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NATURAL BIOACTIVES AND LIVER INTEGRITY: A REVIEW OF HEPATOPROTECTIVE AGENTS

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Abstract

The liver performs essential biological functions such as detoxification, nutrient metabolism, and the synthesis of vital proteins, making it a critical organ for overall health. Due to its metabolic activity and exposure to toxins, the liver is highly susceptible to injury, resulting in conditions like non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and drug- induced hepatotoxicity. While conventional treatments exist, they are often limited by side effects and long-term risks, prompting increased interest in safer alternatives.

Nutraceuticals—naturally occurring compounds found in food—have shown potential in supporting liver health and mitigating hepatic damage.

This review begins with a general overview of liver function and the pathogenesis of common liver disorders, especially NAFLD. It then discusses several nutraceutical agents that have demonstrated hepatoprotective effects. Among these, silymarin (derived from milk thistle) exhibits antioxidant, anti-inflammatory, and membrane-stabilizing properties.

Polyphenols, found in a variety of plant-based foods, help reduce oxidative stress and inflammation. Licorice root extract contributes to liver protection by modulating enzyme activity and enhancing antioxidant defense. Betaine, a compound involved in methylation, has been shown to support lipid metabolism and improve liver function, particularly in fatty liver conditions.

Current evidence supports the use of these nutraceuticals as complementary therapies for liver disorders. However, standardized clinical studies are needed to confirm their efficacy, optimal dosing, and long-term safety. Incorporating such natural agents into routine hepatic care may offer a promising strategy for enhancing liver health and managing chronic liver diseases.

INTRODUCTION

The liver, the largest internal organ, features a polished external surface situated inferior to the diaphragm, filling the right hypochondrium and extending slightly into the left hypochondrium. Displaying a smooth texture, this essential organ presents itself with a distinct reddish-brown coloration. [3, 4]

In adults, the liver constitutes approximately 2% of the total body weight.[4]

Within the anatomical structure of the liver, two prominent lobes, specifically designated as the right

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and left lobes are present. Additionally, the liver exhibits two smaller lobes positioned centrally, recognized as the caudate and quadrate lobes.[5]

Blood is directed into the liver through the portal vein and hepatic artery, both converging at the porta hepatis, marking the point of entry. Exiting the liver, blood flows through the three principal hepatic veins situated at the superior and inferior surfaces, identified as the left, right, and intermediate hepatic veins.[6]

The liver's vascular supply is predominantly derived from the portal vein, which constitutes 80% of the total, actively drawing blood from the spleen and intestines. In parallel, the

hepatic artery complements this supply, furnishing the remaining portion of 20% and ensuring a vital influx of oxygenated blood to sustain the organ's metabolic demands. [4]

The liver's smooth, dome-shaped surface is hidden and protected by the thoracic cage and diaphragm, making it a vital and well-shielded metabolic hub.[7]

The liver produces bile for waste excretion and lipid digestion, containing water, electrolytes, and essential components. It crucially metabolizes xenobiotics for detoxification through

phase I and phase II reactions. Additionally, the liver plays a key role in heme breakdown, with hemolysis occurring in various body locations.[8]

Conditions related with liver:

The liver, being the central organ for metabolism and excretion, is consistently and variably exposed to xenobiotics due to its strategic positioning in the body. Toxins absorbed from the intestinal tract initially enter the liver, leading to a range of liver disorders. As a result, liver diseases represent a significant health concern, spanning from acute hepatitis to hepatocellular carcinoma.[9]

Hepatocyte injury stems from oxidative stress, aberrant cytokine production, perturbed fatty acid metabolism, and insulin resistance, culminating in liver damage through oxidative injury, apoptosis induced by tumor necrosis factor-alpha (TNF-α), or inflammation. The disease

transitions from an initial phase characterized by pure steatosis to a subsequent stage marked by the presence of steatohepatitis (non-alcoholic steatohepatitis, NASH) or the development of fatty liver cirrhosis.[10]

Non-Alcoholic Fatty Liver Disease (NAFLD):

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of steatosis in a minimum of 5% of hepatocytes, devoid of any underlying secondary causes, such as those related to alcohol or drug influences.[11] Hepatic steatosis is precisely defined as the abnormal and disproportionate accumulation of triglycerides within the hepatocytes, reflecting an excess of fat deposits within the liver cells.[12]

Nonalcoholic fatty liver disease (NAFLD) encompasses a diverse pathological range,

spanning from benign, asymptomatic storage of liver fat to the potential development of progressive cardiovascular, metabolic, liver, and kidney diseases, accompanied by elevated cancer risks.[13] NAFLD stands as the predominant cause of liver disease globally, with prevalence estimates varying between 25% and 45% in various studies. Its occurrence correlates with the rising rates of obesity as well as of diabetes.[14]

Individuals identified with Non-Alcoholic Fatty Liver Disease (NAFLD) experience decreased insulin sensitivity not only in muscle but also within both the liver and adipose tissue. This reduced sensitivity in multiple tissues is a key factor contributing to the pathogenesis of NAFLD.[15] Insulin resistance (IR) leads to reduced sensitivity in adipose tissue, rendering it resistant to insulin's anti-lipolytic effect leading to an elevated transportation of free fatty acids (FFA) to the liver and promoting de novo lipogenesis. [15]

NAFLD is a precursor to hepatocellular carcinoma, displaying a spectrum of liver damage akin to alcohol-related conditions. It occurs with alcohol consumption below 20 g/day, primarily linked to insulin resistance and oxidative stress, with the exact mechanisms still not fully understood. [10]

Alcoholic fatty liver disease:

Alcoholic liver disease comprises a spectrum of conditions, initiating with fatty liver and progressing through alcoholic hepatitis. It ultimately evolves into the advanced, irreversible stage of alcoholic cirrhosis, all linked to alcohol consumption.The histologic

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progression unfolds through three stages of alcoholic liver disease. Initially, alcoholic fatty liver or steatosis is characterized by the accumulation of fat in the liver parenchyma. Subsequently, alcoholic hepatitis manifests with inflammation of liver cells. The final stage, alcoholic cirrhosis, represents irreversible liver damage, giving rise to complications such as portal hypertension.[16]

Drug-induced liver injury (DILI):

Drug-induced liver injury (DILI), manifests as an acute or chronic reaction to a natural or synthetic compound. DILI's pathogenesis encompasses two mechanisms: intrinsic and idiosyncratic. The intrinsic mechanism, exemplified by drugs like acetaminophen, is predictable and dose-dependent, causing liver injury with a short latency period due to the accumulation of reactive metabolites. In contrast, the idiosyncratic mechanism is less predictable and not reproducible.[17]

Acetaminophen is a major cause of acute, dose-related DILI. Halothane-induced DILI is immunologically driven with multiple exposures. NSAIDs, antibiotics, and antituberculosis drugs contribute significantly to DILI cases while pirazinamide increases hepatic adverse reactions in combination with other drugs such as rifampin. Beta-lactams, azoles, and HAART (Highly active antiretroviral therapy) also have known associations with DILI.[18]

Nutraceuticals with hepatoprotective effects Milk thistle (Silymarin)

Milk thistle, scientifically known as Silybum marianum, belongs to the Asteraceae family. Its standardized extract from seeds, known as silymarin, comprises a diverse array offlavonolignins, representing the amalgamation of flavonoids and lignins. Among these flavonolignans are silybin, isosilybin A and B, silydianin, and silycristin. [19] Silybin, also known as silibinin, makes up 50-70% of silymarin and exists in two diastereoisomers, namely A and B. Silibinin serves as the principal active ingredient within silymarin.[20]

The raw plant substance contains triglycerides (linoleic, oleic, and palmitic acids), proteins, sugars (xylose, glucose, arabinose, rhamnose), tocoferol, sterols and flavonoids such as taxifolin, quercetin, chrysoeriol, and eriodictyol.[21]

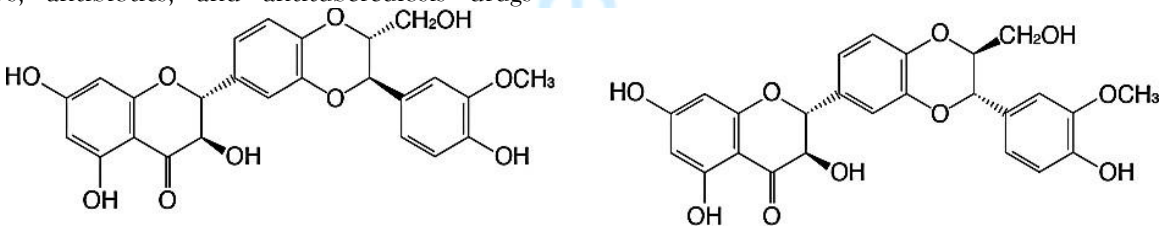

Figure 1: Molecular structures of the silibinin diastereoisomers, silibinin A and silibinin B, depicted by the chemical formula C25H21O10.[2]

Hepatoprotective nature:

Research findings indicate that silymarin possesses a diverse range of effects, with potential hepatoprotective qualities owing to its antioxidant and anti-inflammatory attributes.[22]

Reactive oxygen species (ROS), a byproduct of essential liver processes like detoxification, increases with high toxins or intense fatty acid oxidation, leading to oxidative stress and liver disorders, including fibrosis. Silibinin is recognized for its robust ability to neutralize reactive oxygen species (ROS), inhibiting radicals across diverse cell systems including liver.[2]

Silymarin also elevates liver glutathione production by increasing availability of substrates, particularly cysteine, thereby enhancing the liver's antioxidant capacity. Additionally, it protects liver cells by stabilizing membrane permeability through the inhibition of lipid peroxidation, ensuring the preservation of optimal levels of the endogenous protective antioxidant, glutathione.[23]

Apart from maintaining the level of glutathione, the protective oxidant, Silymarin exhibits protective effects against injury induced by various toxic chemicals, such as carbon

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tetrachloride by inhibiting inflammatory cytokines, including TNF-α, interferon-gamma, IL- 2, and IL-4, through blocking NFκB activation. It also reduces cellular uptake of xenobiotics, such as mushroom poisons, by blocking transporters on hepatocytes.[2]

Bioavailability:

Orally administered, silymarin exhibits low bioavailability.[20] Flavonolignans have poor solubility in aqueous and lipid environments, hindering their passage through the lipid-rich outer membranes of small intestine enterocytes. Moreover, rapid metabolism by Phase II enzymes leads to swift excretion, presenting major obstacles for systemic absorption after oral administration.[24]

Following absorption, silymarin undergoes significant conjugation primarily through glucuronidation. The resultant conjugated compounds are subsequently excreted into both bile and urine.[20]The main phase II metabolite, silibinin glucuronide, is carried through biliary flow to the intestine. Bacterial β-glucuronidase enzymes in the intestine cleave the metabolite, reverting it to silibinin and facilitating enterohepatic circulation. This cyclic process contributes to the efficient elimination and limited systemic presence of silymarin.[20]

Improving systemic bioavailability is achievable by incorporating solubilizing substances
into the extract. Additionally, enhancing the bioavailability of silibinin can be accomplished through its complexation with phosphatidylcholine or β-cyclodextrin [21]

Dose:

The suggested therapeutic dosage for silymarin to confer hepatoprotection is 420 mg/day of extract (standardized to 70-80% silymarin), administered three times daily over a span of 6-8 weeks. Following this initial period, the maintenance dose is adjusted to 280 mg/day. [9]

Polyphenols:

Polyphenols are the compounds naturally occurring in fruits and vegetables including apples, pears, grapes, berries, and cherries. These compounds stem from a shared precursor, either
phenylalanine or its closely related counterpart, shikimic acid. Generally, they exist in conjugated forms, characterized by sugar residues linked to hydroxyl groups.[25]

The fundamental building block in polyphenols is the phenolic ring, and typically, these are categorized as phenolic acids and phenolic alcohols. The classification of polyphenols is
determined by the potency of the phenolic ring, with major classes encompassing phenolic acids, flavonoids, stilbens, phenolic alcohols, and lignans. [26]

Polyphenols are systematically categorized based on the quantity of phenol rings and the specific structural elements that interconnect these rings. Noteworthy classes within this classification include phenolic acids, flavonoids, stilbenes, and lignans. [25]

Phenolic acids are subdivided into hydroxybenzoic and hydroxycinnamic acids. Flavonoids, constituting the most extensive and researched category of polyphenols, are further categorized into subclasses, including flavones, flavonols, flavanones, isoflavones, and anthocyanidins. [26]

Polyphenols, secondary metabolites in plants, serve as a defense against ultraviolet radiation and pathogenic threats. In the context of food, these compounds play a role in influencing color, flavor, odor, bitterness, astringency, and oxidative stability.[25]

Stillbenes:

Stilbenes are primarily encountered in berries, grapes, and red wine. Within this category of polyphenols, three key compounds prevail: resveratrol, along with its derivatives
pterostilbene and piceatannol. [27]

Resveratrol stands out as one of the widely recognized polyphenols, and it is present in various sources including cocoa, peanuts and mulberries. [28] Resveratrol, studied in
preclinical settings, exhibits protective effects against non-alcoholic fatty liver disease (NAFLD). It reduces oxidative stress, hepatocellular damage, and hepatic lipid content by modulating antioxidant enzymes such as glutathione and lipogenic activity. [29] However,

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therapeutic potential of stilbenes is constrained by their restricted bioavailability, attributed to their rapid metabolism.[30]

Derived from resveratrol and found in blueberries, pterostilbene mitigates steatosis by enhancing fatty acid oxidation, promoting VLDL export, and reducing lipid uptake. It further improves hepatic function, addressing insulin resistance and glycogen homeostasis, leading to reduced serum cholesterol and triglyceride levels. [31]

Another derivative of resveratrol, Piceatannol, has also been observed to exert hepatoprotective effects in the liver. Studies indicate its ability to reduce fat accumulation and oxidative stress in liver cells, while also promoting fatty acid β-oxidation and inhibiting oxidative stress induced by fatty acids.[32]

Lignans:

This category of polyphenols is prevalent in diverse plants, with flaxseed and sesame seed being notable sources. Additionally, lignans are also discovered in fish, meat, whole-grain cereals including wheat and oats, oil-rich seeds (like flax or soy), and various beverages, including coffee, tea, and wine.[33] Specific lignans found in polyphenols that have hepatoprotective effects include Sesamin and diglucoside.

Sesamin, predominantly found in sesame seeds, exhibits notable metabolic properties in liver pathologies according to preclinical studies. It is reported to hinder fatty acid synthesis mediated by acetyl-CoA carboxylase and SREBP-1, while concurrently promoting fatty acid oxidation (FAO) through various enzymes. [28] Diglucoside has also been documented to decrease hepatic lipid accumulation, concomitantly reducing lipid peroxidation in the liver and lowering serum cholesterol levels. [34]

Flavonoids:

Flavonoids are the predominant group of polyphenols. Anthocyanins, flavonols, isoflavonoids, flavanones, flavones, and flavanols (catechins) constitute the various subgroups within flavonoids. These compounds, which are the major category of polyphenols and prevalent in the diet of individuals, are particularly found in olive oil, tea, grapes, red wine, onions, citrus fruits, berries, and apples. [28]

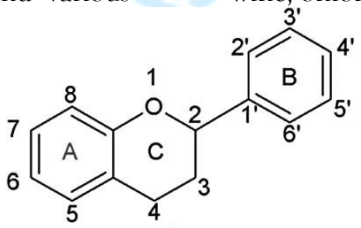

Figure 2: Flavonoids basic structure[1]

Anthocyanins, comprising diverse species like delphinidin and cyanidin, are found abundantly in flowers and berries such as blueberries, raspberries and strawberries. Among them, delphinidin is recognized for its prevalence, with the Maqui berry being its most substantial natural source within the anthocyanin group. [35]

Delphinidin plays a pivotal role in conferring protection and therapeutic benefits in liver diseases characterized by oxidative stress. Its efficacy lies in the ability to suppress proinflammatory cytokines, lipid peroxidation, and oxidative stress, highlighting its potential as a valuable intervention strategy against the intricacies of oxidative-coupled liver conditions.[36]

Cyanidins are present in a variety of fruits, including but not limited to red berries, blackberries, blueberries, grapes, cherries, cranberries, and raspberries. [37] Cyanidin helps prevent fibrosis by blocking the production of collagen type I and reducing the activity of extracellular-regulated kinase 1/2. Furthermore, it encourages the activation of protein kinase A through cAMP, leading to the production of glutathione (GSH) and safeguarding liver cells. [38, 39]

Quercetin, classified as a flavonol, emerges as a promising hepatoprotective compound. Its consistent inclusion in the diet is linked to the

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preservation of liver health and holds potential for preventing damage caused by toxins.[40] Quercetin exhibits potent hepatoprotective effects by reducing Triacylglycerol (TAG) levels, enhancing glucose uptake, and increasing antioxidant enzyme activities. Notably, it positively influences liver health by elevatingalbumin levels and reducing alanine aminotransferase (ALT) activity, highlighting its therapeutic potential for liver protection. [41]

Quercetin is conveniently accessible as a dietary supplement, with recommended daily doses ranging between 200 and 1200 mg. Furthermore, it can be integrated into nutraceuticals through functional foods, offering concentrations typically within the range of 10 to 125 mg per serving. [42] Among vegetables, onions and broccoli exhibit the highest concentrations of flavonols, while fruits, including apples, cherries, and berries, also contribute significantly to these compounds. Additionally, beverages like tea and red wine are noteworthy sources of
flavonols.[43]

Luteolin is a naturally occurring flavone found in various fruits and vegetables in
glycosylated form. Numerous studies have reported on the antioxidant and anti-inflammatory effects associated with luteolin.[44] Luteolin exhibits diverse hepatoprotective mechanisms, including the inhibition of inflammatory factors, reduction of oxidative stress, regulation of lipid balance, attenuation of excessive aggregation of extracellular matrix, and induction of apoptosis and autophagy in liver cancer cells. These properties collectively contribute to the prevention of liver damage.[45] According to a study, the oral administration of luteolin exhibited hepatoprotective effects in rat models when administered at a dosage range of 50–500 mg/kg.[46]

Hesperidin, a flavanone glycoside extracted from citrus fruits, exhibits remarkable
hepatoprotective properties. Its efficacy extends to safeguarding the liver against diverse natural and chemical hepatotoxins, such as carbon tetrachloride and acrylamide. [47]

Catechins, a subset of flavanols, showcase hepatoprotective effects from distinct sources. In green tea, particularly epigallocatechin gallate (EGCG), they guard against liver damage induced by substances like carbon tetrachloride (CCl4). South Sulawesi propolis, rich in catechins, displays potential in protecting the liver from chemotherapy-induced damage.

Additionally, Cleome viscosa leaves' catechins also demonstrate hepatoprotective effects.

[48] Catechins, with potent antioxidant properties, reduce liver oxidative stress by scavenging reactive oxygen species and chelating metal ions. They alleviate vascular dysfunction-related conditions and protect against mitochondrial dysfunction, enhancing liver health. [48, 49]

Research shows that the hepatoprotective potential of isoflavonoids isolated from Maackia amurensis roots is notable. Upon administration, the extract demonstrates efficacy in
restoring antioxidant protection enzyme activity and concurrently modulating glutathione
levels. Additionally, it attenuates the formation of hazardous peroxidation products, exerting a normalizing influence on the intricate phospholipid pattern within the liver.[50]

Phenolic Acids:

Phenolic acids are subdivided into hydroxybenzoic and hydroxycinnamic acids. [26]

Caffeic acid, a phenolic acid, addresses diabetic liver injury by modulating lipid peroxidation and antioxidant enzymes, offering therapeutic potential for liver health in diabetes. Caffeic acid is present in fruits, green tea, wine, and components of coffee beans as part of the diet.

Ferulic acid, a phenolic acid, combats CCl4-induced acute liver injury through its antioxidant, anticancer, and anti-inflammatory properties.[36]

Hydroxybenzoic acids, including gallic, vanillic, protocatechuic, and syringic acids, show evidence of exerting hepatoprotective effects. Gallic acid, predominantly present in tea
leaves, berries, wine and grapes has exhibited efficacy in safeguarding against hepatic steatosis in (NAFLD).[51]

The consumption of gallic acid in conjunction with other hepatoprotective agents has the
potential to amplify its effects. Scientific studies suggest that the combination of gallic acid and catechin demonstrates a synergistic hepatoprotective activity. [52]

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Some other hepatoprotective agents to boost the collective efficacy in promoting liver health includes vanillic acid, syringic acid and protocatechuic acid. [51, 52]

Licorice root extract:

Licorice has a historical application in traditional Chinese medicine for treating diverse liver diseases including drug-induced liver injury (DILI).[53]

Scientific studies confirm the hepatoprotective activity of licorice root extract, attributed to its active component, glycyrrhizic acid. The compound demonstrates hepatoprotective and antioxidant effects, safeguarding the liver against oxidative damage caused by substances such as carbon tetrachloride (CCl4).[54-56] It is indicated that licorice extract prevent hepatotoxicity and mitigate liver injury, potentially through the enhancement of antioxidative and anti-inflammatory capacities.[55]

According to research, the recommended dose is 2 to 5 mL three times a day when using a licorice tincture (typically 1:5 strength). Some studies also suggest a standardized licorice extract dosage of 250 to 300 mg three times a day, having 20% glycyrrhizic acid.[57]

Betaine:

Rich sources of betaine include cereals, certain vegetables, and most seafood. Common wheat, quinoa grains, are notable sources. Additionally, wholegrain flour, bread, pasta, breakfast cereals, spinach, and beetroot contain betaine. Among seafood, mussels, oysters, and scallops are particularly rich in this compound.[58]

Betaine has demonstrated hepatoprotective effects, ameliorating liver damage and dysfunction. It also enhances antioxidant activity and regulates mitochondrial function. [59- 62]

Betaine has been shown to exert its hepatoprotective effects through various mechanisms, including enhancing antioxidant activity, reducing oxidative stress, endoplasmic stress, liver fibrosis, and necrosis, as well as promoting liver regeneration[60]

Human studies indicate betaine's rapid absorption within 1–2 hours, maintaining serum concentrations from 20 to 70 µmol/L. In both healthy and homocystinuric individuals, it swiftly reaches a maximum concentration of 0.94 mmol/L after 0.90 hours, with an elimination half-life of 14.38 hours. Notably, even at high doses (e.g., 100 mg/kg), betaine is primarily metabolized rather than excreted.[58]

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