



THE EXTENT OF THE USE OF HEPATOPROTECTIVE DRUGS AND THE RELEVANCE OF THEIR IMPROVEMENT

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ABSTRACT

*Although they are not regarded as glamorous pursuits, cross-sectional studies offer crucial insights into public health because they are firmly grounded in facts and statistics. The study's objectives are to determine how frequently patients with chronic illnesses—aside from chronic liver disorders—consume HP nutritional supplements and to examine the behaviors associated with these patients' use of these supplements. Over the course of a year, a total of 954 patients from four private pharmaceutical facilities who were looking for prescription drugs for chronic illnesses under different payment options (full payment, gratuity, or compensated) were carefully chosen. We looked at the frequency of HP use in connection to several prescription drugs for long-term illnesses. Each of these patients was given the opportunity to take part in a nutritional status evaluation and was asked to fill out a questionnaire regarding their supplement intake patterns. 65 patients agreed to have their nutritional status assessed, and 195 patients agreed to take part in the survey. 77.2% of the 954 patients include HP in their treatment plan. The group with seven medications consumed the most (83.33%), followed by the group with three substances (82.84%). Compared to men (62.60%; 293 from 383), women utilize HP at a higher rate (80.58%; 444 from 551), and the majority of patients (59.5%) used extracts of *Silybum marianum* L. 64.61% of respondents to the survey reported taking supplements, with HP being used by the majority (59.52%). Merely 32.54% of patients follow medical professionals' advice. 55.56% of the patients who use supplements said their health has improved. Additionally, patients who incorporate supplements into their daily regimen typically see improvements in their general nutritional health. The recent study found that hepatoprotective nutritional supplements are used by most individuals with chronic diseases. The majority of the time, patients either discover HP through the media or begin using it on their own. When patients include nutritional supplements into their everyday regimen, their health often improves. Using HP for longer than two months is linked to this health improvement. These gains in health status were also corroborated by the findings*

of clinical investigations, which included BMI, fat mass, sarcopenic index, and hydration level.

Introduction. One important organ that is involved in many types of metabolic activity is the liver. Liver damage can be caused by a variety of factors, including drug addiction, viral infections, excessive alcohol consumption, biological and chemical agents, and a corresponding autoimmune attack on the hepatocyte. If the damage cannot be undone, hepatic form and function will be broken and impeded. Hepatic cirrhosis, fibrosis, fatty liver, and even liver carcinoma can result in long-term hepatic damage, which might lead to an epidemiological problem. Alternative therapies that employ phytochemicals sourced from natural resources are currently being adopted for a number of illnesses. Global health is significantly impacted by chronic diseases. According to the World Health Organization (WHO), chronic diseases are distinguished by a number of important characteristics, such as their protracted nature, the residual disabilities that result from them, the fact that the underlying cause of the disease is non-reversible pathological changes, the requirement for specialized patient training for rehabilitation, or the need for prolonged periods of care, supervision, or observation [1-4]. Multi-morbidity, the term for the high frequency of people with several chronic diseases, tends to rise with age in developed nations. Since healthcare systems around the world have historically concentrated on treating acute episodes rather than providing structured, long-term care for people with chronic disorders, managing chronic diseases presents a significant challenge to these systems. Chronic diseases are characterized by the need for constant monitoring, care, and supervision. Chronic condition treatment is a good fit for primary care, which is characterized by attributes like continuity, coordination, and tackling complexity. Evidence supporting the necessity of shifting healthcare systems and policies toward chronic care, with a focus on bolstering primary care, is mounting. Strong primary care systems in nations usually result in better health outcomes at reduced costs. Over the past thirty years, specialists in the field of liver disease have studied drug-induced liver harm in great detail [5-11]. Chronic drug use is known to result in long-term harm, including cirrhosis and liver scarring, when the liver's capacity to repair finally fails. Over 10% of the world's population suffers from liver illnesses, which continue to be a major global health concern despite recent therapeutic advancements and substantial advancements in contemporary medicine. Because liver cirrhosis has a high death rate in Western countries, chronic hepatic diseases continue to be a major global concern. Products known as nutritional supplements are made to supply vital elements that a person's diet might not be enough supplying. Patients with chronic illnesses may benefit greatly from natural hepatoprotective products made from herbs like *Silybum marianum L. Gaertn.*, *Cynara scolymus L.*, *Cichorium intybus L.*, *Capparis spinosa L.*, *Glycyrrhiza glabra L.*, *Ganoderma lucidum Karst.*, *Chlorella ssp.*, and other species that contain a variety of bioactive compounds. These naturally occurring hepatoprotective compounds can function as active agents in a variety of chronic conditions since they have distinct structures but the same therapeutic action. Numerous phytomolecules derived from different plant sources, such as flavonoids, alkaloids, glycosides, and saponins, have been shown to be effective hepatoprotective agents [12-18]. Plants have been used as traditional sources of medicinal compounds since the dawn of civilization. Since the invention of modern medicine and single-use pharmaceuticals, phytoconstituents produced from plants and their synthetic and semisynthetic equivalents have been a significant route to novel pharmaceutical products. Therefore, safe and reasonably priced therapeutic alternatives must be created in order to effectively counter this

threat. For generations, people have intentionally used natural secondary metabolites to cure a variety of ailments. The FDA approved over 35% of medications and their components derived from natural sources between 1981 and 2010. These organic compounds already have potent anti-inflammatory and therapeutic effects. Many plant-derived bioactive compounds, mainly flavonoids, might reduce inflammation by reducing the levels of numerous cytokines, including interleukin-6, interleukin-1, and TNF- α , as well as possible mediators including prostaglandin, reactive oxygen species, and cyclo-oxygenase-2. Because flavonoids have been associated to a variety of bioactivities in the human body, such as antimutagenic, antioxidant, antiviral, and anti-inflammatory actions, they are advantageous to use in various dietary regimens [19-24].

The main purpose of this brief review is to analyze the extent of the use of hepatoprotective drugs and the relevance of their improvement based on authoritative scientific papers on modern measures.

Flavonoids and Their Subclasses' Chemical Structure. Flavonoids are naturally occurring phenolic metabolites that are primarily found in plants. In the 1930s, an orange extract that was thought to belong to a new family of vitamins was later discovered to be a flavonoid. To date, more than 8000 different flavonoids have been found and documented in the literature. Flavonoids are found both outwardly and inwardly in various plant tissues. Flavonoids have been classified as antimalarial, cytotoxic, anticancer, cardioprotective, hepatoprotective, antileishmanial, antitrypanosomal, anti-inflammatory, and neuroprotective antiamebic. They are also useful in the treatment of diabetes, Alzheimer's disease, and age-related factors. These characteristics are usually ascribed to their degree of selectivity in protein binding ability, activity in scavenging free radicals, and metal chelation capability. A fifteen-carbon skeleton connected to two benzene rings A and B by a C (heterocyclic pyrene) ring is the fundamental component of flavonoids, which can take many different forms. While each chemical within a class varies in the sequence of A and B-ring substitution, different classes of flavonoids differ in the degree of oxidation and the arrangement of C-ring substitution [3-8]. Depending on the carbon in the C ring to which the B ring is linked, as well as the extent of ring oxidation and substitution, flavonoids can be further classified into a variety of subgroups. C. A B ring is attached to the third position of the ring C in flavonoids that are categorized as isoflavones. Neo-flavonoids are those that have the B ring attached in the fourth position; for all those that have the ring B attached in the second position, subgroups can be created based on the structural properties of the ring C. Flavonols or catechins, flavonols, anthocyanins, flavones, flavanones, and chalcones are among the various classes into which flavonoids are subdivided. Because glycosylated or methylated molecules have greater bioactivity, bioavailability, and stability, flavonoids naturally occur in plants in these forms. Flavonoids have been glycosylated using a biological instrument known as glycosyltransferase, which catalyzes the joining of a sugar moiety to an aglycone portion to create glycosides. In the presence of this enzyme, the hydroxyl group in flavonoids is methylated, much how methyltransferase binds methyl moieties to aglycone to form methoxides. Through the carbon or oxygen atoms, methylation can produce C-methylated or O-methylated compounds, respectively. Experimental findings showed that the methylation of flavonoids significantly changed the methylated product's pharmacological and biological properties in comparison to its parent molecule [12-19].

The dietary sources of flavonoids and their subclasses. A class of chemical molecules containing a range of phenolic metabolites, flavonoids—also referred to as dietary flavonoids—are mostly found in drinks and foods produced from plants, including flowers, bark, cereals, herbs, fruits, cocoa, tea, and wine. Flavonoids are divided into twelve different categories based on their chemical structure, and only about half of them are important for nutrition. The oxo group at position four and the 2,3-double bond on ring C, which allows for conjugation between rings A and B and drastically alters the redox properties of flavonols, set

them apart from flavones. Flavonols are one of the subclasses of flavonoids. However, they differ from flavones in that they have the only nonphenolic group, a hydroxyl group, at position three. Although flavonols and flavones are quite similar, plants don't seem to reduce or oxidize the former into the former [5-10]. Flavonols are abundantly distributed throughout the leaves, stems, fruits, and flowers of higher plants. The aglycons isorhamnetin, kaempferol, galangin, isorhamnetin, rhamnetin, quercetin, fisetin, and myricetin are among the most studied. Flavonols, which are represented by the glycosides quercetin and kaempferol, are found in onions, broccoli, tea, and fruit. Flavonols with hepatoprotective properties include isorhamnetin, quercetin, and rhamnocitrin. It has been utilized historically in many ways as a phytopharmaceutical, choleric agent, appetite stimulant, and for the treatment of many other illnesses. These vibrant hues are significant pharmacological or nutraceutical substances. As a nutraceutical, anthocyanin's bioavailability is crucial for maintaining health and averting illness. The anticancer, antimetastatic, and antioxidant properties of anthocyanins have piqued the interest of the scientific community. In a variety of Alzheimer's disease models, anthocyanin has been shown in twelve scientific research to reduce apoptosis, cholinergic dysfunction, synaptotoxicity, cognitive impairments, tau hyperphosphorylation, neuronal extracellular calcium, oxidative stress, and disruption of the amyloidogenic pathway [11-17].

Hepatoprotective properties of flavonoids. Flavonoids target many systems to function as hepatoprotective agents. The liver is known to be a crucial regulator that plays a major role in the development of liver diseases that are highly prevalent, and it is especially vulnerable to attacks from reactive oxygen species. The primary causes of hepatic diseases include viral infections like Hepatitis A-E, autoimmune diseases, high dosages of drugs (like acetaminophen and antibiotics), excessive alcohol consumption, and exposure to hazardous chemicals such as carbon tetrachloride, D-galactosamine, peroxidized oil, chlorinated hydrocarbon, aflatoxin, dimethylnitrosamine, and thioacetamide. A sizable portion of the world's population suffers from nonalcoholic fatty liver disease (NAFLD), the most common chronic liver condition. In the absence of moderate alcohol use or other liver disease-related conditions such as autoimmune diseases, viral hepatitis, and drug-induced disorders, nonalcoholic fatty liver disease (NAFLD) is defined by the accumulation of fat (more than 5%) in the hepatocytes. Alcohol-associated liver disease and nonalcoholic fatty liver disorders are the most common causes of chronic hepatic disease [21-15]. Although there are significant differences, they both appear to have cirrhosis, fatty liver/steatosis, hepatocellular cancer, fibrosis, and steatohepatitis. Conversely, venous sclerosis, venous or intravenous fibrosis, and inflammatory cell infiltration are more common in ALD than NAFLD. iNOS is the main regulator in many experimental hepatic damage models, especially CCl₄-induced hepatitis. Proinflammatory genes, such as COX-2 and TNF- α , are triggered by an early rise in TNF- α levels. Improved superoxide dismutase, catalase, total antioxidant capacity, reduced nitric oxide synthase, nuclear factor erythroid-derived 2-related factor, and heme-oxygenase-1 are all facilitated by the five flavonoids: luteolin, hesperetin, 3',4'-dimethoxy hesperetin, chrysin, and apigenin. They prevented the phosphorylation of I κ B α , NF- κ B, and IKK by the NF- κ B signaling pathway. They also prevented the blood serum levels of proinflammatory cytokines and alanine and aspartate aminotransferase (ALT and AST) from rising. Furthermore, five flavonoids prevented hepatocyte apoptosis by increasing the Bcl-2/Bax ratio and decreasing the production of caspase family proteins. These flavonoids seem to shield the liver from D-GalN/LPS-induced acute hepatic damage [26-31].

Pharmacokinetics, Advantages, and Limitations of Flavonoids against Liver Diseases. In the case of liver damage, the pharmacokinetics of flavonoids may be altered due to changes in liver metabolism and clearance. For example, some studies have suggested that flavonoids may accumulate in the liver during liver disease, potentially leading to higher local concentrations and increased efficacy. On the other hand, other studies have reported

decreased flavonoid bioavailability in patients with liver disease, which may limit their therapeutic potential. Flavonoids have shown countless health benefits, their low bioavailability has been a concern. Phase 2 metabolism is known to affect the bioavailability of flavonoids in humans. Usually, most flavonoids undergo sulfation, methylation, and glucuronidation in the small intestine and liver, and conjugated metabolites can be found in plasma after flavonoid ingestion. Despite the bioactivity expressed in different in vitro systems, the bioavailability of flavonoids would be a determinant factor of their bioactivity in vivo studies [2-8]. Therefore, enhancement of bioavailability would be of utmost importance to exert health effects in, in vivo approach. In this regard, numerous attempts have been made to increase bioavailability such as improving intestinal absorption via the use of absorption enhancers, novel delivery systems, improving metabolic stability, and changing the site of absorption from the large intestine to the small intestine. But there are drawbacks to using flavonoids to treat liver illness as well. As previously stated, their limited bioavailability may restrict their efficacy, and patients with liver impairment may see changes in their liver metabolism. Additionally, flavonoids may have negative interactions with other drugs or supplements. Furthermore, more study is required to ascertain the safety and effectiveness of flavonoid supplements in treating liver illness because the ideal dosage and period of use are not well known [11-19]. Although the flavonoids have been shown to be hepatoprotective in all of the investigations, some reliable information regarding their effectiveness, dosage, and possibility for safe usage is still needed. Numerous clinical trials have been conducted for the same purpose, and some are still ongoing. A summary of significant research on clinical trials of flavonoids for hepatoprotection is provided here. The various flavonoids discussed in this review have been found to be effective against various liver-associated diseases, and numerous studies of their hepatoprotective activity in humans have been clinically investigated [20-25].

Discussion. In addition to being an extremely steady auxiliary gland for the digestive system, the liver is an essential organ involved in many types of metabolic activity. Chronic disorders like hepatocellular carcinoma, liver cirrhosis, liver fibrosis, and other hepatic ailments are significantly influenced by the onset and progression of long-term or persistent inflammation and oxidative stress, regardless of the cause. There are numerous resources that can support the liver's health and improve its capacity for metabolism. The food can regulate many phases of inflammation and hepatic illnesses since it is a rich source of bioactive and antioxidant substances, such as flavonoids and polyphenols. Bioactive substances known as flavonoids and their derivatives, such as flavones, anthocyanins, iso-flavonoids, flavanones, flavanols, and flavan-3-ols, are abundant in a wide variety of food sources, including fruits, vegetables, nuts, cereals, drinks, and herbal medicinal plants [4-8]. The most recent studies on flavonoids have shown that they have the ability to control hepatoprotective effects. This is because their hepatoprotective, antioxidative, and immune-modulating properties make them vital components of pharmaceutical and nutraceutical products. The specifics of their hepatoprotective effect are still unknown, though. This thorough review's goal is to examine the hepatoprotective and antioxidant properties of flavonoid structure and enhanced sources in relation to liver toxicity or injury. Over time, plants have been used for a variety of purposes, including as food and medicine. In the past, people have mostly used the roots and fruits of plants, frequently ignoring other plant components. Recognized as a crucial organ, the liver carries out a number of vital tasks. These include the storage of vitamins, minerals, and carbohydrates, as well as the synthesis of proteins, cholesterol, and bile. Additionally, the liver is essential to the body's detoxification process because it breaks down drugs, alcohol, and metabolic waste products to keep the body's metabolism in balance. As a result, it is especially susceptible to oxidative damage. The majority of hepatoprotective supplements (HP) typically combine both hepatoprotective and antioxidant benefits [13-18]. The effectiveness of hepatoprotective strategies in halting the development of liver lesions

brought on by medication therapies was investigated in a 2022 study. The study found that these strategies were quite successful and did not pose any serious health hazards. This indicates that the application of natural HP may be a viable remedy for liver damage, a serious health concern that is the subject of the current study. According to the study's findings, 76.93% of the participants with chronic illnesses take hepatoprotective supplements. *Silybum marianum L. Gaertn.* is the most well-known, suggested, and utilized HP, as evidenced by the large number of patients who decide to use supplements based on this plant. Generalizing our findings to the Romanian population may not be feasible due to the sample's limitations, specifically the sampling methods, sociodemographic features, and sample size. In order to provide more accurate results, it would be required to recruit more participants in order to form a more varied cohort in terms of age and gender. This would allow for a more precise evaluation of the chronic disease and the kind and duration of treatment. It is important to note, nonetheless, that no comparable research has been done on the usage of HP in Romania's chronic disease population up to this point. As a result, this study serves as a reference and can be used similarly to different age groups, disease types, or the general public [21-27].

Conclusion. The majority of patients with chronic illnesses use hepatoprotective nutritional supplements, according to the current study. Most of the time, patients either start using HP on their own or learn about it from the media. In general, patients' health improves when they include nutritional supplements in their daily routine. This improvement in health is associated with using HP for more than two months. Additionally, the results of clinical analyses, which included BMI, fat mass, sarcopenic index, and hydration level, supported these improvements in health status.

Liver illness, or hepatotoxicity, is a popular topic of growing concern due to an increase in instances. According to the material mentioned above, chronic inflammation can lead to the development of liver problems. Dietary flavonoids play a significant role in the onset and treatment of pathological disorders because of their anti-inflammatory, hepatoprotective, and antioxidant qualities. By reducing the thresholds of several cytokines, such as interleukin-1, interleukin-6, and TNF- α , lowering its primary mediators, prostaglandins, COX-2, and ROS, and blocking NF- κ B/P65, IKK, and I κ B α in the NF- κ B signaling, recent clinical studies of six major hepatoprotective flavonoids have confirmed positive effects on liver diseases. The study found that flavonoids also inhibit the previously described Caspase family protein and increase the Bcl-2/Bax ratio, which prevents hepatic apoptosis. Therefore, include flavonoids in your diet may be an excellent way to avoid liver problems. To assess the hepatoprotective potential of flavonoids to safely treat hepatic diseases, however, more precise, dose-dependent clinical trials are still needed.

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