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Systematic evaluation of plant extract-mediated modulation of hepatic and renal biomarkers in rodent models: A molecular perspective

Duaa A. H. Al-Jubori * and Marwa Najim Obied Al-Shujairi

Department of Medical Laboratory Technics, Al-Mussaib Technical Institute, Al-Furat Al-Awsat Technical University, Babylon, Iraq.

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Abstract

Background: Chronic hepatic and renal diseases are a worldwide public health problem and there are limitations of the traditional treatments. Each of these plants has a variety of phytochemicals with antioxidant, anti-inflammatory, anti-apoptotic properties, which can serve as alternative therapeutic agents.

Objective: This systematic review aims to elucidate on the effect of the plant extracts on the hepatic and renal biomarkers in the rodent models and its mechanism of action.

Methodology: A systematic literature search was performed, and studies on the effect of plant extracts on liver and kidney function was synthesized, focusing on the oxidative stress, inflammation, fibrosis and apoptosis pathways.

Results: The major plant extracts which consistently showed hepatoprotective and nephroprotective properties on rodents were curcumin, silymarin, quercetin, naringenin, apigenin, baicalin, rosmarinic acid, ellagic acid, green tea extract (GTE) and pomegranate. The effects of these are mainly mediated through the activation of the Nrf2/HO-1 signaling pathway, NF-κB inhibition, NLRP3 inflammasomes modulation, TGF-β1/Smad signaling pathway and through the regulation of the expression of apoptosis-related proteins. The efficiency was observed through these phytochemicals that were able to effectively combat the oxidative stress and reduce both fibrotic remodeling and apoptosis and consequently restored the function of both liver and kidney.

Conclusions: Plants derived medicine offers a significant potential for treating liver and kidney disorders. Future studies should be directed towards standardization, accurate identification of the molecular target, on bioavailability assessment and the long-term safety studies to help transferring the investigations to clinical practices and generate safe and effective interventions.

Keywords: Chronic Hepatic; Kidney Function; Liver Function; Plant Extracts

1. Introduction

Liver and kidneys are essential organs that are crucial for in maintaining physiological stability in the body by participating in metabolic, detoxification and excretory processes. The burden of chronic diseases involving these organs, including non-alcoholic fatty liver disease (NAFLD), cirrhosis, acute kidney injury (AKI) and chronic kidney disease (CKD) are prevalent globally, and often resulting in end-stage organ failure and the need for organ invasive procedures, such as dialysis and transplantation. The pathogenesis of these conditions is complex and includes a series of molecular events such as oxidative stress, inflammation, apoptosis and fibrotic remodeling. Although conventional

* Corresponding author: Duaa A. H. Al-Jubori

pharmacological therapies are effective partially effective, they often have limitations and present side effects and absence of complete therapeutic effectiveness. Thus, alternative and complementary therapeutic approaches, especially natural compounds, have become a topic of increasing interest.

The phytochemicals found in plant extracts encompass a wide variety of compounds, including flavonoids, polyphenols, alkaloids, and terpenoids, and have been used in traditional medicine for centuries for their medicinal properties. Many of these traditional uses have since been supported by modern scientific research, which has shown that these natural compounds have a wide spectrum of biological activity such as antioxidant, anti-inflammatory, anti-apoptotic and anti-fibrotic activities. These properties make plant extracts highly promising for regulation of the pathological processes underlying the hepatic and renal diseases. Rodent models, such as mice and rats, are essential resources for preclinical studies and play a pivotal role in investigating disease mechanisms and assessing the efficacy and safety of potential therapeutic agents in a controlled environment prior to human trials. These models can be used to evaluate changes in hepatic and renal biomarkers that are critical to organ function and organ damage, including ALP, AST, ALT, bilirubin, BUN, creatinine and a number of inflammatory cytokines.

The research in this systematic review is designed to gauge and critically review the existing scientific literature on the modulatory effect of plant extracts on hepatic and renal biomarker levels in rodent models. The main focus is to understand the molecular mechanisms by which these effects occur, providing insights into the interaction of phytochemicals with cellular pathways and their protective or recovery-enhancing properties. This review aims to synthesize findings from robust studies about the potent active constituents of these extracts and their ability to effectively manage liver and kidney diseases, which can support the specific development of new drugs and/or evidence-based therapeutic applications. The following sections will systematically explore the molecular mechanisms that are associated with liver and kidneys intervention with plant extract based on the extensive body of literature in this domain from the collection of scientific reported literature from reputable scientific databases such as Scopus and Clarivate. This will help in better understanding of pharmacology of natural products in relation to liver and kidney diseases and help in developing novel effective and safe therapeutic strategies.

2. Molecular mechanisms of plant extract-mediated modulation

2.1. Oxidative Stress and Inflammation

Reactive oxygen species (ROS) are produced as reactive intermediates in the initiation and progression of hepatic and renal pathologies, and the imbalance between ROS production and their detoxification is known as oxidative stress. Overproduction of ROS induces cellular damage, lipid peroxidation, protein carbonylation, DNA damage and ultimately organ dysfunction. In parallel, inflammation is a complex biological reaction to harmful stimuli, and it is intricately related to oxidative stress, forming a vicious cycle, which contributes to further damage to tissues. Extracts from plants with high antioxidant and anti-inflammatory activities have shown considerable potential for reducing these harmful effects in animal models.[1-3]

A key molecular target for plant-derived compounds in fighting oxidative stress is the Nuclear factor erythroid 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway. Nrf2 is a key regulator of antioxidant and detoxifying enzymes. Once activated, Nrf2 moves to the nucleus and binds to antioxidant response elements (AREs) that promote expression of genes coding for antioxidant enzymes, including HO-1, glutathione S-transferases (GSTs), and NAD(P)H:quinone oxidoreductase 1 (NQO1). The Nrf2/HO-1 signaling was shown to be enhanced by plant extracts and their active components in several studies, both in liver and kidney tissues, by boosting the intrinsic antioxidant defense system. For example, the hepatoprotective and nephroprotective effects of curcumin, a major polyphenol of *Curcuma longa*, are well studied by Nrf2 activation.[4,5] In the similarly, ellagic acid,[6] and nanoparticles derived from garlic have been found to protect liver injury through the activation of the Nrf2/HO-1 pathway.[7] These results highlight the potential of natural Nrf2 activators as therapeutic agents to protect against oxidative damage in hepatic and renal diseases.[8-11] Phytochemical activation of Nrf2 causes a concerted transcriptional response that neutralizes present ROS and also prevents generation of ROS, which will protect the cellular components from oxidative damage. This complex molecular choreography involving plant chemicals and cellular defenses is a fundamental characteristic of plant defense mechanisms.

Oxidative stress is responsible for the activation of many signaling pathways, such as Nuclear Factor-κB (NF-κB) and the Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, which are involved in inflammation. NF-κB is an important transcription factor involved in the regulation of the pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6), chemokines and adhesion molecules. The multiprotein NLRP3 inflammasome is activated by various danger signals, resulting in maturation and release of two powerful pro-inflammatory cytokines, IL-1β and IL-18, which

have been associated with sterile inflammation and pyroptosis. Extracts from these plants have been demonstrated to regulate these inflammatory pathways and decrease tissue damage. Quercetin is a commonly occurring flavonoids which have been seen to have anti-inflammatory properties, as it is able to inhibit the activation of NF-κB and suppress the production of pro-inflammatory mediators in the hepatic inflammation models.[12] Quercetin has also been suggested to have immunomodulatory effects in renal conditions, specifically, acting on inflammation and oxidative stress in diabetic nephropathy.[13] Other natural products with an effect on the NLRP3 inflammasome have likewise demonstrated potential efficacy in many liver diseases, positioning them as anti-inflammatory agents.[14-16] Moreover, some compounds such as apigenin and hesperidin have been found to prevent cisplatin nephrotoxicity by their regulation of NF-κB and MAPK pathway, which further reveals the anti-inflammatory effect of plant extract.[17,18] These plant compounds disrupt the inflammatory signaling pathways, offering a holistic approach to reducing inflammation and averting long-term tissue damage.

2.2. Fibrosis and Apoptosis

Chronic liver and kidney injuries often trigger excessive synthesis of extracellular matrix (ECM) proteins with organ scarring and failure (fibrosis). One of the major pathways leading to fibrogenesis is the "transforming growth factor (TGF)- β1 (TGF-β1)/Smad pathway. Once activated, this pathway leads to the proliferation of myofibroblasts, and stimulates the production of ECM components. Extracts from plants have been shown to interrupt this pathway, and so could be useful as anti-fibrotic agents. For example, Cordyceps sinensis extract has demonstrated inhibitory effect on the TGF-β1/Smad signaling pathway, which reduces renal fibrosis in nephrectomy rats.[19] The extract of Eucommiae cortex (EC) has exerted a similar effect to inhibit renal fibrosis through the TGF-β1/Smad pathway.[20-22] These discoveries indicate that phytochemicals may directly affect one of the primary signaling pathways associated with fibrotic processes, and provide a therapeutic approach to prevent and/or reverse organ scarring. The molecular mechanisms include downregulation of TGF-β1 expression, blockade of Smad phosphorylation, and down-regulation of ECM components such as collagen production, which help to maintain the organ structure and function.

Programmed cell death (apoptosis) is another a significant process involved in the pathogenesis of hepatic and renal diseases. Apoptosis is a normal process, but defects in this process may involve tissue damage and organ dysfunction. Plant extracts have anti-apoptotic effects which which contributes to preventing premature cellular demise. The mechanisms are related to the modulation of various apoptotic pathways such as the intrinsic (mitochondrial) and the extrinsic (death receptor) pathway through the regulation of the expression of pro-apoptotic proteins (e.g., Bax, caspase-3) and anti-apoptotic proteins (e.g., Bcl-2). For example, curcumin has been found to decrease apoptosis in hepatic fibrosis models.[23] Besides being an antioxidant and anti-inflammatory, rosmarinic acid is also known to inhibit apoptosis and also improve cisplatin induced nephrotoxicity.[24] Moreover, plant extracts may adjust pathways that control cell survival, boost the therapeutic value of these extracts in decreasing organ injury. The interaction of oxidative stress, inflammatory response, fibrosis and apoptosis is complex and the effects of many plant extracts are multi-targeted – that is they impact on several processes in this pathway. A noteworthy characteristic of botanical extracts is as they can affect more holistically with more complex diseases.

3. Specific Plant Extracts and Their Modulatory Effects

Many plant extracts and their individual compounds have been studied for hepatoprotective and nephroprotective effects using various animal models. These extracts have been clustered by their key bioactive ingredients and their common molecular targets for a cohesive overview.

3.1. Flavonoid-Rich Extracts and Their Multi-Targeted Actions

The flavonoids are one of the most important groups of plant secondary metabolites known for their exceptional antioxidant and anti-inflammatory activities. Multiple extracts and single compounds rich in flavonoids have shown pronounced effects on the modulation of hepatic and renal biomarkers. The widely distributed quercetin is a potent antioxidant, anti-inflammatory and anti-apoptotic compound. Quercetin has been found to reduce the inflammatory response by regulating the NF-κB pathway and alleviating oxidative stress in rodent models of liver damage.[12] It is usually seen to up-regulate the expression of Nrf2/HO-1 and down-regulate pro-inflammatory mediators in exerting its protective effect against liver damage.[12] Quercetin's immunomodulatory properties have shown protective effects against inflammatory reactions and oxidative stress, and even ferroptosis, in diabetic nephropathy models.[13] Likewise, another widely present flavonoid, rutin was found to provide hepatoprotection in rats against carbon tetrachloride toxicity which may be attributed to its potent free radical scavenging and anti-lipid peroxidative effects.[25] These flavonoids typically exert anti-inflammatory effects through multiple mechanisms, including stabilization of mast cells, which prevents the release of histamine, and inhibition of enzymes that participate in inflammation. They are also able to chelate metal ions which enhances their antioxidant properties preventing the formation of harmful free radicals.

Naringenin, which is found in citrus fruits, has been found to possess hepatoprotective activity against carbon tetrachloride-induced liver fibrosis in rats through its anti-inflammatory and anti-oxidative properties.[26,27] It also has nephroprotective effects against cisplatin-induced nephrotoxicity, which is typically mediated by antioxidant and anti-inflammatory effects.[26] The protective mechanisms of naringenin involve activation of Nrf2, suppression of NF-κB, and modulation of different apoptotic pathways, which helps in decreasing the cellular damage and enhancing organ function. It also helps in regulating lipid metabolism and glucose homeostasis making it a therapeutic target in metabolic associated liver and kidney diseases. Apigenin has been found to protect against the nephrotoxicity caused by cisplatin in rats by regulating the MAPK and apoptotic and NF-κB pathways, with its anti-inflammatory and anti-apoptotic effects being responsible for this protective effect.[17] These compounds typically act by attenuating the cell cycle to give damaged cells to promote recovery, eliminating damaged cells, and promoting the healing of healthy cells; all of which aid organ recovery and protect it.

The compound baicalin, which is found in *Scutellaria baicalensis*, has been reported to have protective effects against carbon tetrachloride-induced liver injury in mice, where it helps to prevent oxidative stress and inflammation.[28] It has been found to be capable of reducing the activation of liver stellate cells, an important step in liver fibrogenesis. Baicalin's anti-fibrotic effects are particularly significant as they directly address the progression of liver scarring. Silymarin is a combination of flavonolignans derived from *Silybum marianum* and is well known for its hepatoprotective action. In rodent models of chemically induced liver injury, silymarin has been shown to maintain the architecture of the liver, lower transaminase levels, and to decrease oxidative stress and inflammation.[29,30] Its mechanisms involve the stimulation of antioxidant defense, stabilization of hepatocyte membranes and regulation of inflammatory cytokine production.[29,30] Other systematic reviews have also confirmed its anti-inflammatory and anti-oxidative properties recently.[31] The protective effects of silymarin are also said to be due to its cell cycle modulatory, antifibrogenic (stellate cell activation inhibitory), and liver regenerator properties. Its multi-dimensional activities make it effective in several liver diseases and hence it forms an integral part of the natural hepatoprotective strategies. This synergic action between the various flavonoids highlights their role in the prevention of chronic liver diseases.

3.2. Polyphenol and Phenolic Acid-Rich Extracts

Another group of phytochemicals that plays an important role in modulating organ biomarkers is polyphenols and phenolic acids. Curcumin, a polyphenol compound derived from *Curcuma longa*, is a well-studied compound, which possesses a strong antioxidant, anti-inflammatory and antifibrotic activity. Curcumin has been found to reduce hepatic enzymes (ALT, AST), alleviate oxidative stress by upregulating Nrf2/HO-1 pathway and inhibit inflammatory responses by blocking the activation of NF-κB in rodent models of liver injury.[4,5,32] In models of non-alcoholic steatohepatitis (NASH), for example, curcumin inhibited chronic kidney injury by regulating the endoplasmic reticulum stress and MAPK pathways.[5] It is nephroprotective in a number of models of acute renal injury, in which it prevents oxidative injury and inflammation.[4,32] Additional research has shed light on the fact that curcumin acts on multiple signaling pathways essential to cell proliferation, survival, and differentiation, including the PI3K/Akt, STAT3 and Wnt/β-catenin pathways, adding to the many modes of action of curcumin to protect against liver and kidney damage. Curcumin's multifaceted activity, specifically targeting several molecular pathways, renders it a promising therapeutic agent.

The Lamiaceae herbs contain rosmarinic acid which has been found to be nephroprotective in mice with cisplatin-induced nephrotoxicity. The mechanisms are anti-oxidative stress, anti-inflammatory and anti-apoptotic properties, preserving renal function.[24] The antioxidant properties of rosmarinic acid and its ability to inhibit pro-inflammatory cytokines, as well as modulate cell death pathways, may make it a useful compound for the prevention of drug-induced nephrotoxicity. Supplementing with ellagic acid was found to improve liver damage in mice induced by cisplatin, by inhibiting the NF-κB pathway and stimulating the Nrf2/HO-1 pathway, which suggests its dual anti-inflammatory and anti-oxidant effects.[6] Usually these phenolics act as free radical scavengers and metal chelators to reduce the oxidative damage and the initiation of the inflammatory cascades. Moreover, they can help in controlling the expression of different genes such as antioxidant and anti-inflammatory pathways, which also helps in their protecting effects.

The extract of green tea (*Camellia sinensis*) contains a high amount of catechins especially epigallocatechin gallate (EGCG) which has been shown to have hepatoprotective and nephroprotective effect against CCl_4 toxicity in rats, primarily due to its potent antioxidant properties.[33] By acting on multiple signaling pathways such as NF-κB, MAPK and PI3K/Akt, EGCG's anti-inflammatory, anti-apoptotic and anti-fibrotic properties provide all-round protection to the liver and kidney tissues. Hepatoprotective activity of Pomegranate (*Punica granatum*) extract in rats may be attributed to its high content of antioxidants (mainly punicalagins and ellagic acid) that have a scavenging effect on free radicals and inhibit inflammatory responses.[34] Together, these extracts contain a large number of polyphenols, and these molecules are involved in important organ protection by multiple molecular mechanisms, such as inhibition of pro-inflammatory enzymes and activation of cellular protection mechanisms.

3.3. Alkaloid, Saponin, and Terpenoid-Rich Extracts

The extracts, which are rich in alkaloids, saponins and terpenoids, have also significant protective effects, exerting diverse mechanisms of action. *Platycodon grandiflorum* extracts contain saponins (platycosides) which have been shown to have hepatoprotective activity in mice with carbon tetrachloride-induced liver injury, in addition to anti-inflammatory, antioxidant, and anti-fibrotic activity.[35] Platycosides are its active compounds and help to protect the liver cells from damage while promoting their regeneration, through anti-inflammatory, antioxidant and anti-fibrotic effects. The extract from the rhizome of *Rauwolfia serpentina* was found to possess hepatoprotective activity in rats, which may provide a scientific rationale for its traditional use for liver complaints, based on its antioxidant and anti-inflammatory activity.[36] The alkaloids present in *Rauwolfia serpentina* contribute to its antioxidant and anti-inflammatory properties, which are crucial in protecting the liver from various insults. It remains to be fully understood the molecular mechanism of its hepatoprotective effects.

Nigella sativa has a wide range of pharmacological effects and has been shown to have nephroprotective effects in rats through the modulation of oxidative stress and inflammatory pathways, with thymoquinone (a terpenoid compound) being the main compound in the seeds responsible for these effects.[37] It contains thymoquinone, its primary bioactive component, that is responsible for its antioxidant, anti-inflammatory, and immunomodulatory properties which play significant roles in the prevention of various kidney injuries. It is a potential therapeutic agent for renal diseases, due to its ability to modulate oxidative stress and inflammatory pathways. The hepatoprotective activity of extracts from *Tinospora cordifolia* was demonstrated in rat studies, and it has been suggested that its diterpenoids and alkaloids are responsible for its immunomodulatory, antioxidant and anti-inflammatory activity.[38] These extracts reveal the variety of plant chemical classes that are involved in organ protection and that may synergistically interact with one or more components.

3.4. Diverse Botanical Extracts with Broad Protective Profiles

A number of other plant extracts have been found to have considerable hepatoprotective and nephroprotective effects which mostly involve the above mechanisms. Gum Arabic from *Acacia senegal* was found to be protective against cisplatin induced nephrotoxicity in rats, and its main mechanism of action was by inhibiting the lipid peroxidation and oxidative damage.[39] Other renal benefits attributed to gum Arabic include the capacity to enhance renal hemodynamics, reduce proteinuria and mitigate renal inflammation and fibrosis. It also has some prebiotic effects, which may mediate its beneficial effects by altering the gut microbiota and lowering systemic inflammation. Ginger extract (Zingiber officinale) containing gingerols and shogaols has been shown to have hepatoprotective properties, which included the inhibition of oxidative stress, suppression of inflammatory cytokines and protection of hepatocytes from damage in rats.[40] The wide pharmacological spectrum is making ginger an effective dietary supplementation and possible therapeutic drug for liver diseases. From direct antioxidant effects to modulating gut health, these extracts are representative of the many tactics plants use to provide organ protection.

Many other plants have been demonstrated to be effective in rodent models. Several have demonstrated hepatoprotective and/or nephroprotective effects including *Solanum nigrum*,[41] *Cassia occidentalis*,[42] *Sonchus asper*,[43] *Boerhaavia diffusa*,[44] *Moringa oleifera*,[45] *Tribulus terrestris*,[46] *Asparagus racemosus*,[47] *Phyllanthus niruri*,[48] *Ocimum sanctum*,[49] and *Withania somnifera*.[49] These are all due to the synergistic activity of their complex phytochemical compositions that provides protection against oxidative stress and inflammation, and stimulates cell survival and regeneration. An in-depth investigation of liver and kidney disease by these multiple plant sources are crucial for the identification of new therapeutic agents and understanding the complete therapeutic potential of these plants. Numerous of these plants have been used for hundreds of years for medicinal purposes and now are subjected of scientific documentation of their purported benefits, which are at the molecular level. The great diversity of plant rich compounds capable of altering hepatic and renal biomarkers in the rodent model, often by mechanisms that act on multiple molecular pathways, is illustrated. These various works have produced comparable findings; all giving a positive outlook with regards to the therapeutic potential offered from these natural agents.

Future Directions and Challenges

Although there are strong indications of the effectiveness of plant extracts on the liver and kidney markers in the rodents, there are some important points and future implications to consider before utilizing plant extracts for clinical use. One of the issues is standardization of the plant extract. Plant extract chemical composition may vary significantly according to the geographical origin, the time of harvest and the methods used for extraction and the parts of the plants used. This variability may lead to biological activity variability and reproducibility between studies and can create a challenging in defining dose-response relationships and comparing results between studies. Further studies will be needed to make standardized extracts with a definite chemical composition, to ensure efficacy and safety.[1,2] This

standardisation is crucial for attaining the reproducibility of the results of research and for making this technique, if it is to be used in therapeutic applications, reliable. Besides, analytical tools are needed for quality control and quantification of the active compounds for consistency and potency of plant-based interventions. A primary limitation is the variabilities and unreproducibility which can be a severe challenge and if the plant extracts are not standardized, then the therapeutic potential of the same may not be completely tapped out.

Modes of action and exact elucidation of molecular targets is also important. Although numerous studies have indicated that several pathways, such as the Nrf2/HO-1 pathway and the NF-κB pathway, are involved, a more precise understanding of the role of the specific protein-ligand interactions, the signaling cascades involved, and the possible off-target effects is important. Comprehensive insights into the complex molecular networks controlled by plant extracts can be obtained by combining advanced omics technologies (proteomics, metabolomics and transcriptomics) with systems biology approaches. The extensive mechanistic information will not only prove valuable for the traditional application but will also give us a starting point to rationally design new therapeutic approaches.[3,4] This will push the field of observation to prediction and targeting, in drug discovery. The use of computational modeling and high throughput screening assays can speed up the process of finding chemical scaffolds and their molecular targets for highly effective and selective development of plant based drugs. To gain insight into the exact mechanisms will also help in the identification of possible synergism when using two or more plant extracts or isolated compounds.

Bioavailability and pharmacokinetics of bioactive constituents in plant extract is also important. Numerous phytochemicals are not very soluble in water and they have low oral bioavailability and therefore not as effective therapeutically. Novel drug delivery systems like nanoparticles, liposomes and phytosomes may confer an additional benefit to these compounds as their absorption, distribution, metabolism and excretion (ADME) properties may be improved which ultimately result in improving the therapeutic index.[5,6] Furthermore, potential drug-herb interactions need to be studied to minimize negative interactions and maximize patient safety especially when patients are receiving more than one medication.[7,8] To incorporate plant-based therapies into standard medical care while ensuring patient safety, it is crucial to understand these interactions. Various methods to enhance bioavailability, including micronization, encapsulation and absorption enhancers are actively being investigated. Extended pharmacokinetical studies need to be carried out to obtain an optimal dosage regimen and to ensure delivery of the active compounds into the organs of action at therapeutic levels. Moreover, thorough toxicological testing, including acute, sub-chronic, and chronic toxicity studies, is crucial to assess the safety profile of plant extracts for prolonged use.

Long term efficacy and safety studies are also of critical importance. Although in vivo studies in rodent models are essential for obtaining preclinical evidence, chronic hepatorenal effects of the plant extracts and any potential toxicities should be thoroughly investigated. This includes the evaluation of their impact in more chronic models, which more accurately reflect the human situation, on disease progression, quality of life and overall survival. Further, more complex and human relevant animal models will be essential to help bridge the translational gap and more closely recapitulate the complexity of liver and kidney diseases in humans.[9,10] This will help ensure that promising preclinical findings can be translated to effective human therapies. After successful preclinical validation, the ultimate stage is clinical trials to validate efficacy and safety in human populations. These trials need to be well designed, randomized, placebo-controlled, and adequately powered to allow for strong conclusions to be drawn for clinical use. Ethical issues also need to be taken into account when using a natural product in human trials.

Finally, the combination of traditional knowledge and modern scientific methods is a promising option. Ethnobotanical research can be used to select plants that have a long history of safe use and efficacy that can then be examined scientifically and validated. This combined approach may help to speed up the identification and development of new plant-based treatments for liver and kidney diseases. Pharmacologists, botanists, chemists, and clinicians will need to work together to overcome these challenges and fully realize the therapeutic potential of plant extracts.[11,12] It is important to have an interdisciplinary approach to fully understand and utilize natural products. The use of AI and ML to process large datasets of ethnobotanical information and make predictions about bioactivities can also help expedite the process of discovery. The future of plant-based medicine is about integrating between tradition and innovation, between wisdom and science, to find a balance that honors our heritage while advancing medical understanding and care.

4. Conclusion

A comprehensive systematic review of the systematic assessment of plant extract mediated modulation of hepatic and renal biomarkers, in rodents has been critically explored in this review from a molecular perspective. It was readily clear from the data that a variety of hepatoprotective and nephroprotective effects are present in the extracts of various kinds of plants and the bioactive molecules present in these plant extracts. These effects are mostly through modulation

of key molecular pathways of Oxidative Stress (e.g. Nrf2/HO-1), Inflammation (e.g. NF-κB, NLRP3 inflammasome), Fibrosis (e.g. TGF-β1/Smad) and Apoptosis. The many examples that have yielded beneficial outcome in different rodent model liver and kidney injury include curcumin, silymarin and quercetin. All these studies have yielded results that are consistent and indicate that the therapeutic potential of these natural agents in hepatic and renal diseases is significant and can be used as complementary or alternative therapies. Nevertheless, future endeavors are needed to overcome challenges associated with standardization, to further explore accurate molecular mechanisms, to enhance bioavailability, to perform in-depth long-term safety and efficacy testing, and to promote a synergetic integration of traditional knowledge and science. Plant extracts hold promise for developing new, effective, and safe therapeutic approaches that could help enhance patient outcomes in the global effort to combat liver and kidney diseases by addressing these obstacles. The transition from traditional medicine to evidence-based clinical practice remains multifaceted, but the strong data from the rodent models offers a solid basis for further study and eventual translation into the clinic.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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