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Hepatotoxicity and Nephrotoxicity of Polyherbal Mixtures: A Histopathological Review in Diabetic Contexts

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ABSTRACT

Polyherbal mixtures (PHMs) have gained significant attention in the management of diabetes mellitus due to their potential to provide a multifaceted approach to therapy. These mixtures, which often combine extracts from different plant species, possess diverse therapeutic effects, including antioxidant, anti-inflammatory, and hypoglycemic properties. The antioxidant action of PHMs helps neutralize free radicals, mitigating the oxidative stress that plays a crucial role in the pathogenesis of diabetes and its complications. Anti-inflammatory effects further reduce the chronic inflammation commonly seen in diabetic patients, while hypoglycemic properties aid in regulating blood glucose levels, making PHMs an attractive alternative or adjunct to conventional treatments. However, the growing popularity of PHMs has raised significant safety concerns, particularly regarding their potential to cause hepatotoxicity and nephrotoxicity. Both the liver and kidneys play essential roles in the detoxification, metabolism, and excretion of various xenobiotics, including those from herbal products. This makes these organs highly susceptible to damage induced by the phytochemicals present in PHMs. The review critically examines the histopathological changes observed in both liver and kidney tissues in diabetic models treated with PHMs. These include hepatocellular necrosis, fatty degeneration, tubular necrosis, and glomerular atrophy, as reported in both preclinical and clinical studies. Furthermore, the review discusses various risk factors contributing to PHM-induced toxicity, such as phytochemical interactions, bioaccumulation of toxic substances, lack of standardization in formulation, and variations in dosage. Emphasizing the importance of robust toxicological evaluations, the review advocates for the development of standardization protocols and regulatory oversight for the production and usage of PHMs. Ensuring their safety is critical for promoting their use as viable therapeutics in diabetic care.

Keywords: Polyherbal mixtures; Hepatotoxicity; Nephrotoxicity; Histopathology; Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that affects millions worldwide, characterized by sustained high blood glucose levels due to defects in insulin secretion, insulin action, or both [1]. Diabetes leads to serious complications, including cardiovascular disease, neuropathy, retinopathy, and nephropathy [2]. Furthermore, the management of diabetes remains challenging, with conventional therapies often providing insufficient control over blood glucose levels and posing various side effects. Polyherbal mixtures (PHMs), composed of combinations of plant extracts, have gained attention as alternative treatments due to their perceived efficacy and fewer side effects compared to synthetic drugs. Herbal medicines have been used for centuries in various cultures for their therapeutic benefits. In the context of diabetes, PHMs are particularly favored for their ability to offer multifaceted actions such as anti-inflammatory, antioxidant, anti-hyperglycemic, and insulin-sensitizing properties [3]. These mixtures often combine extracts from medicinal plants such as Vernonia amygdalina, Ocimum gratissimum, and Allium sativum, among others,

to improve glycemic control and reduce complications associated with the disease [4]. However, despite the promising effects of PHMs, their safety profiles remain poorly understood, especially concerning hepatotoxicity and nephrotoxicity. The liver and kidneys are critical organs responsible for the detoxification and excretion of metabolites, including phytochemicals from herbal products [5]. The presence of bioactive compounds such as flavonoids, alkaloids, and saponins in PHMs, while therapeutically beneficial, can lead to organ-specific toxicity [6]. This review aims to examine the histopathological changes induced by PHMs in diabetic models, focusing on liver and kidney damage, and to highlight the risk factors contributing to toxicity.

Polyherbal Formulations in Diabetes Management

The use of PHMs for diabetes management is rooted in the belief that these mixtures can provide a holistic approach to treating the disease. Traditionally, single herbal plants have been used for therapeutic purposes, but more recently, polyherbal formulations have been developed to maximize synergistic effects [7]. Polyherbal formulations often include several herbs, each contributing different therapeutic actions. For instance, Vernonia amygdalina has demonstrated hypoglycemic properties, while Ocimum gratissimum has antioxidant and anti-inflammatory effects, contributing to reduced oxidative stress in diabetic individuals [8]. One of the primary advantages of PHMs is their ability to target multiple pathways involved in the pathogenesis of diabetes [9]. These formulations can help: - Regulate blood glucose levels by inhibiting carbohydrate-digesting enzymes (e.g., alpha-glucosidase and alpha-amylase) [10], increase insulin sensitivity through modulation of insulin receptor signaling pathways [11] reduce oxidative stress by scavenging free radicals and reducing the load on the antioxidant defense system [12], modulate inflammation by inhibiting inflammatory cytokines like TNF-α and IL-6 [13] Nevertheless, despite these benefits, the safety of these herbal mixtures needs to be scrutinized, especially since many of them are taken long-term by diabetic patients. Safety concerns arise due to the risk of toxic effects on the liver and kidneys, which are central to detoxifying and processing many of the active components in PHMs [14]

Mechanisms of Hepatotoxicity Induced by Polyherbal Mixtures

The liver is the principal organ responsible for metabolizing various compounds, including the phytochemicals found in herbal formulations [15]. As such, it is particularly vulnerable to the toxic effects of these substances. Hepatotoxicity from PHMs is commonly linked to oxidative stress, disruption of cellular integrity, and inflammation.

Oxidative Stress and Inflammatory Pathways

Phytochemicals such as flavonoids, alkaloids, and tannins, while beneficial in therapeutic doses, can induce oxidative stress in higher concentrations [16]. This stress results from the excessive production of reactive oxygen species (ROS), which damage cellular components, including lipids, proteins, and DNA [17]. In the liver, this leads to hepatocellular damage, manifested as necrosis, fatty degeneration (steatosis), and fibrosis [17]. Studies have shown that PHMs containing Vernonia amygdalina, for example, can induce lipid peroxidation, contributing to liver dysfunction and cellular damage [18]. Furthermore, inflammation plays a critical role in the pathogenesis of hepatotoxicity. Many PHMs trigger the release of pro-inflammatory cytokines such as TNF-α and IL-1, which exacerbate liver injury by promoting cellular apoptosis and fibrosis [13]

Mitochondrial Dysfunction

The liver's detoxifying function heavily relies on mitochondria, which produce energy and regulate apoptosis [19]. PHMs, especially those with high concentrations of alkaloids, can disrupt mitochondrial function, leading to energy depletion and further exacerbating hepatic injury [20]. Dysfunctional mitochondria also release cytochrome c, initiating caspase activation and programmed cell death (apoptosis) in hepatocytes [21].

Mechanisms of Nephrotoxicity Induced by Polyherbal Mixtures

The kidneys are critical organs for maintaining homeostasis by filtering blood, excreting waste products, and regulating electrolytes [22]. However, they are also highly susceptible to damage from the phytochemicals present in polyherbal mixtures (PHMs) [22]. Nephrotoxicity induced by PHMs is commonly observed in diabetic animal models and is linked to oxidative stress, inflammatory processes, and structural changes that compromise renal function [23]. These toxic effects can lead to long-term damage if not properly addressed.

Renal Tubular Damage

One of the most frequently observed histopathological changes in PHM-induced nephrotoxicity is tubular necrosis, often accompanied by vacuolar degeneration and cell sloughing [24]. These alterations occur due

to the accumulation of bioactive compounds from the herbal mixture within renal tubular cells. The resulting oxidative stress damages cellular structures, including mitochondria and the plasma membrane, which are essential for maintaining renal tubular cell integrity [25]. This oxidative damage leads to cell apoptosis or necrosis, contributing to dysfunction in the kidney's filtration ability. In addition, tubular cells may become obstructed due to sloughing, further impairing kidney function and exacerbating renal injury [26].

Glomerular Atrophy and Interstitial Fibrosis

Another critical effect of PHM-induced nephrotoxicity is the presence of glomerular atrophy and interstitial fibrosis. Glomerular atrophy refers to the shrinking and loss of function of the glomeruli, which are essential for the filtration of blood [27]. Oxidative stress in the glomeruli can damage endothelial cells, podocytes, and the glomerular basement membrane, impairing their ability to filter blood effectively [28]. As the kidney attempts to repair itself, fibrotic changes in the renal interstitium may occur, characterized by the accumulation of extracellular matrix proteins such as collagen [29]. These fibrotic changes are often a response to chronic inflammation, which is promoted by the persistent presence of phytochemicals that induce inflammatory cytokine release [30]. Over time, fibrosis can lead to the progressive decline in kidney function, contributing to renal failure if left untreated [31].

Risk Factors Influencing Toxicity of Polyherbal Mixtures

The toxicity of polyherbal mixtures (PHMs) can be influenced by various factors that contribute to their safety and efficacy. These factors include:

Lack of Standardization

One of the primary concerns regarding the safety of PHMs is the variability in their composition. Unlike pharmaceutical drugs, which undergo rigorous standardization processes, the quality and concentration of bioactive compounds in PHMs can vary significantly depending on the source of the plants, the preparation methods, and the dosage used [32]. This lack of standardization increases the likelihood of unpredictable outcomes, such as unanticipated toxic effects, as patients may receive inconsistent amounts of active compounds with each dose [33]. This inconsistency in formulation can also complicate the determination of safe therapeutic doses and effective treatment regimens.

Bioaccumulation of Heavy Metals

Another significant risk factor for PHM toxicity is the potential for heavy metal contamination. Many medicinal herbs are grown in environments with polluted soil or water, leading to the accumulation of toxic metals such as lead, arsenic, and cadmium in plant tissues [34]. These metals can then be transferred to humans when consumed, potentially causing organ toxicity, particularly in the liver and kidneys [35]. Over time, bioaccumulation of heavy metals can result in chronic poisoning, contributing to long-term health complications.

Herb-Drug Interactions

Diabetic patients often take various medications, including insulin and oral hypoglycemic agents, to control their blood glucose levels. When combined with PHMs, these medications may interact with the bioactive compounds in the herbal mixtures. Such interactions can alter the pharmacokinetics of the drugs, affecting their absorption, metabolism, or excretion, potentially leading to reduced efficacy or increased toxicity [36]. For example, certain phytochemicals may enhance the hypoglycemic effect of oral agents, leading to dangerously low blood sugar levels [37].

High Dosage and Long-term Use

Chronic use of PHMs, especially in high doses, can significantly increase the risk of toxicity. Prolonged exposure to high levels of certain bioactive compounds, such as alkaloids or flavonoids, can overwhelm the body's natural detoxification mechanisms, particularly the liver and kidneys [38,39]. This can lead to bioaccumulation of harmful substances and result in organ damage over time. The risks are compounded in diabetic patients, whose organ function may already be compromised due to the disease itself [39].

Recommendations for Safer Use of Polyherbal Mixtures

To mitigate the risks associated with PHMs, the following recommendations are suggested:

Comprehensive Phytochemical Profiling: Accurate identification and quantification of bioactive compounds in PHMs can help assess potential toxicity and ensure safe use.

Standardization of Formulation Protocols: Clear guidelines for the preparation, dosage, and administration of PHMs should be established to minimize variability and maximize therapeutic efficacy.

Toxicological Screening: Rigorous preclinical and clinical trials should be conducted to evaluate the hepatotoxic and nephrotoxic effects of PHMs across different doses and durations of use.

Regulatory Oversight: Governments and health authorities should regulate PHM production and usage to ensure that only safe and effective products reach the market.
Pharmacovigilance Systems: Post-market surveillance and reporting of adverse effects should be strengthened to detect and manage potential toxicity in real-world settings.

CONCLUSION

Polyherbal mixtures represent a promising alternative in the management of diabetes mellitus. However, their potential hepatotoxic and nephrotoxic effects necessitate careful evaluation. Histopathological evidence indicates that while PHMs can provide therapeutic benefits, they also pose risks to liver and kidney health, especially in diabetic individuals. Further research into the toxicological mechanisms and standardization of PHMs is essential to enhance their safety and efficacy.

REFERENCES

1. Goyal R, Singhal M, Jialal I. Type 2 diabetes. In: StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/
2. Alum, E. U., Krishnamoorthy, R., Gatasheh, M. K., Subbarayan, S., Vijayalakshmi, P., Uti, D. E. Protective Role of Jimson Weed in Mitigating Dyslipidemia, Cardiovascular, and Renal Dysfunction in Diabetic Rat Models: In Vivo and in Silico Evidence. Natural Product Communications. 2024;19(12). doi:10.1177/1934578X241299279
3. Tran N, Pham B, Le L. Bioactive Compounds in Anti-Diabetic Plants: From Herbal Medicine to Modern drug discovery. Biology. 2020;9(9):252. doi:10.3390/biology9090252
4. 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
5. Mancak M. Evidence-based herbal treatments in liver diseases. Hepatology Forum. 2023:50–60. doi:10.14744/hf.2022.2022.0052
6. Roy A, Khan A, Ahmad I, Alghamdi S, Rajab BS, Babalghith AO, et al. Flavonoids a Bioactive Compound from Medicinal Plants and Its Therapeutic Applications. BioMed Research International. 2022:1–9. doi:10.1155/2022/5445291
7. Mitaki, N.B., Fasogbon, I.V., Ojiakor, O.V., Makena, W., Ikuomola, E. O., Dangana, R.S., et al. A systematic review of plant-based therapy for the management of diabetes mellitus in the East Africa community. Phytomedicine Plus, 2025; 5(1): 100717. https://doi.org/10.1016/j.phyplu.2024.100717
8. Okon UA, Umoren IU. Comparison of antioxidant activity of insulin, Ocimum gratissimum L., and Vernonia amygdalina L. in type 1 diabetic rat model. Journal of Integrative Medicine. 2017;15(4):302–9. doi:10.1016/S2095-4964(17)60332-7
9. Sameer A, Banday M, Nissar S. Pathophysiology of diabetes: An overview. Avicenna Journal of Medicine. 2020;10(4):174. doi:10.4103/ajm.ajm_53_20
10. Balachandran A, Okechukwu PN, Gunasekaran B, Małgorzata J, Beata MM, Froemming GRA, et al. Herb5GluCon: A Novel Polyherbal Formulation with Dual-Action Inhibiting Properties Against Oxidative Stress and Glycoside Hydrolases – An In silico and In vitro Approach. Phytomedicine Plus. 2024:100716. doi:10.1016/j.phyplu.2024.100716
11. Aslam B, Hussain A, Faisal MN, Kousar S, Roobi A, Sajid MR, et al. Polyherbal extract improves glycometabolic control in alloxan-induced diabetic rats. PubMed. 2024;27(2):170–9. Available from: https://pubmed.ncbi.nlm.nih.gov/38234664
12. Essola NN, Takuissu GRN, Fonkoua M, Fotso JAY, Mandob D, Ngondi JL, et al. Effectiveness of 3 polyherbal formulations (ECXAPU, ECXA, and ECPU) on the management of oxidative stress and hyperglycemia. Nutrition and Metabolic Insights. 2022;15. doi:10.1177/11786388221118875
13. Nisar A, Jagtap S, Vyavahare S, Deshpande M, Harsulkar A, Ranjekar P, et al. Phytochemicals in the treatment of inflammation-associated diseases: the journey from preclinical trials to clinical practice. Frontiers in Pharmacology. 2023;14. doi:10.3389/fphar.2023.1177050
14. 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
15. 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

16. Uroko Robert Ikechukwu., Agbafor Amarachi, Uchenna Oluomachi Nancy, Achi Ngozi Kalu, Egba Simeon Ikechukwu, Nweje-Anyalowu Paul Chukwuemaka and Ngwu Ogochukwu Rita. Evaluation of Antioxidant Activity of Aqueous Extracts of Palm Friuts *(Elaeis guineensis)* Asian Journal of Biochemistry, 2017; 12: 49-57
17. Ochulor Okechukwu C., Njoku Obioma U., Uroko Robert I and Egba Simeon I. Nutritional composition of *Jatropha tanjorensis* leaves and effects of its aqueous extract on carbon tetrachloride induced oxidative stress in male Wistar albino rats. Biomedical Research 2018; 29(19): 3569-3576
18. Tokofai BM, Idoh K, Oke OE, Agbonon A. Hepatoprotective Effects of Vernonia amygdalina (Astereaceae) Extract on CCl4-Induced Liver Injury in Broiler Chickens. Animals. 2021;11(12):3371. doi:10.3390/ani11123371
19. Esposti DD, Hamelin J, Bosselut N, Saffroy R, Sebagh M, Pommier A, et al. Mitochondrial roles and cytoprotection in chronic liver injury. Biochemistry Research International. 2012;2012:1–16. doi:10.1155/2012/387626
20. Uroko RI., Egba SI., Uchenna ON., Ojiakor CA., Agbafor A., and Alaribe, CA (2018) Therapeutic effects of methalonic extracts of Funtumia Africana leaves on antioxidants and hematological indices of carbon tetra chloride induced oxidative stress on rats. Drug Invention Today 12(1)
21. Kari S, Subramanian K, Altomonte IA, Murugesan A, Yli-Harja O, Kandhavelu M. Programmed cell death detection methods: a systematic review and a categorical comparison. APOPTOSIS. 2022;27(7–8):482–508. doi:10.1007/s10495-022-01735-y
22. Egba, SI., Ogbodo, JO., Ogbodo PO and Obike CA (2017) Toxicological Evaluation of Two Named Herbal Remedies Sold Across Orumba South Local Government of Anambra State, South-Eastern Nigeria. Asian Journal of Research in Biochemistry, 1(1):1-6
23. Al-Kuraishy H, Al-Naimi M, Rasheed H, Hussien N, Al-Gareeb A. Nephrotoxicity: Role and significance of renal biomarkers in the early detection of acute renal injury. Journal of Advanced Pharmaceutical Technology & Research. 2019;10(3):95. doi:10.4103/japtr.japtr_336_18
24. Hanif MO, Bali A, Ramphul K. Acute renal tubular necrosis. In: StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507815/
25. Ranasinghe R, Mathai M, Zulli A. Cytoprotective remedies for ameliorating nephrotoxicity induced by renal oxidative stress. Life Sciences. 2023;318:121466. doi:10.1016/j.lfs.2023.121466
26. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Comprehensive Physiology. 2012:1303–53. doi:10.1002/cphy.c110041
27. Murray IV, Paolini MA. Histology, kidney and glomerulus. In: StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554544/
28. Rabelink TJ, Heerspink HJL, De Zeeuw D. The Pathophysiology of proteinuria. In: Elsevier eBooks. 2014. p. 92–105. doi:10.1016/b978-0-12-411602-3.00009-3
29. Huang R, Fu P, Ma L. Kidney fibrosis: from mechanisms to therapeutic medicines. Signal Transduction and Targeted Therapy. 2023;8(1). doi:10.1038/s41392-023-01379-7
30. Ikechukwu ES, Polycarp NO, Patricia EM, Gavin CI, Humphrey CO, Chukwuka WE. Toxicological Evaluation and Possible Reversal of Diabetic Toxicological Complications by PHF5 an Antidiabetic Herbal Formula in Wistar Albino Rats. Asian J. Res. Biochem. 2021 8(3):34-43. Available from: https://journalajrb.com/index.php/AJRB/article/view/125
31. Liu Y. Renal fibrosis: New insights into the pathogenesis and therapeutics. Kidney International. 2006;69(2):213–7. doi:10.1038/sj.ki.5000054
32. Uti DE, Atangwho IJ, Alum EU, Egba SI, Ugwu OP-C, Ikechukwu GC. Natural Antidiabetic Agents: Current Evidence and Development Pathways from Medicinal Plants to Clinical use. Natural Product Communications. 2025;20(3). doi:10.1177/1934578X251323393
33. Wang H, Chen Y, Wang L, Liu Q, Yang S, Wang C. Advancing herbal medicine: enhancing product quality and safety through robust quality control practices. Frontiers in Pharmacology. 2023;14. doi:10.3389/fphar.2023.1265178
34. Ogbodo, John Onyebuchi, Egba, Simeon Ikechukwu., Ogbodo, Chizaramekpere Grace., Onwurah Ikechukwu, Emmanuel and Njoku, Obioma Uzoma. Effects of Exposure to Volatile Organic Compounds (VOCS) Content From Paint on Automobile Paint Workers in Nsukka, South Eastern Nigeria. Heliyon 2024; 10(17) e37015

35. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Frontiers in Pharmacology. 2021;12. doi:10.3389/fphar.2021.643972
36. Rombolà L, Scuteri D, Marilisa S, Watanabe C, Morrone LA, Bagetta G, et al. Pharmacokinetic Interactions between Herbal Medicines and Drugs: Their Mechanisms and Clinical Relevance. Life. 2020;10(7):106. doi:10.3390/life10070106
37. Golovinskaia O, Wang CK. The hypoglycemic potential of phenolics from functional foods and their mechanisms. Food Science and Human Wellness. 2022;12(4):986–1007. doi:10.1016/j.fshw.2022.10.020
38. Eze Chukwuka W., Egba Simeon, Nweze Emeka I., Ezeh Richard C. and Ugwudike Patrick. Ameliorative Effects of *Allium cepa* and *Allium sativum* on Diabetes Mellitus and Dyslipidemia in Alloxan-induced Diabetic *Rattus novergicus*. *Trends Applied Sci Res*, 2020; 15(2): 145-150
39. Islas JF, Acosta E, G-Buentello Z, Delgado-Gallegos JL, Moreno-Treviño MG, Escalante B, et al. An overview of Neem (Azadirachta indica) and its potential impact on health. Journal of Functional Foods. 2020;74:104171. doi:10.1016/j.jff.2020.104171

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