of cells with curcuma oil and the corresponding sesquiterpenoids reduced oxidative stress, triggered apoptosis in cancer cells and inhibited tumor growth [36].

4.PEPPER

Cytotoxicity against McA-RH7777 rat hepatoma cells and against primary normal rat hepatocytes of pepper extracts, especially P. putumayoense, which was also protective on the latter system, through ROS accumulation . A 24-kD glycoprotein of Zanthoxylum piperitum was also found to have chemo preventive potential. In Balb/c mice that had been treated with diethyl nitrosamine, this glycoprotein (20 mg/kg) modulus perforin, granzyme B, NK cell activity as well as proapoptotic molecules such as Bid, caspase-3 and cytochrome c thereby suppressing liver carcinogenesis. Metastasis of tumours relies on MMP-2/-9-induced degradation of extracellular matrix under blockade by their inhibitors, TIMP-1/-2. Zanthoxylum avicennae extract inhibited proliferation by the induction of G2/M arrest and apoptosis, and also decreased invasion through the regulation of MMP-2/-9 (down) and TIMP-1/-2 (up) in HA22T cells. These effects were associated with phosphatase-2A activation. The essential oil of Zanthoxylum schinifolium, which contains a large amount of geranyl acetate, citronella and sabinene, augmented ROS-dependent apoptosis in HepG , cell lead to increase apoptotic cell death.[37]

5. GINGER

Ginger has been recognized as a potential agent for anti-cancer. In another study of rat model, induced by chemical liver cancer, treatment with daily ginger (50 mg/kg) was observed to cause significantly decrease in the serum liver cancer markers like α-fetoprotein and CEA and hepatic growth factor level . Its protective mechanisms seem to be related with its anti-inflammatory and pro-apoptotic properties. For instance, ginger therapy (100 mg/kg) inhibited inflammatory pathways evidenced by reduced NF-κB and TNF-α levels in a rat hepatoma model. Ginger extracts exhibited their antiproliferative activity in Hep-2 cells in a dose-dependent manner (IC50 = 900 μg/Ml) by apoptosis induced ROS, and geraniol, pinostrobin, and clavatol were found to be active components as confirmed with GC-MS . In contrast, 6-shogaol and 6-gingerol inhibited the metastasis of liver cancer cells by downregulating MMP-9 and urokinase-type plasminogen (6-shogaol) and up-regulating TIMP-1 expression . Similarly, 6-shogaol induced ROS-dependent caspase-mediated apoptosis in a human multidrug-resistant hepatoma cell line, suggesting its useful therapeutic potential [38].

HERBAL PLANTS USED FOR HEPATOPROTECTIVE

1.LAWSONIA INERMIS L.(HENNA)

Lawsonia inermis L is used for a long time for medicine as well as for cosmetics purposes such as hepatic and gastrointestinal disorders, it reduce tissue damage in leprosy, management of food diabetic complications and ulcers . The plant based medicines are pharmacologically important showing various In-vitro and in-vivo biological activities such as antioxidant and antimicrobial properties which are mostly investigated. Many beneficial effects have been described but also some adverse reaction reactions have been observed in the people lacking glucose-6-phosphate dehydrogenase and also in the products containing adulterated substances.

Henna adulteration is common and it lead to erroneous scientific effects. However the lack of extensive information on phytochemical profiles has not yet provided in an adequate evidence required for reliable quality control standard's, impending the safe and effective clinical application of herbal medicines. Many in-vivo studies have been conducted for its toxicity and pharmacological activities.[39]

2.MORINGA OLEIFERA LAM (M. OLEIFERA)

Moringa oleifera has been used for a long time for its medicinal uses , as it have more nutritional value. It is also rich in polyphenols ,vitamin C , vitamin E, beta-carotene and it is a good source of antioxidants. Moringa oleifera is now well known for its broad spectrum of biological activities including anti-inflammatory, anti-cancer, hepatoprotective , and neuroprotective effects . Many researchers also demonstrated its therapeutic value in diabetes, rheumatoid arthritis, atherosclerosis, infertility ,pain , depression as well as thyroid function regulations. Due to these characteristics, M. oleifera raised scientific attention in the last 10 years and exhibited a broader focus of investigations on its pharmacological effects and underlying mechanism.[40]

3.CANNABES SATIVA L

Cannabis sativa L. is usually a flock medicine and it have a psychotic activity . The classification of cannabis is usually difficult due to its genetic variability.

The genus cannabis was initially categorized into 3 species = c sativa L , a fiber type plant , c indica lam , a drug type with high contents of psycho active tetrahydro cannabinol and c. ruderalis , displaying intermediate characteristics. But because of the easy

with which these species can cross breed, a monotype classification is favoured, based on one species cannabis sativa is characterized into different chemotypes. Cannabinoid profile type has five base chemotype.[41]

4.RAPHANUS SATIVUS (RADISH)

The aerial and underground parts of Raphanus sativus is used In the treatment of urinary infections ,stomach disorders , ulcers ,cardiac disorders , hepatic inflammation . It is used in the ancient times a log back. The presence of secondary metabolites such as glucosinolates, isothiocyanates, and polyphenols provide a great pharmaceutical effect.[42]

5.TAMARINDUS INDICA (T. indica)

Tamarindus indica is a tree which is native to India . It can grow up to 27 meters height and 7 meters grith ,it consists of pale yellow and pink flowers . The tree shows wide growth in the dry regions such as Africa to Senegal in west, Sudan and Ethiopia in east, Mozambique and Madagascar in South. Many of them believe that the tree would came from Africa to India .The tree can be seen in many of the countries such as Thailand, Bangladesh, Indonesia in Asia; Mexico, Costa Rica in America.

The plant has a great nutritional value which is helpful for both industrial and economic purposes, each part of it have a specific medicinal values such as root, body, fruit, and leaves. The tree consists of fruits which are said to be sweet and have acidic in nature, the sweetness is more in their growth season. The plant is used for medicine in olden days to treat various diseases such as wound healing, abdominal pain, diarrhoea , dysentery, parasitic infestation, fever, malaria and respiratory problems. Due to its laxative and aphrodisiac properties it is most commonly used in tropical countries.[43]

Results

Accumulating evidence indicates that several nutraceuticals exert beneficial effects on key pathogenic mechanisms involved in non-alcoholic fatty liver disease (NAFLD), although the strength of clinical evidence varies considerably. Antioxidant vitamins have been the most extensively studied. Vitamin E supplementation has shown improvement in histological features of non-alcoholic steatohepatitis (NASH), particularly by reducing oxidative stress and hepatic inflammation; however, concerns regarding the safety of long-term high-dose use limit its widespread application. Vitamin C, despite its antioxidant capacity and ability to regenerate vitamin E, has produced inconsistent results across clinical trials.

Vitamin D deficiency is frequently observed in NAFLD and correlates with insulin resistance and disease severity, yet interventional studies have not consistently demonstrated improvements in liver enzymes or histology. Metabolic modulators such as L-carnitine and betaine have shown promising effects in experimental models by enhancing mitochondrial fatty-acid oxidation and reducing lipid accumulation, but human data remain limited and inconclusive.

In contrast, omega-3 polyunsaturated fatty acids (PUFAs) have demonstrated more consistent benefits in randomized controlled trials, including reductions in serum triglycerides, aminotransferase levels, and hepatic steatosis, with good safety profiles. Plant-derived compounds—such as silymarin, polyphenols, anthocyanins, curcumin, and berberine—along with probiotics, fruits, vegetables, and spices, show hepatoprotective, anti-inflammatory, and antioxidant effects in preclinical studies and small clinical trials.

Overall, nutraceuticals appear to offer supportive benefits in NAFLD management, but robust, large-scale randomized trials with histological endpoints are required to confirm efficacy and safety.

Discussion

Non-alcoholic fatty liver disease (NAFLD) is a multifactorial condition arising from the interplay of metabolic dysregulation, oxidative stress, chronic inflammation, and alterations in the gut–liver axis. Although lifestyle modification remains the foundation of NAFLD management, increasing attention has been directed toward nutraceuticals as adjunctive strategies to mitigate disease progression and reduce associated cardiometabolic risk, particularly in patients with non-alcoholic steatohepatitis (NASH).

Oxidative stress is a central mechanism implicated in the progression of NAFLD from simple steatosis to steatohepatitis and fibrosis. Accordingly, antioxidant vitamins, especially vitamins E and C, have been widely investigated. Vitamin E has demonstrated histological benefits in non-diabetic patients with NASH through its ability to reduce oxidative injury and hepatic inflammation; however, concerns regarding the long-term safety of high-dose supplementation have limited its routine clinical application. In contrast, vitamin C, despite its antioxidant properties and its role in regenerating vitamin E, has produced inconsistent outcomes in clinical studies, likely due to heterogeneity in study design and baseline nutritional status.

Vitamin D deficiency has been consistently associated with insulin resistance, metabolic syndrome, and increased NAFLD severity. While experimental studies suggest potential anti-inflammatory and anti-fibrotic effects, interventional trials have not demonstrated consistent improvements in liver-related endpoints, thereby restricting its role primarily to the correction of deficiency rather than as a targeted therapeutic agent.

Among metabolic modulators, L-carnitine and betaine have shown favorable effects in experimental models by enhancing mitochondrial function and lipid metabolism; however, evidence from human studies remains inconclusive. In contrast, omega-3 polyunsaturated fatty acids have demonstrated more consistent clinical benefits, including reductions in serum triglycerides, aminotransferase levels, and hepatic steatosis, supporting their potential role as adjunctive therapy, particularly in patients with hypertriglyceridaemia.

Dietary patterns enriched with plant-derived polyphenols, probiotics, fruits, vegetables, and spices further highlight the importance of whole-food–based bioactive compounds in modulating oxidative stress, inflammation, and gut microbiota. Collectively, nutraceuticals represent promising supportive interventions in NAFLD management; however, well-designed, large-scale randomized controlled trials incorporating histological endpoints are necessary to clearly define their efficacy, safety, and clinical relevance.

Conclusion

Non-alcoholic fatty liver disease (NAFLD) represents a significant and growing burden on healthcare systems worldwide. Although the majority of individuals with hepatic steatosis do not progress to advanced liver disease, they face an increased risk of cardiovascular morbidity and mortality. Consequently, management of NAFLD should adopt a comprehensive approach that extends beyond targeting insulin resistance and metabolic syndrome, and should also incorporate strategies aimed at reducing oxidative stress, dyslipidaemia, and overall cardiovascular risk.

In this context, nutraceuticals may play a supportive role in the management of NAFLD, particularly when used alongside standard therapies for cardio-metabolic risk factors. Several nutraceutical compounds—especially those rich in antioxidants and polyphenols—have demonstrated encouraging effects. In contrast, evidence supporting vitamin D and carnitine supplementation remains inconsistent. Notably, vitamin E has shown efficacy in nondiabetic patients with more advanced non alcoholic steatohepatitis (NASH); however, concerns persist regarding the safety of the high doses typically recommended.

Importantly, the current body of evidence is largely derived from small, heterogeneous clinical trials, varying widely in study design, inclusion criteria, sample size, type of intervention, and treatment duration. As a result, there is presently insufficient evidence to either endorse or discourage the routine use of nutraceuticals in patients with NAFLD. Well-designed randomized controlled trials with histological endpoints are required to clarify their therapeutic role.

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