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Hepatotoxicity of Phytochemicals: A Systematic Review of the Mechanisms Behind Liver Damage and Protective Interventions

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ABSTRACT

Phytochemicals, bioactive compounds derived from plants, have garnered significant attention for their therapeutic potential in treating a wide array of diseases. However, increasing evidence suggests that certain phytochemicals, particularly in high doses or with prolonged use, can induce hepatotoxicity, leading to liver damage. The liver, as the primary organ responsible for detoxifying the body, is particularly susceptible to damage from both endogenous and exogenous substances, including phytochemicals. This systematic review explores the mechanisms behind phytochemical-induced hepatotoxicity, focusing on oxidative stress, mitochondrial dysfunction, inflammatory responses, and gene expression alterations. Additionally, it discusses protective interventions, including the use of other phytochemicals, antioxidants, and pharmaceutical agents that may mitigate liver damage. Given the growing use of plant-based medicines and dietary supplements, understanding the hepatotoxic potential of phytochemicals is crucial for their safe use. The review aims to provide a comprehensive overview of the mechanisms of hepatotoxicity associated with phytochemicals, highlighting the risks and offering insights into preventive and therapeutic strategies.

Keywords: Hepatotoxicity, Phytochemicals, Liver Damage, Mechanisms of Toxicity, Protective Interventions

INTRODUCTION

Phytochemicals, naturally occurring bioactive compounds found in plants, have been utilized for centuries in various traditional medicine systems worldwide, including Ayurveda, Traditional Chinese Medicine, and Indigenous healing practices [1]. These plant-derived compounds are often lauded for their diverse therapeutic effects, which include antioxidant, anti-inflammatory, antimicrobial, and anticancer properties [2]. Phytochemicals are commonly consumed through herbal remedies, teas, dietary supplements, and functional foods, and they have gained popularity in modern complementary and alternative medicine (CAM) [3]. With an increasing interest in plant-based treatments, the global use of phytochemicals continues to rise, driven by their perceived natural origins and therapeutic efficacy.

Among the numerous health benefits attributed to phytochemicals, their hepatoprotective properties are particularly noteworthy [4]. Certain phytochemicals, such as flavonoids, polyphenols, terpenoids, and alkaloids, are known to exert protective effects against liver damage caused by various factors, including oxidative stress, alcohol consumption, and pharmaceutical drugs [5]. However, despite their widespread use and potential health benefits, phytochemicals also pose significant risks, particularly when consumed in excessive doses or over extended periods. The liver, as the primary organ responsible for detoxification and metabolism of numerous substances, is highly susceptible to damage from both endogenous and exogenous compounds, including phytochemicals [6,7]. Although most phytochemicals undergo biotransformation in the liver without causing harm, certain compounds have been shown to induce hepatotoxicity [7]. Hepatotoxicity refers to liver damage caused by chemical substances, and the liver is vulnerable to various types of injury, including oxidative stress, inflammation, mitochondrial dysfunction, and fibrogenesis [8]. The hepatotoxic effects of certain phytochemicals, particularly when consumed without adequate knowledge of dosage or quality control, can lead to conditions ranging from mild liver enzyme elevation to severe liver injury, including acute liver failure or chronic liver diseases like cirrhosis [9]. Understanding the mechanisms behind phytochemical-induced hepatotoxicity and exploring potential protective interventions is essential to ensure the safe use of these plant-based compounds in clinical and therapeutic settings.

Mechanisms of Hepatotoxicity Induced by Phytochemicals

Phytochemicals can cause liver damage through several mechanisms, which often overlap and compound each other. These mechanisms include oxidative stress, mitochondrial dysfunction, inflammatory responses, and changes in gene expression. Understanding these pathways is essential to elucidating the hepatotoxic effects of phytochemicals.

1. Oxidative Stress

One of the primary mechanisms behind hepatotoxicity induced by phytochemicals is oxidative stress [10]. Many phytochemicals, especially polyphenols, flavonoids, and terpenoids, can generate reactive oxygen species (ROS) during their metabolism in the liver [11]. ROS, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, can damage cellular components like lipids, proteins, and DNA [12]. In the liver, oxidative stress can lead to hepatocellular injury, inflammation, and fibrosis. For example, compounds like curcumin, a well-known flavonoid from turmeric, exhibit both antioxidant and pro-oxidant effects, depending on the dose and duration of exposure [13]. At higher concentrations, curcumin can induce oxidative stress, resulting in hepatotoxicity [14].

2. Mitochondrial Dysfunction

Mitochondrial dysfunction is another significant pathway in phytochemical-induced hepatotoxicity [15]. Mitochondria play a critical role in energy production and cellular metabolism in hepatocytes [16]. Certain phytochemicals, such as those found in the Aristolochia species, are known to disrupt mitochondrial function by impairing the electron transport chain and altering mitochondrial membrane potential [17]. This results in the generation of excess ROS and depletion of cellular ATP, ultimately leading to liver cell death through necrosis or apoptosis. Mitochondrial dysfunction also promotes inflammation and fibrosis, contributing to chronic liver damage [18].

3. Inflammatory Responses

Phytochemicals can also trigger inflammatory responses that exacerbate liver injury. Compounds like silymarin (derived from milk thistle) and boswellic acid (from Boswellia serrata) are known for their anti-inflammatory properties [19]. However, other phytochemicals, when consumed in large doses or over long periods, can provoke inflammation. For instance, certain alkaloids found in Piper longum and Ephedra species have been linked to hepatic inflammation, which is often accompanied by the activation of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukins. Chronic inflammation can lead to liver fibrosis and, ultimately, cirrhosis or liver failure [20].

4. Alterations in Gene Expression

Many phytochemicals can influence gene expression by interacting with nuclear receptors or by affecting transcription factors involved in hepatic detoxification [21]. Some compounds, like phytosterols found in plant oils, may activate the peroxisome proliferator-activated receptor (PPAR), which regulates lipid metabolism and inflammation in the liver [22]. However, certain phytochemicals may alter gene expression in ways that increase susceptibility to liver damage, such as by upregulating genes associated with apoptosis or fibrosis [23]. This mechanism is particularly concerning when long-term use of phytochemicals leads to cumulative genetic changes that impair liver function.

Protective Interventions Against Phytochemical-Induced Hepatotoxicity

Several strategies have been proposed to prevent or mitigate liver damage caused by phytochemicals. These interventions encompass the use of protective phytochemicals, antioxidants, pharmaceutical agents, and the regulation of phytochemical dosages. These approaches aim to minimize liver injury, reduce oxidative stress, and support liver regeneration, ensuring the safe use of phytochemicals.

1. Antioxidants and Phytochemicals with Protective Properties

Many herbs and dietary supplements contain antioxidants that can counteract the oxidative stress induced by hepatotoxic phytochemicals. Oxidative stress is a major contributor to liver damage, and antioxidants can neutralize free radicals and reduce cellular damage [24]. For example, silymarin, a flavonoid derived from the milk thistle plant, has been extensively studied for its hepatoprotective effects [25]. Silymarin has been shown to inhibit oxidative damage, reduce inflammation, and promote liver cell regeneration [26]. It exerts these effects by scavenging reactive oxygen species (ROS), stabilizing cell membranes, and enhancing glutathione levels, a key antioxidant in the liver.

Similarly, other phytochemicals, such as resveratrol, curcumin, and green tea polyphenols, possess antioxidant properties that help protect the liver from oxidative damage. Resveratrol, a polyphenol found in grapes, has demonstrated anti-inflammatory and antioxidant effects that may reduce liver fibrosis and inflammation [27]. Curcumin, the active compound in turmeric, has shown potential in protecting liver cells by inhibiting the inflammatory pathways and oxidative stress induced by hepatotoxic substances [28]. Green tea polyphenols, particularly epigallocatechin gallate (EGCG), are also known to enhance liver function and protect against drug-induced liver injury due to their potent antioxidant effects [29].

2. Pharmaceutical Agents

In cases of severe hepatotoxicity, pharmaceutical agents may be necessary to manage liver injury. For instance, N-acetylcysteine (NAC) is widely used as an antidote for acetaminophen-induced liver toxicity [30]. NAC works by replenishing glutathione levels in the liver, which helps neutralize ROS and protect hepatocytes from oxidative damage [31]. NAC has shown promise in alleviating liver damage caused by a variety of hepatotoxic substances, including certain phytochemicals. Additionally, drugs like corticosteroids and anti-inflammatory agents may help manage liver inflammation caused by phytochemical exposure [32]. These medications can reduce the inflammatory response and prevent further liver damage in cases of acute hepatotoxicity.

3. Regulation of Phytochemical Dosages

Proper dosage and monitoring of phytochemical intake are crucial for minimizing the risk of hepatotoxicity. Many adverse effects related to phytochemicals are dose-dependent, meaning that higher concentrations or prolonged use can lead to liver damage [33]. In some cases, small doses of certain phytochemicals may provide therapeutic benefits, while higher doses may overwhelm the liver's detoxification processes and cause harm. Standardized doses of herbal supplements should be recommended to avoid excessive intake, and consumers should be educated on the potential risks associated with self-medication using herbal products [34]. Healthcare professionals should monitor liver function in patients who are consuming herbs with known hepatotoxic potential, especially in vulnerable populations such as the elderly or those with pre-existing liver conditions. Establishing clear guidelines for the safe use of phytochemicals can help mitigate the risk of liver toxicity and ensure the efficacy of plant-based remedies. In conclusion, while phytochemicals have therapeutic potential, their hepatotoxic effects should not be underestimated. Protective interventions, such as the use of antioxidants, pharmaceutical agents, and careful regulation of dosages, are crucial to minimize liver damage. By understanding the mechanisms of phytochemical-induced hepatotoxicity and implementing these protective strategies, healthcare providers can ensure the safe and effective use of phytochemicals in clinical practice.

CONCLUSION

While phytochemicals offer numerous health benefits, their potential to induce hepatotoxicity, particularly when used improperly or in excessive doses, cannot be overlooked. The mechanisms of liver damage associated with phytochemicals include oxidative stress, mitochondrial dysfunction, inflammation, and alterations in gene expression. Protective interventions, such as antioxidants, pharmaceutical agents, and proper dosing, are essential for mitigating these risks. As the use of phytochemicals in traditional and modern medicine continues to grow, it is crucial to understand their hepatotoxic potential and implement strategies to ensure their safe use in clinical practice.

REFERENCES

1. Chaachouay N, Zidane L. Plant-Derived Natural Products: a source for drug discovery and development. Drugs and Drug Candidates. 2024;3(1):184–207. doi:10.3390/ddc3010011
2. Alum EU. Climate change and its impact on the bioactive compound profile of medicinal plants: implications for global health. *Plant Signaling & Behavior*, 2024; *19*(1), 2419683. doi: 10.1080/15592324.2024.2419683. Epub 2024 Oct 26. PMID: 39460932.
3. Hossain MdS, Wazed MA, Asha S, Amin MdR, Shimul IM. Dietary Phytochemicals in Health and Disease: Mechanisms, Clinical Evidence, and Applications—A Comprehensive Review. Food Science & Nutrition. 2025;13(3). doi:10.1002/fsn3.70101
4. Datta S, Aggarwal D, Sehrawat N, Yadav M, Sharma V, Sharma A, et al. Hepatoprotective effects of natural drugs: Current trends, scope, relevance and future perspectives. Phytomedicine. 2023;121:155100. doi:10.1016/j.phymed.2023.155100
5. Alum EU. Role of phytochemicals in cardiovascular disease management: Insights into mechanisms, efficacy, and clinical application. Phytomedicine Plus, 2025; 5(1),100695. https://doi.org/10.1016/j.phyplu.2024.100695.
6. Aja O. A., Egba S. I., Uhuo Emmanuel Nnaemeka, Alaebo Prince Ogocukwu, Mba Obinna Joseph, and Oriaku Chinwe Edith. Hepatoprotective potentials of aqueous chloroform and methanol leaf extracts Whitfieldia lateritia 2, 4-dinitrophenylhydrazine induced anaemia in rats. Bio-research and Biotechnology, 2022; 20(2) 1434-1445
7. Uroko, Robert I.., Adamude, Fatima A.., Egba, Simeon I., Ani, Chijioke C and 1 Ekpenyong, James E. Hepatoprotective Effects of Methanol Extract of *Acanthus montanus* (*acanthaceae*) Leaves on Acetaminophen Induced Liver Injury in Rats. *Pharmacologyonline*, 2020; 1: 248-260
8. Chen P, Zou F, Liu W. Recent advancement in prevention against hepatotoxicity, molecular mechanisms, and bioavailability of gallic acid, a natural phenolic compound: challenges and perspectives. Frontiers in Pharmacology. 2025;16. doi:10.3389/fphar.2025.1549526
9. Aja, P. M., Igwenyi, I. O., Ugwu, O. P. C., Orji, O. U., Alum, E. U. Evaluation of Anti-diabetic Effect and Liver Function Indices of Ethanol Extracts of *Moringa oleifera* and *Cajanus cajan* Leaves in Alloxan Induced Diabetic Albino Rats. Global Veterinaria 2015; 14(3): 439-447. DOI: 10.5829/idosi.gv.2015.14.03.93129.

10. Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, et al. The role of oxidative stress and antioxidants in liver diseases. International Journal of Molecular Sciences. 2015;16(11):26087–124. doi:10.3390/ijms161125942
11. Ukpabi-Ugo Jacinta Chigozie., Monanu, Michael Okechukwu., Patrick-Iwuanyanwu, Kingsley and Egbachukwu Simeon Ikechukwu. Potential hepatoprotective effect of different solvent fractions of *Ocimum gratissimum* (O G) in a paracetamol-induced hepatotoxicity in Wistar albino rats. *ScopeMed* 2016; 5(1): 10-16
12. Alum EU. Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy. KIU J. Health Sci. 2024; 4(2):71-84. https://doi.org/10.59568/KJHS-2024-4-2-06.
13. Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, Zam W, et al. Turmeric and its major compound curcumin on Health: Bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Frontiers in Pharmacology. 2020;11. doi:10.3389/fphar.2020.01021
14. Farzaei MH, Zobeiri M, Parvizi F, El-Senduny FF, Marmouzi I, Coy-Barrera E, et al. Curcumin in liver Diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients. 2018;10(7):855. doi:10.3390/nu10070855
15. Jaeschke H. Mitochondrial dysfunction as a mechanism of drug-induced hepatotoxicity: current understanding and future perspectives. Journal of Clinical and Translational Research. 2018. doi:10.18053/jctres.04.201801.005
16. Morio B, Panthu B, Bassot A, Rieusset J. Role of mitochondria in liver metabolic health and diseases. Cell Calcium. 2020;94:102336. doi:10.1016/j.ceca.2020.102336
17. Lukinich-Gruia AT, Calma CL, Szekely FAE, Cristea IM, Pricop MA, Simina AG, et al. Mitochondrial dysfunction in aristolochic acid I-Induced Kidney Diseases: What we know and what we do not know. Applied Sciences. 2024;14(17):7961. doi:10.3390/app14177961
18. Mansouri A, Gattolliat CH, Asselah T. Mitochondrial dysfunction and signaling in chronic liver diseases. Gastroenterology. 2018;155(3):629–47. doi:10.1053/J.GASTRO.2018.06.083
19. Eltahir H, Fawzy M, Mohamed E, Alrehany M, Shehata A, Abouzied M. Antioxidant, anti-inflammatory and anti-fibrotic effects of Boswellia serrate gum resin in CCl_4-induced hepatotoxicity. Experimental and Therapeutic Medicine. 2019. doi:10.3892/ETM.2019.8353
20. Yin Z, Song R, Yu T, Fu Y, Ding Y, Nie H. Natural compounds regulate macrophage polarization and alleviate inflammation against ALI/ARDS. Biomolecules. 2025;15(2):192. doi:10.3390/biom15020192
21. Sen A, Anakk S. Jekyll and Hyde: nuclear receptors ignite and extinguish hepatic oxidative milieu. Trends in Endocrinology and Metabolism. 2021;32(10):790–802. doi:10.1016/J.TEM.2021.07.009
22. Bakrim S, Omari NE, Khan EJ, Khalid A, Abdalla AN, Chook JB, et al. Phytosterols activating nuclear receptors are involving in steroid hormone-dependent cancers: Myth or fact? Biomedicine & Pharmacotherapy. 2023;169:115783. doi:10.1016/J.BIOPHA.2023.115783
23. Shalapy NM, Liu M, Kang W. Protective effects of hepatic diseases by bioactive phytochemicals in Fusarium oxysporum – A review. Heliyon. 2024;10(5):e26562. doi:10.1016/J.HELIYON.2024.E26562
24. Ogugua Victor Nwadiogbu., Uroko Robert Ikechukwu., Egba, Simeon Ikechukwu and Agu Obiora (2017) Hepatoprotective and Healthy Kidney Promoting Potentials of Methanol Extract of *Nauclea latifolia* in Alloxan Induced Diabetic Male Wistar Albino Rats. *Asian Journal of Biochemistry*,2017; 12: 71-78
25. Dhande D, Dhok A, Anjankar A, Nagpure S. Silymarin as an antioxidant therapy in Chronic liver diseases: A Comprehensive review. Cureus. 2024. doi:10.7759/cureus.67083
26. Surai P. Silymarin as a natural antioxidant: An overview of the current evidence and perspectives. Antioxidants. 2015;4(1):204–47. doi:10.3390/antiox4010204
27. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-Inflammatory action and mechanisms of resveratrol. Molecules. 2021;26(1):229. doi:10.3390/molecules26010229
28. Subramaniyan V, Lubau NSA, Mukerjee N, Kumarasamy V. Alcohol-induced liver injury in signalling pathways and curcumin's therapeutic potential. Toxicology Reports. 2023;11:355–67. doi:10.1016/j.toxrep.2023.10.005
29. Khan IM, Gul H, Khan S, Nassar N, Khalid A, Swelum AA, et al. Green tea polyphenol epigallocatechin-3-gallate mediates an antioxidant response via NRF2 Pathway in Heat-Stressed Poultry: a review. Poultry Science. 2025;104(5):105071. doi:10.1016/j.psj.2025.105071
30. Ogbonna OA., Egba, SI., Uhuo EN., Omeoga HC., Obeagu EI. Toxic outcomes of ciprofloxacin and gentamicin co-administration and possible ameliorating role for antioxidant vitamins C and E in Wistar Rats. Elite Journal of Medicine, 2024; 2(3): 1-14.
31. Thong-Ngam D. N-acetylcysteine attenuates oxidative stress and liver pathology in rats with non-alcoholic steatohepatitis. World Journal of Gastroenterology. 2007;13(38):5127. doi:10.3748/WJG.V13.I38.5127

32. Ntamo Y, Ziqubu K, Chellan N, Nkambule BB, Nyambuya TM, Mazibuko-Mbeje SE, et al. Drug-Induced liver injury: Clinical evidence of N-Acetyl cysteine protective effects. Oxidative Medicine and Cellular Longevity. 2021;2021(1). doi:10.1155/2021/3320325
33. Rodríguez-Negrete EV, Morales-González Á, Madrigal-Santillán EO, Sánchez-Reyes K, Álvarez-González I, Madrigal-Bujaidar E, et al. Phytochemicals and their usefulness in the maintenance of health. Plants. 2024;13(4):523. doi:10.3390/plants13040523
34. Alum EU. Sustainable harvesting of medicinal plants: balancing therapeutic benefits with environmental conservation. *Agroecology and Sustainable Food Systems*, 2024; 1–6. https://doi.org/10.1080/21683565.2024.2421948

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