©IDOSR PUBLICATIONS

ISSN: 2579-079X

International Digital Organization for Scientific Research IDOSR JST/26/1130000
IDOSR JOURNAL OF SCIENCE AND TECHNOLOGY 12(1):109-113, 2026.
https://doi.org/10.59298/IDOSR/JST/26/113.109113

Hepatoprotective Mechanisms of Natural Antioxidants in Diabetes-Induced Liver Dysfunction

Kamanzi Ntakirutimana G.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, insulin resistance, and impaired glucose homeostasis. Among its complications, liver dysfunction is common, often manifesting as non-alcoholic fatty liver disease, steatohepatitis, oxidative damage, inflammation, and fibrosis. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defenses, plays a central role in diabetic liver injury. ROS damage hepatocyte membranes, proteins, and DNA, triggering apoptosis, inflammation, and mitochondrial dysfunction. Natural antioxidants from plants, fruits, and dietary sources offer hepatoprotective effects by scavenging ROS, enhancing enzymes like superoxide dismutase, catalase, and glutathione peroxidase, modulating inflammatory pathways such as NF-κB and MAPK, and improving lipid and glucose metabolism. Preclinical and limited clinical studies demonstrate reductions in oxidative stress, improved liver function, and preservation of hepatocyte integrity. Optimizing bioavailability, dosing, and long-term safety is essential for clinical translation of these therapies.

Keywords: Diabetes mellitus, oxidative stress, natural antioxidants, hepatoprotection, liver dysfunction

INTRODUCTION

Diabetes mellitus is a major global health challenge, affecting millions of individuals worldwide and contributing to significant morbidity and mortality [1]. Beyond its well-known metabolic and vascular complications, the liver is increasingly recognized as a key target organ affected by chronic hyperglycemia and insulin resistance [2]. Diabetic liver injury commonly manifests as non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH), fibrosis, and ultimately cirrhosis if left unchecked [3]. Hepatic dysfunction in diabetes arises from the combined effects of lipid accumulation, oxidative stress, inflammation, and mitochondrial impairment [4]. Oxidative stress plays a central role in the pathogenesis of diabetes-induced liver injury [5]. Excess glucose and fatty acid metabolism in hepatocytes increases the generation of reactive oxygen species, which overwhelm endogenous antioxidant systems [6]. These ROS damage cellular membranes through lipid peroxidation, impair protein function via oxidation, and induce DNA strand breaks, ultimately leading to hepatocyte apoptosis or necrosis [7]. ROS also trigger activation of inflammatory transcription factors, such as NF-κB and c-Jun N-terminal kinase (JNK), which exacerbate cytokine release, immune cell recruitment, and liver tissue injury [8]. In addition, mitochondrial dysfunction in diabetic hepatocytes amplifies ROS production, while endoplasmic reticulum stress and defective autophagy further compromise cellular homeostasis [9].

Natural antioxidants, obtained from plants, fruits, vegetables, and other dietary sources, have emerged as promising hepatoprotective agents in diabetes. Bioactive compounds such as polyphenols, flavonoids, carotenoids, and vitamins exert multiple protective actions. They neutralize ROS directly, enhance endogenous antioxidant enzyme activities, reduce inflammation, and restore metabolic balance within hepatocytes [10]. These multifaceted effects make natural antioxidants attractive candidates for preventing or mitigating diabetes-induced liver injury. Experimental studies have consistently demonstrated the capacity of these compounds to reduce lipid peroxidation, preserve mitochondrial function, suppress inflammatory signaling, and improve overall hepatic architecture in diabetic models. Translating these findings into clinical practice, however, requires addressing challenges such as bioavailability, dosing, and long-term safety. This review provides a detailed overview of the mechanisms by which natural antioxidants protect the liver under diabetic conditions, evaluates supporting experimental and clinical evidence, and discusses current limitations and future directions for antioxidant-based hepatoprotective strategies.

2. Mechanisms of Diabetes-Induced Liver Dysfunction

Chronic hyperglycemia and insulin resistance in diabetes drive several interconnected pathological processes in the liver, ultimately contributing to hepatocyte injury and functional impairment. One of the primary mechanisms is oxidative stress [11]. Elevated glucose and fatty acid flux through mitochondrial oxidative phosphorylation increases the production of reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and hydrogen peroxide [12]. These reactive molecules attack cellular lipids, proteins, and nucleic acids, leading to lipid peroxidation, protein oxidation, DNA damage, and the activation of apoptotic pathways [12]. Persistent oxidative stress overwhelms hepatocyte defenses, contributing to cell death and tissue injury [13]. Insulin resistance also promotes hepatic lipid accumulation [14]. Dysregulated lipogenesis and impaired fatty acid oxidation result in steatosis, which itself enhances ROS generation and triggers inflammatory responses [15]. The accumulation of triglycerides and other lipids within hepatocytes establishes a feed-forward loop, amplifying oxidative damage and sustaining chronic inflammation [16].

Inflammatory signaling is closely intertwined with oxidative stress in diabetic livers. ROS activate pro-inflammatory transcription factors, particularly nuclear factor kappa B (NF-κB), which increases the expression of cytokines such as tumor necrosis factor-alpha and interleukin-6 [17]. This cytokine surge recruits immune cells into hepatic tissue, intensifying inflammation and exacerbating hepatocyte injury. The combination of oxidative stress and inflammation not only damages parenchymal cells but also alters the liver microenvironment, promoting fibrosis and impaired metabolic regulation [18].

Mitochondrial dysfunction is another central feature of diabetic liver injury. Excessive ROS damages mitochondrial DNA and respiratory proteins, impairing oxidative phosphorylation and reducing ATP synthesis [19]. Dysfunctional mitochondria generate additional ROS, creating a vicious cycle that compromises hepatocyte energy homeostasis and increases susceptibility to apoptosis [20]. Furthermore, mitochondrial impairment interferes with fatty acid oxidation, worsening lipid accumulation and contributing to non-alcoholic fatty liver disease progression [21].

Endoplasmic reticulum (ER) stress is also a key mechanism in diabetes-induced liver dysfunction. High glucose and ROS perturb protein folding in the ER, triggering the unfolded protein response. Chronic ER stress activates apoptotic signaling pathways, further reducing hepatocyte viability and contributing to liver injury [22]. Together, oxidative stress, lipid accumulation, inflammation, mitochondrial dysfunction, and ER stress converge to drive the progression of diabetic liver disease.

3. Hepatoprotective Mechanisms of Natural Antioxidants

Natural antioxidants protect the liver in diabetes through several complementary mechanisms. They directly scavenge ROS, neutralizing free radicals before they can damage lipids, proteins, or DNA, thereby preserving cellular membranes and maintaining hepatocyte integrity [23]. Polyphenols such as those found in green tea, resveratrol, and other plant-derived compounds have been shown to reduce lipid peroxidation and malondialdehyde levels in experimental models of diabetic liver injury [25]. In addition to direct ROS neutralization, natural antioxidants enhance endogenous defense systems. Compounds including quercetin, curcumin, and vitamin E upregulate hepatic antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, restoring redox balance and improving the liver's capacity to manage oxidative insults [25].

Natural antioxidants also exert anti-inflammatory effects by inhibiting key signaling pathways such as NF-κB and mitogen-activated protein kinase [26]. Suppression of these pathways reduces the production of pro-inflammatory cytokines, limits immune cell infiltration, and prevents further hepatocyte injury. Furthermore, antioxidants modulate lipid metabolism. Activation of AMP-activated protein kinase signaling enhances fatty acid oxidation and suppresses lipogenesis, mitigating steatosis and preventing the establishment of lipid-driven oxidative damage [27]. Mitochondrial protection is another critical aspect, as antioxidants stabilize mitochondrial membrane potential, reduce ROS generation, and improve ATP synthesis, thereby supporting hepatocyte energy balance and survival [28].

Lastly, natural antioxidants have anti-fibrotic effects. By decreasing oxidative stress and inflammation, they inhibit the activation of hepatic stellate cells, reduce extracellular matrix deposition, and slow fibrosis progression [29]. These multifaceted actions make natural antioxidants highly valuable in mitigating the complex hepatic injury observed in diabetes and provide a mechanistic basis for their therapeutic potential in protecting liver function under diabetic conditions.

Challenges and Future Directions

Despite substantial preclinical and emerging clinical evidence supporting the hepatoprotective potential of natural antioxidants in diabetes, several challenges must be addressed before their widespread clinical application can be realized. One major limitation is bioavailability and metabolism. Many plant-derived antioxidants, including polyphenols and flavonoids, exhibit poor oral absorption, rapid gastrointestinal metabolism, and limited tissue distribution [30]. Consequently, the effective concentration reaching the liver may be insufficient to achieve

therapeutic effects. To overcome this, advanced delivery strategies such as encapsulation in nanoparticles, liposomal formulations, polymer conjugates, and other targeted delivery systems are being investigated. These approaches aim to improve stability, prolong circulation time, and enhance hepatic uptake of bioactive compounds [31].

Dose optimization is another critical consideration. While antioxidants are generally regarded as safe at moderate doses, excessive intake may paradoxically induce pro-oxidant effects, exacerbating oxidative stress and cellular injury. Establishing the therapeutic window for different antioxidants, alone or in combination, is therefore essential to maximize efficacy while minimizing risks. Long-term studies assessing cumulative effects are particularly needed in the context of chronic conditions such as diabetes. Interindividual variability also presents a significant challenge. Genetic differences in antioxidant enzyme expression, polymorphisms affecting metabolism, comorbidities, dietary patterns, and gut microbiota composition can all influence how individuals respond to antioxidant interventions. Personalized approaches that consider these factors may enhance therapeutic outcomes and reduce variability in clinical response [32].

Another limitation is the scarcity of large-scale, long-term clinical trials. Many studies to date have small sample sizes, short durations, or heterogeneity in antioxidant formulations, making it difficult to draw definitive conclusions regarding efficacy, safety, and optimal therapeutic protocols. Future research should emphasize standardized preparations, precise dosing regimens, combination therapies with conventional diabetes management strategies, and rigorous evaluation of biochemical, histological, and clinical endpoints. Mechanistic studies integrating omics technologies and systems biology approaches may also provide insights into the complex interactions between oxidative stress, hepatic metabolism, and antioxidant action.

Addressing these challenges will be critical to translating promising experimental findings into effective, evidence-based therapies for diabetic liver dysfunction. Integration of antioxidant therapy into comprehensive management strategies, including glycemic control, lifestyle modification, and pharmacological interventions, has the potential to enhance outcomes and mitigate progression of liver injury.

CONCLUSION

Oxidative stress is a central mediator of diabetes-induced liver dysfunction, driving hepatocyte injury, lipid accumulation, inflammation, mitochondrial impairment, and fibrosis. Natural antioxidants offer multi-targeted hepatoprotective effects through direct ROS scavenging, enhancement of endogenous antioxidant defenses, suppression of inflammatory signaling, modulation of lipid metabolism, preservation of mitochondrial function, and inhibition of fibrogenesis. Experimental studies in animal models consistently demonstrate reductions in oxidative stress, improvements in hepatic enzyme activity, preservation of hepatocyte structure, and attenuation of steatosis and fibrosis. Emerging clinical evidence suggests similar benefits, including improved liver enzyme profiles, reduced oxidative stress biomarkers, and decreased hepatic fat content. To fully realize the therapeutic potential of natural antioxidants, challenges such as limited bioavailability, dose optimization, interindividual variability, and long-term safety must be addressed. Continued research focusing on standardized formulations, targeted delivery systems, combination therapies, and large-scale randomized clinical trials is essential. Overall, natural antioxidants represent a promising adjunct strategy to mitigate oxidative stress and preserve liver function in diabetes, offering a multi-faceted approach to complement conventional interventions and improve metabolic and hepatic outcomes.

REFERENCES

1. Uti DE, Atangwho IJ, Alum EU, Egba SI, Ugwu OPC, 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
2. Umoru, G. U., Uti, D. E., Aja, P. M., Ugwu, O. P., Orji, O. U., Nwali, B. U., Ezeani, N., Edwin, N., Orinya, F. O. Hepato-protective effect of Ethanol Leaf Extract of *Datura stramonium* in Alloxan-induced Diabetic Albino Rats. *Journal of Chemical Society of Nigeria*. 2022; 47 (3): 1165 – 1176. https://doi.org/10.46602/jcsn.v47i5.819.
3. 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.
4. 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
5. Ugwu, O. P. C., Alum, E. U. and Uhama, K. C. (2024). Dual Burden of Diabetes Mellitus and Malaria: Exploring the Role of Phytochemicals and Vitamins in Disease Management. Research Invention Journal of Research in Medical Sciences. 3(2):38-49.
6. Zhang Z, Yang H, Han F, Guo P. Reactive oxygen species as key molecules in the pathogenesis of alcoholic fatty liver disease and nonalcoholic fatty liver disease: future perspectives. Current Issues in Molecular Biology. 2025;47(6):464. doi:10.3390/cimb47060464

7. Alum, E.U., Uti, D.E. & Offor, C.E. Redox Signaling Disruption and Antioxidants in Toxicology: From Precision Therapy to Potential Hazards. *Cell Biochem Biophys* (2025). https://doi.org/10.1007/s12013-025-01846-8
8. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxidants and Redox Signaling. 2013;20(7):1126–67. doi:10.1089/ars.2012.5149
9. Veluthakal R, Esparza D, Hoolachan JM, Balakrishnan R, Ahn M, Oh E, et al. Mitochondrial dysfunction, oxidative stress, and Inter-Organ miscommunications in T2D progression. International Journal of Molecular Sciences. 2024;25(3):1504. doi:10.3390/ijms25031504
10. Clemente-Suárez VJ, Martín-Rodríguez A, Beltrán-Velasco AI, Rubio-Zarapuz A, Martínez-Guardado I, Valcárcel-Martín R, et al. Functional and therapeutic roles of Plant-Derived antioxidants in Type 2 diabetes mellitus: Mechanisms, challenges, and considerations for special populations. Antioxidants. 2025;14(6):725. doi:10.3390/antiox14060725
11. Ikpozu EN, Offor CE, Igwenyi, I.O, Ibiam, U.A., Obaroh, I.O. et al. RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 2025;22(2). doi:10.1177/14791641251334726
12. De Almeida AJPO, De Oliveira JCPL, Da Silva Pontes LV, De Souza Júnior JF, Gonçalves TAF, Dantas SH, et al. ROS: Basic Concepts, Sources, Cellular Signaling, and its Implications in Aging Pathways. Oxidative Medicine and Cellular Longevity. 2022;2022:1–23. doi:10.1155/2022/1225578
13. Mello T, Zanieri F, Ceni E, Galli A. Oxidative stress in the healthy and wounded hepatocyte: A Cellular Organelles perspective. Oxidative Medicine and Cellular Longevity. 2015;2016(1). doi:10.1155/2016/8327410
14. Onyango AN. Excessive gluconeogenesis causes the hepatic insulin resistance paradox and its sequelae. Heliyon. 2022;8(12):e12294. doi:10.1016/j.heliyon.2022.e12294
15. Izah, S.C., Betiang, P.A., Ugwu, O.P.C., Ainebyoona, C., Uti, D.E., Echegu, D.A., Alum, B.N. The Ketogenic Diet in Obesity Management: Friend or Foe?. *Cell Biochem Biophys* (2025). https://doi.org/10.1007/s12013-025-01878-0
16. Alum, E.U. Circadian nutrition and obesity: timing as a nutritional strategy. *J Health Popul Nutr* **44**, 367 (2025). https://doi.org/10.1186/s41043-025-01102-y
17. Lingappan K. NF-κB in oxidative stress. Current Opinion in Toxicology. 2017;7:81–6. doi:10.1016/j.cotox.2017.11.002
18. 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
19. Iheagwam FN, Joseph AJ, Adedoyin ED, Iheagwam OT, Ejoh SA. Mitochondrial dysfunction in diabetes: shedding light on a widespread oversight. Pathophysiology. 2025;32(1):9. doi:10.3390/pathophysiology32010009
20. Guo C, Sun L, Chen X, Zhang D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. PubMed. 2013;8(21):2003–14. Available from: https://pubmed.ncbi.nlm.nih.gov/25206509
21. Zheng Y, Wang S, Wu J, Wang Y. Mitochondrial metabolic dysfunction and non-alcoholic fatty liver disease: new insights from pathogenic mechanisms to clinically targeted therapy. Journal of Translational Medicine. 2023;21(1). doi:10.1186/s12967-023-04367-1
22. Amen OM, Sarker SD, Ghildyal R, Arya A. Endoplasmic reticulum stress activates unfolded protein response signaling and mediates inflammation, obesity, and cardiac dysfunction: therapeutic and Molecular approach. Frontiers in Pharmacology. 2019;10. doi:10.3389/fphar.2019.00977
23. Godfrey Ogochukwu Ezema, Ndukaku Yusuf Omeh, Egba Simeon Ikechukwu, Ejiofor C Agbo, Adachukwu Ada Ikeyiand Emmanuel Ifeanyi Obeagu. Evaluation of Biochemical Parameters of Patients with Type 2 Diabetes Mellitus Based on Age and Gender in Umuahia (2023) Asian Journal of Dental and Health Sciences 2023; 3(2):32-36
24. Krawczyk M, Burzynska-Pedziwiatr I, Wozniak LA, Bukowiecka-Matusiak M. Impact of polyphenols on inflammatory and oxidative stress factors in diabetes mellitus: nutritional antioxidants and their application in improving antidiabetic therapy. Biomolecules. 2023;13(9):1402. doi:10.3390/biom13091402
25. Bouyahya A, Bakrim S, Aboulaghras S, Kadri KE, Aanniz T, Khalid A, et al. Bioactive compounds from nature: Antioxidants targeting cellular transformation in response to epigenetic perturbations induced by oxidative stress. Biomedicine & Pharmacotherapy. 2024;174:116432. doi:10.1016/j.biopha.2024.116432
26. Clemente-Suárez VJ, Martín-Rodríguez A, Beltrán-Velasco AI, Rubio-Zarapuz A, Martínez-Guardado I, Valcárcel-Martín R, et al. Functional and therapeutic roles of Plant-Derived antioxidants in Type 2 diabetes mellitus: Mechanisms, challenges, and considerations for special populations. Antioxidants. 2025;14(6):725. doi:10.3390/antiox14060725

27. Arroyave-Ospina JC, Wu Z, Geng Y, Moshage H. Role of oxidative stress in the pathogenesis of Non-Alcoholic fatty liver disease: Implications for prevention and therapy. Antioxidants. 2021;10(2):174. doi:10.3390/antiox10020174
28. Shi S, Wang L, Van Der Laan LJW, Pan Q, Verstegen MMA. Mitochondrial dysfunction and oxidative stress in liver transplantation and underlying Diseases: New insights and therapeutics. Transplantation. 2021;105(11):2362–73. doi:10.1097/tp.0000000000003691
29. Ciceu A, Fenyvesi F, Hermenean A, Ardelean S, Dumitra S, Puticiu M. Advancements in Plant-Based Therapeutics for Hepatic Fibrosis: molecular mechanisms and nanoparticulate drug delivery systems. International Journal of Molecular Sciences. 2024;25(17):9346. doi:10.3390/ijms25179346
30. Chimaroke Onyeabo, Paul Anyiam Ndubuisi, Anthony Cemaluk Egbuonu, Prince Chimezie Odika, Simeon Ikechukwu Egba, Obedience Okon Nnana, Polycarp Nnacheta Okafor. Natural products-characterized Moringa oleifera leaves methanolic extractand anti-diabetic properties mechanisms of its fractions in streptozotocin-induced diabetic rats The Nigerian Journal of Pharmacy, 2022; 56(1):18-29
31. Nwuruku, O.A., Ugwu, O.P.-C., Uti, D.E., Edwin, N.: Harnessing nature: plant-derived nanocarriers for targeted drug delivery in cancer therapy. Phytomedicine Plus. 5, 100828 (2025). https://doi.org/10.1016/j.phyplu.2025.100828
32. Alum, E.U. Optimizing patient education for sustainable self-management in type 2 diabetes. *Discov Public Health* **22**, 44 (2025). https://doi.org/10.1186/s12982-025-00445-5

CITE AS: Kamanzi Ntakirutimana G. (2026). Hepatoprotective Mechanisms of Natural Antioxidants in Diabetes-Induced Liver Dysfunction.
IDOSR JOURNAL OF SCIENCE AND TECHNOLOGY 12(1):109-113. https://doi.org/10.59298/IDOSR/JST/26/113.109113