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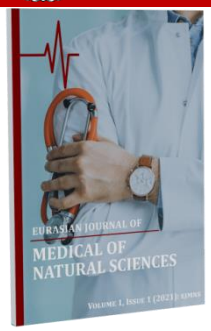

THE RELEVANCE OF THE SEARCH FOR HEPATOPROTECTORS AND HEPATOPROTECTORS WITH HIGH ACTIVITY USED IN THE TREATMENT OF HEPATITIS CAUSED BY DRUGS

Sokhib Rashidov Zamon o'g'li[1]
Nodira Pardaeva Botir qizi[2]
Gulzoda Quchqorova Qakhramon qizi[3]
Sevara Rakhmatullaeva Shukhrat qizi[4]
Alferid Rakhmonqulov Tolqin o'g'li[5]
[1,2,3,4,5]Department of pharmacology of Tashkent medical academy
e- mail: rashidovsohib9295@gmail.com
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ABSTRACT

Acute or chronic liver damage brought on by medicines or natural chemicals is known as drug-induced hepatotoxicity. The appearance is comparable to numerous hepatobiliary illnesses, making diagnosis challenging. The elimination of the offending agent and careful observation for resolution constitute the main treatment. The pathophysiology, assessment, and management of drug-induced hepatotoxicity are explained in this activity. It also discusses how the interprofessional team might help patients receive better care. Based on experimental validation, natural bioactive components generated from plant secondary metabolites have been pronounced as valuable options for predicting and mitigating hepatotoxic effects and their chronic consequences. This review aims to clarify the commonly used modern medicine for liver disease treatment, the hepatoprotective activity of major phytoconstituents, the mechanism of action of some promising natural agents, and the results of clinical trials for treating patients with various liver diseases using natural phytoconstituents. Even though a much greater number of plant species have been linked to hepatoprotective properties, the selection process was based on how well they were formulated and then incorporated into contemporary medical systems. With the ultimate goal of identifying these plants as potential sources of novel hepatoprotective herbal medicines, the gathered data was also critically examined to offer insights and suggestions for further research.

Introduction. The largest organ in the human body, the liver, weighs over 1.5 kg in a fully developed adult and accounts for 2% of total body weight. The liver plays a defense role in the body against harmful external chemical substances since it is the location of drug metabolism and biotransformation. As a result, the liver is exposed to various amounts of

medications, chemicals, and other xenobiotics, ultimately leading to liver damage. Hepatic disorders might have hundreds of different causes. Microbes (hepatitis virus A, B, C, and Cytomegalovirus); metabolic syndrome diseases (fatty liver disease from obesity, hemochromatosis, and Wilson's disease); xenobiotics (alcohol, drugs, and chemicals); hereditary hepatic diseases; autoimmune diseases (biliary cirrhosis, hepatitis, and sclerosing cholangitis); and liver cancers are the most significant causes of hepatic disease [1-4]. Liver problems are categorized as high priority health care categories. An estimated 500 million individuals worldwide suffer from chronic hepatitis, a severe form of liver disease, according to a World Health Organization estimate. Because herbal medicines are safe, readily available, affordable, and environmentally friendly, they may be a viable treatment for the current liver issues. Because of their well-established and potent therapeutic qualities, medicinal plants have grown in significance within healthcare systems worldwide. An estimated 80% of people on the planet use medications that contain substances derived from plants [5,6,7]. In an effort to develop practical treatments to halt or at least slow the progression of liver fibrosis, numerous investigations have recently been carried out on synthetic substances, such as derivatives of barbituric acid and glycerrhetinic acid. To the best of our knowledge, quinazoline and its derivatives have demonstrated pharmacological efficacy as a cancer chemotherapeutic drug and as a potentially effective coronavirus (COVID-19) therapy. Through their molecular docking analysis and investigation of the connection between quinazoline compound structure and activity, the authors recently reported that quinazoline derivatives exhibited very good antioxidant and anti-inflammatory effects. Additionally [8-12]. revealed that a synthesized phenyl chloromethine-quniazoline derivative has demonstrated the ability to induce apoptosis in hepatic cancer cells both in vitro and in vivo. To determine the hepatoprotective effect of a quinazoline Schiff base compound (Q-Br) against sub-chronic thioacetamide toxicity in rats, this study was carried out. As far as we are aware, the new quinazoline derivative Q-Br has not been the subject of any experimental investigation. Thus, using Silymarin as a reference medication, the current investigation was aimed to assess the anti-oxidative and antifibrotic mechanism of Q-Br in the liver tissues of rats by histologically examining the liver tissues of the animals treated with low- and high-doses of Q-Br chemical [13-17]. The goal of the current review was to gather information based on studies on some fruits (grapefruit, cranberries, and grapes) and plants (cactus pear fruit, chamomile, silymarin, and spirulina) that are commonly consumed by humans and have shown hepatoprotective potential. Additionally, a resin (propolis) and certain phytochemicals extracted from fruits, plants, yeasts, and algae that have been tested in various hepatotoxicity models were examined. Gathering information based on studies on commonly consumed fruits and plants that have shown hepatoprotective potential, as well as analyzing a resin and certain phytochemicals extracted from fruits, plants, yeasts, and algae that have been tested in various hepatotoxicity models, were the goals of the current review. With these objectives in mind, the authors of this publication have made an effort to stimulate the development of new research in this field and to give information and bibliographic assistance to scientists investigating substances with this potential [18-22].

The main purpose of this presented manuscript is to summarize the results of scientific research in recent years in the context of the relevance of the search for hepatoprotectors and highly active hepatoprotectors used in the treatment of medicinal hepatitis

Etiology of hepatotoxity with drygs Female sex, advanced age, and elevated body mass index (BMI) are among the patient risk factors linked to the development of DILI. The National Institute of Diabetes and Digestive and Kidney Diseases has a searchable database called LiverTox that lists over 1000 drugs and herbal remedies that are known to induce hepatotoxicity. Acetaminophen is the most frequent cause of intrinsic DILI, whereas aspirin, tetracycline, and vitamin A are less frequently implicated. Cases of idiosyncratic DILI are brought on by:

Antibiotics: isoniazid, ciprofloxacin, amoxicillin-clavulanate, and sulfamethoxazole-trimethoprim.

Drugs that don't cause inflammation.

Green tea extract, anabolic steroids, and multi-ingredient nutritional supplements are examples of herbal and dietary supplements.

Cardiovascular medications: amiodarone, statins.

Agents of the central nervous system: phenytoin and valproate.

Tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha inhibitors, and methotrexate are examples of anti-cancer medications [1-11].

Drug-induced liver injury, has grown to be a significant public health issue. The initial step in managing DILI is to stop taking any questionable medications, although further therapies, such as medication and supportive measures, are required. The treatment medications were categorized into hepatoprotective medications (N-acetylcysteine and glutathione, preparation of glycyrrhizin acid, polyene phosphatidylcholine, bicyclol, silymarin), anticholestatic medications (ursodeoxycholic acid, S-adenosylmethionine, cholestyramine), immunosuppressants (glucocorticoids), and specific treatment agents (L-carnitine, anticoagulants) based on clinical patterns and disease severity grades of DILI. The current work examined the body of research on DILI in clinical practice that is based on evidence-based medicine. The report also covered unmet needs, the limitations of the clinical research it included, and the future of DILI therapy [1-11]. In the not-too-distant future, innovative treatment and preventative strategies for DILI could be developed because to exciting work in the field of nanotechnology. In order to prevent DILI, it is being actively investigated if it is possible to directly distribute inhibitors of inflammatory cytokines, apoptosis, and other cellular processes that result in liver cell necrosis and death to hepatocytes or other substructures [12-15].

A gift from nature to humanity, medicinal herbs play a vital role in maintaining, enhancing, and preserving our health. Nine species were chosen from various genera based on their ethnomedical history in treating various liver-related pathological disorders in the world in order to investigate the hepatoprotective capabilities of common medicinal plants. Additionally, the information that was accessible was critically examined in order to obtain fresh perspectives and guidance for further research aimed at proving that these natural items are effective hepatoprotective drugs or dietary supplements [14-18]. Numerous in vivo

experimental models, such as those involving carbon tetrachloride, paracetamol, iron, mercuric chloride, thioacetamide, cyclophosphamide, β-d-galactosamine, cumene hydroperoxide, α-naphthyl-isothiocyanate, physical stress, and alcohol-induced hepatotoxicity in rats and mice, have been used to study the species' hepatoprotective properties. The ability of each plant to have hepatoprotective qualities was constant. Additionally, it was discovered that three bioactive isolates—schaftoside, echinocystic acid, and eclalbasaponin II—had encouraging hepatoprotective potential. To determine the relative hepatoprotective potentials of the nine species in question, however, more thorough comparative research is necessary in the future. The identification of hepatoprotective phytoconstituents from these plants and the creation of poly-herbal formulations from them may pave the way for the creation of medicinal hepatoprotective medicines [7-12].

Problems with toxicity and quality assurance. Since most research focuses on the antihepatotoxic properties of herbs and herbal products, the current body of literature is insufficient to evaluate the safety of the majority of hepatoprotective and liver-regenerative herbs and products. Large doses (1 g/kg) of A. membranaceus root extracts caused mutagenicity in mice when injected directly into the stomach lining, but some earlier studies on rats indicate that no negative effects were seen when the extracts were administered intraperitoneally at a dose of 0.5 g/kg for 30 days. Another study found that PLC/PRF/5 cells were not significantly harmed by different glycyrrhizin doses when tested in vitro [11-14]. Despite the fact that a number of herbal remedies exhibit promise in treating both acute and chronic liver illnesses, premarketing drug testing and pharmacovigilance are still necessary, just like with any other medication. Since there is currently inadequate data to justify the use of herbal remedies for chronic liver illnesses outside of clinical trials, publications pertaining to the cytotoxicity of medicinal plants should be encouraged. Furthermore, there are problems like the Food and Drug Administration or other comparable regulatory bodies not approving the plant products or extracts as drugs [5-9].

Future possibilities. An excellent therapeutic option for liver problems may be provided by herbal remedies. Nine specific South Asian herbs with a wide range of traditional uses due to their hepatoprotective properties were the subject of the current thorough analysis. The effects of herbal remedies in the treatment of hepatotoxicity have been illustrated, as have the cellular effects of these plants that result in their hepatoprotective properties. The lack of adequate acute, sub-acute, and chronic safety reports is the main barrier to using these plants in the creation of hepatoprotective formulations. As a result, significant toxicological research on these plants using cellular, hepatic, and hematological markers is required. Additionally, a comparative analysis of these plants should be tried in the same experimental animal model that addresses both plant-based and polyherbal formulations [1,2,3,4,5]. Even though the biochemical level has demonstrated the hepatoprotective qualities of several plant extracts, the data is still lacking since certain plants still have one or more pertinent markers that need to be investigated. A comparative study should enable the assessment of their hepatoprotective qualities using all pertinent markers. It may also result in the creation of a more effective polyherbal formulation that contains individual plants in comparatively small amounts, thereby minimizing the toxicities

associated with each plant. Future research must first identify the bioactive compounds found in these plants, and then pharmacologically assess the compounds that show promise for hepatoprotective effects. Since there are now very few modern hepatoprotective medications with practical clinical utility, the discovery of new compounds with comparable potential will undoubtedly support the process of developing innovative therapies [11-16].

Discussion. Due to the widespread use of medications that have adverse effects on the liver in today's modern society, liver cirrhosis has grown to be a serious issue. Thus, the goal of this trial was to identify novel therapeutic approaches to lessen liver cirrhosis. As previously indicated, quinazoline-based compounds demonstrated a wide range of biological activities, which encouraged more research into these compounds in order to develop alternative therapies for liver illnesses that are more effective and have less adverse effects. Reactive oxygen species (ROS) buildup from damaged hepatocytes is crucial for the development of fibrosis and cancer. Scientific evidence supporting the preventive action of the produced chemical Q-Br against liver injury is presented in this work [1-4]. The quinazoline derivative Q-Br concurrently demonstrated hepatoprotective therapy against sub-chronic TAA hepatotoxicity by restoring normal liver state, as proven by macroscopy and an ICG bio-imaging research that demonstrated rapid liver clearance of ICG. A thorough review of the literature on hepatoprotective plants makes it abundantly evident that herbal medications hold great promise for the management of liver disorders. The scientific worth of a few chosen plants that were investigated for their hepatoprotective mechanism of action was discussed in this article [5-9]. Most investigations have found that the main hepatoprotective mechanism is to fight oxidative stress, which harms the liver. We have compiled the impact of several herb extracts and components on liver damage while taking biochemical parameter changes into account. We also provided the potential information about the phytochemical components of various plants that is currently available in the literature. In the future, the bioactive compounds from these plants must be identified, and the promising molecules for hepatoprotective actions must then be evaluated pharmacologically. Modern hepatoprotective medications with practical clinical utility are still extremely few, thus the discovery of new compounds with comparable potential will undoubtedly support the process of developing new treatments. In the not-too-distant future, exciting research in the field of nanotechnology may lead to the development of innovative preventative and treatment strategies for DILI. One promising avenue for the future is the direct delivery of inhibitors of inflammatory cytokines, apoptosis, and other cellular processes that result in liver cell necrosis and death to hepatocytes or other substructures in order to prevent DILI [14-25].

Conclusions. In order to support the future pharmaceutical development of therapeutically useful hepatoprotective regimens, more study is recommended to clarify the pharmacological principle of these natural-based chemical agents.

The biochemistry analysis showed that the oxidative stress parameters and several liver indicators were recovered. The histology study showed that the liver architecture had significantly improved. Screening using immunohistochemistry revealed impressive anti-fibrotic properties. When combined, these findings point to a promising treatment option for

halting the progression of liver fibrosis. Consequently, more research on Q-Br's hepatoprotective effects at the cellular level is warranted.

Therefore, we draw the conclusion that one of the most significant sources of hepatoprotective and liver-regenerating medications is herbs and herbal preparations. To identify, describe, and standardize the active substances, beneficial compounds, and their preparations for the treatment of liver illnesses, more study is necessary. Furthermore, one of the best solutions for the treatment of liver disorders as well as other illnesses and infections in the near future may be a mix of contemporary and conventional therapy with traditional herbal treatments.

Finally, identification of bioactive molecules from these plants must be undertaken in future followed by pharmacological evaluation of the promising molecules for hepatoprotective activities. The availability of modern hepatoprotective drugs with realistic clinical utility is still very limited and identification of new molecules with similar potentials will surely advocate the process of novel drug discovery as well as development.

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