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Interplay Between Oxidative Stress and Antioxidant Defenses in the Pathogenesis and Management of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a global metabolic disorder characterized by chronic hyperglycaemia and an array of microvascular and macrovascular complications. A substantial body of evidence implicates oxidative stress-an imbalance between reactive oxygen species (ROS) production and antioxidant defenses a central mechanism in the initiation and progression of diabetic pathology. Hyperglycaemia potentiates ROS generation through multiple biochemical pathways, including increased mitochondrial electron transport chain leakage, activation of the polyol pathway, advanced glycation end-product (AGE) formation, protein kinase C (PKC) activation, and enhanced hexosamine flux. These ROS-driven processes damage cellular macromolecules, impair signalling, and trigger inflammatory cascades that contribute to β-cell dysfunction, insulin resistance, endothelial injury, neuropathy, nephropathy, and hepatopathy. Endogenous antioxidant systems (enzymatic: superoxide dismutase, catalase, glutathione peroxidase; non-enzymatic: glutathione, vitamins C and E, and thiol-containing proteins) attempt to neutralize oxidative insults, but are often overwhelmed in diabetes. Therapeutic strategies aiming to rebalance redox homeostasis-ranging from lifestyle modifications and glycaemic control to pharmacological antioxidants and agents that upregulate endogenous defenses-show promise in ameliorating diabetic complications. This review synthesizes mechanistic links between oxidative stress and diabetic pathophysiology, discusses biomarkers and experimental models used to study redox imbalance, evaluates antioxidant-based interventions, and highlights gaps and future directions for translating redox biology into clinical practice.

Keywords: Diabetes mellitus, oxidative stress, antioxidants, reactive oxygen species, β-cell dysfunction

INTRODUCTION

Diabetes mellitus represents a complex and heterogeneous group of chronic metabolic disorders characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both [1-5]. The two principal forms, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), differ in their etiology but converge on similar molecular mechanisms of cellular injury. Type 1 diabetes arises primarily from autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency, while type 2 diabetes develops as a consequence of peripheral insulin resistance coupled with a progressive decline in β-cell function [6-8]. Despite these differences, oxidative stress has emerged as a central unifying factor in the onset and progression of both types. Under normal physiological conditions, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are continuously generated as by-products of aerobic metabolism and play vital roles in cellular signaling, immune defense, and homeostasis [9-13]. However, in diabetes, the delicate balance between ROS production and antioxidant defense systems is disrupted, resulting in oxidative stress [14-18]. Persistent hyperglycaemia induces metabolic disturbances that amplify ROS generation while simultaneously impairing endogenous antioxidant mechanisms [19-24]. This imbalance leads to cumulative oxidative damage to lipids, proteins, and nucleic acids, contributing to insulin resistance, β-cell dysfunction, and the development of chronic diabetic complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease [25-28]. The reciprocal relationship between oxidative stress and hyperglycaemia forms a vicious cycle in which oxidative injury promotes further metabolic dysregulation, aggravating disease progression. Understanding this interplay between oxidative stress and antioxidant defense

mechanisms is crucial for developing therapeutic strategies aimed at mitigating the burden of diabetes and its complications.

2. Mechanisms of ROS Generation in Diabetes

Several interrelated biochemical pathways contribute to excessive ROS formation under hyperglycaemic conditions. One of the major sources is mitochondrial dysfunction. Elevated intracellular glucose increases flux through the tricarboxylic acid (TCA) cycle, leading to an accumulation of reduced electron carriers such as NADH and $FADH_2$. These excess electrons overload the mitochondrial electron transport chain, resulting in electron leakage at complexes I and III and the formation of superoxide anion (O_2•−) [29-34]. Chronic overproduction of mitochondrial ROS damages mitochondrial DNA, respiratory enzymes, and membranes, further impairing energy metabolism and intensifying oxidative injury [35-39]. The polyol pathway also contributes to oxidative stress in diabetes. In this pathway, the enzyme aldose reductase reduces glucose to sorbitol, consuming NADPH in the process [40-43]. Since NADPH is required for regenerating reduced glutathione (GSH), its depletion weakens cellular antioxidant capacity. Accumulation of sorbitol within cells further disturbs osmotic balance, leading to cell dysfunction and oxidative vulnerability [44-48].

Another critical mechanism involves the formation of advanced glycation end-products (AGEs). Persistent hyperglycaemia promotes non-enzymatic glycation of proteins, lipids, and nucleic acids, resulting in the generation of AGEs that bind to specific receptors (RAGE) on cell surfaces [49-55]. This interaction activates NADPH oxidases and pro-inflammatory transcription factors such as NF-κB, triggering ROS overproduction, cytokine release, and endothelial inflammation [56-61]. Activation of protein kinase C (PKC) represents another oxidative mechanism. Elevated diacylglycerol levels in hyperglycaemia activate various PKC isoforms that stimulate NADPH oxidase, decrease nitric oxide bioavailability, and promote vasoconstriction and vascular permeability-key features of diabetic vascular dysfunction [62-69]. The hexosamine pathway also plays a role by diverting excess glucose into fructose-6-phosphate, which undergoes O-GlcNAcylation of proteins, altering enzyme activities and transcription factors involved in oxidative stress regulation [70-76]. This modification impairs mitochondrial function and suppresses antioxidant enzyme expression. Finally, chronic inflammation associated with diabetes exacerbates oxidative stress. Hyperglycaemia-induced metabolic alterations activate macrophages and neutrophils, which generate ROS and RNS as part of the inflammatory response [77-80]. The combined effects of these pathways result in sustained oxidative stress, cellular injury, and the progression of diabetic complications.

3. Cellular Targets and Consequences of Oxidative Damage

Reactive oxygen species (ROS) exert widespread effects on cellular structures and signalling pathways, disrupting metabolic homeostasis and accelerating diabetic complications. Among the most vulnerable targets are pancreatic β-cells, insulin signalling mechanisms, endothelial cells, neuronal tissues, and lipid membranes [81-85].

Pancreatic β-cells are particularly sensitive to oxidative stress because they possess inherently low levels of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [86]. Excess ROS generated during chronic hyperglycaemia directly damage β-cell membranes, DNA, and mitochondria, impairing insulin gene expression and secretion. Persistent oxidative damage triggers apoptotic pathways, leading to a progressive decline in β-cell mass and worsening glycaemic control [87]. This oxidative injury establishes a vicious cycle where reduced insulin output further enhances hyperglycaemia and subsequent ROS formation. In peripheral tissues, oxidative stress interferes with insulin signal transduction [88]. ROS and reactive nitrogen species can oxidize cysteine residues or nitrify tyrosine residues on insulin receptor substrates (IRS) and downstream kinases such as Akt, impairing phosphorylation events necessary for glucose uptake [89]. The resulting insulin resistance limits glucose transport into skeletal muscle and adipose tissue, aggravating hyperglycaemia and further promoting oxidative stress. Endothelial dysfunction is another major consequence of oxidative stress in diabetes. ROS rapidly react with nitric oxide (NO), forming peroxynitrite and reducing NO bioavailability [90]. This reaction disrupts vascular tone regulation, promotes vasoconstriction, and enhances platelet aggregation. Additionally, ROS induces uncoupling of endothelial nitric oxide synthase (eNOS), causing it to generate superoxide instead of NO, perpetuating vascular oxidative stress [91-92]. The resulting endothelial damage contributes to the development of atherosclerosis, hypertension, and other cardiovascular complications of diabetes.

Nephrotoxicity and neuropathy also stem from ROS-induced cellular damage. In diabetic kidneys, oxidative stress alters glomerular basement membrane integrity, promotes mesangial expansion, and stimulates pro-fibrotic cytokines, leading to diabetic nephropathy [21]. Similarly, oxidative damage to neuronal mitochondria, Schwann cells, and axonal membranes triggers neuropathic pain and sensory deficits characteristic of diabetic neuropathy [22]. Moreover, oxidative attack on lipids initiates lipid peroxidation, generating reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [23]. These secondary products form adducts with proteins and DNA, altering their structure and function. Lipid peroxidation propagates membrane instability, impairs cellular communication, and exacerbates inflammatory signalling, contributing to metabolic dysregulation and tissue degeneration observed in chronic diabetes [24].

4. Antioxidant Defenses in Diabetes

Cells rely on an intricate network of antioxidant systems to counteract oxidative damage. These include both enzymatic and non-enzymatic components that work synergistically to maintain redox homeostasis.

The enzymatic antioxidants constitute the first line of defense. Superoxide dismutases (SOD1 in the cytosol and SOD2 in mitochondria) catalyze the dismutation of superoxide radicals into hydrogen peroxide (H_2O_2) [25]. This H_2O_2 is subsequently detoxified by catalase in peroxisomes and glutathione peroxidase (GPx) in the cytosol and mitochondria [26]. Thioredoxin and peroxiredoxins also play vital roles in reducing peroxides and maintaining thiol redox balance [27].

Non-enzymatic antioxidants complement these enzymes by directly scavenging free radicals and regenerating oxidized antioxidant molecules. Glutathione (GSH), a tripeptide composed of glutamate, cysteine, and glycine, acts as a major intracellular redox buffer [28]. Vitamins C and E interrupt chain reactions of lipid peroxidation, while carotenoids, uric acid, and flavonoids contribute additional protective effects [29]. Metal-binding proteins such as ferritin and ceruloplasmin limit ROS generation by sequestering redox-active metals [30].

Adaptive antioxidant responses are regulated by the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2). Under oxidative stress, Nrf2 dissociates from its inhibitor Keap1 and translocates to the nucleus, activating genes that encode detoxifying and antioxidant enzymes [31]. However, in diabetic conditions, Nrf2 activity is often suppressed, reducing the ability of cells to mount effective antioxidant defenses. Numerous studies have demonstrated diminished activities of SOD, catalase, and GPx in diabetic patients, alongside decreased GSH levels [32]. This reduction, combined with elevated ROS production, shifts the redox equilibrium toward a pro-oxidant state. Consequently, insufficient antioxidant protection contributes to oxidative damage of β-cells, endothelium, and other tissues, reinforcing the progression of diabetic complications [33]. Strengthening these antioxidant defenses remains a critical therapeutic goal for mitigating oxidative injury in diabetes.

5. Therapeutic Strategies Targeting Oxidative Stress

Restoring redox balance in diabetes requires a multifaceted approach that addresses both the sources of oxidative stress and the weakening of endogenous antioxidant defenses. Current strategies range from lifestyle interventions and improved glycaemic control to pharmacological and nutraceutical therapies that modulate redox homeostasis and mitochondrial function.

5.1 Glycaemic Control and Lifestyle

Maintaining optimal glycaemic control remains the cornerstone of preventing oxidative stress in diabetes. Chronic hyperglycaemia accelerates ROS formation through multiple metabolic pathways; hence, reducing blood glucose directly limits oxidative injury. Lifestyle modifications such as calorie restriction, weight loss, and regular physical exercise improve insulin sensitivity, enhance mitochondrial efficiency, and reduce systemic inflammation [34]. Exercise has been shown to upregulate endogenous antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, while diets rich in fruits, vegetables, and whole grains provide natural antioxidants and anti-inflammatory compounds [35]. Stress management and adequate sleep also play indirect roles by reducing cortisol-mediated metabolic stress, which can otherwise exacerbate ROS production [36].

5.2 Pharmacologic Agents with Antioxidant Actions

Several conventional antidiabetic medications possess intrinsic antioxidant properties beyond their glucose-lowering effects. Metformin, a first-line oral antidiabetic, improves mitochondrial respiration and reduces superoxide production by activating AMP-activated protein kinase (AMPK) [37]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to attenuate oxidative stress and inflammation in vascular tissues, possibly through modulation of mitochondrial and endothelial function [38]. Additionally, drugs such as pioglitazone and other thiazolidinediones exert antioxidant effects by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), which enhances cellular redox balance [39]. Direct antioxidant therapies, including N-acetylcysteine (a glutathione precursor) and alpha-lipoic acid, act by replenishing thiol pools and scavenging free radicals [40]. Although promising, their clinical benefits depend on timing, dosage, and patient metabolic status.

5.3 Nutraceuticals and Dietary Antioxidants

Plant-derived bioactive compounds, particularly polyphenols such as resveratrol, quercetin, and curcumin, exhibit potent antioxidant and anti-inflammatory properties. They scavenge ROS, enhance Nrf2 activation, and improve mitochondrial biogenesis. Vitamins C and E remain among the most studied dietary antioxidants, reducing lipid peroxidation and protecting cell membranes from oxidative damage [41]. However, clinical trial outcomes are inconsistent-while some studies report improved oxidative biomarkers and endothelial function, others show limited benefits or even potential interference with physiological ROS signalling. The efficacy of dietary antioxidants appears to depend on individual redox status, combination with other therapies, and long-term adherence to balanced nutrition rather than supplementation alone.

5.4 Nrf2 Activators and Mitochondria-Targeted Antioxidants

A more targeted therapeutic strategy involves activating endogenous antioxidant pathways, particularly through the nuclear factor erythroid 2–2-related factor 2 (Nrf2). Pharmacologic Nrf2 activators, including bardoxolone methyl and naturally occurring compounds such as sulforaphane and curcumin, enhance the expression of detoxifying and antioxidant enzymes, thereby strengthening intrinsic cellular defenses [42]. Another emerging approach focuses on mitochondria-targeted antioxidants, such as mitoQ and SS peptides, which are designed to accumulate within mitochondria and neutralize ROS at their main site of production [43]. Preliminary studies indicate that these compounds improve mitochondrial function and reduce oxidative damage in diabetic models, though further clinical trials are needed to establish efficacy and safety.

5.5 Enzyme Modulators and NADPH Oxidase Inhibitors

NADPH oxidases (NOX enzymes) are significant sources of superoxide generation in diabetes. Selective NOX inhibitors are under investigation as potential therapeutic agents to limit ROS overproduction without impairing essential immune functions [44]. Similarly, compounds that modulate mitochondrial electron transport chain activity or prevent mitochondrial uncoupling can decrease electron leakage and ROS formation [45]. Although these enzyme-targeted therapies are still largely experimental, they represent promising directions in the development of redox-based pharmacological interventions for diabetes management.

In summary, successful redox-targeted therapy for diabetes requires an integrative approach combining lifestyle modification, glycaemic control, and pharmacologic or nutraceutical agents tailored to individual oxidative stress profiles.

CONCLUSION

Oxidative stress is a central and multifactorial driver of diabetic pathogenesis and complications. While antioxidant defenses are inherently poised to counter ROS, chronic hyperglycaemia and associated metabolic derangements often overwhelm these systems. Therapeutic strategies that restore redox balance by reducing ROS production, enhancing endogenous antioxidant capacity, or selectively scavenging harmful species hold promise for mitigating β-cell failure, insulin resistance, and end-organ damage. Success will depend on precise mechanistic understanding, careful patient selection, and combination therapies that preserve physiological ROS signalling while preventing pathological oxidative injury. Translating redox biology into effective clinical interventions remains an achievable but complex goal that warrants continued, focused research.

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. Ugwu, O.P.C., Kungu, E., Inyangat, R., Obeagu, E. I., Alum, E. U., Okon, M. B., Subbarayan, S. and Sankarapandiyan, V. Exploring Indigenous Medicinal Plants for Managing Diabetes Mellitus in Uganda: Ethnobotanical Insights, Pharmacotherapeutic Strategies, and National Development Alignment. INOSR Experimental Sciences. 2023; 12(2):214-224. https://doi.org/10.59298/INOSRES/2023/2.17.1000.
3. 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
4. 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
5. 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
6. Satapati S, Sunny NE, Kucejova B, Fu X, He TT, Méndez-Lucas A, et al. Elevated TCA cycle function in the pathology of diet-induced hepatic insulin resistance and fatty liver. Journal of Lipid Research. 2012;53(6):1080–92. doi:10.1194/jlr.m023382
7. Juan CA, De La Lastra JMP, Plou FJ, Pérez-Lebeña E. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International Journal of Molecular Sciences. 2021;22(9):4642. doi:10.3390/ijms22094642
8. Srikanth KK, Orrick JA. Biochemistry, polyol or sorbitol pathways. StatPearls - NCBI Bookshelf. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576381/#_ncbi_dlg_citbx_NBK576381
9. Guan H, Zhao S, Fang X, Miao R, Zhang Y, Zhang Y, et al. Frontier technologies for investigating endothelial heterogeneity and function in diabetic vascular disease: An updated review. Biomedicine & Pharmacotherapy. 2025;191:118445. doi:10.1016/j.biopha.2025.118445

10. Khalid M, Petroianu G, Adem A. Advanced Glycation End Products and Diabetes mellitus: Mechanisms and perspectives. Biomolecules. 2022;12(4):542. doi:10.3390/biom12040542
11. Geraldes P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. Circulation Research. 2010;106(8):1319–31. doi:10.1161/CIRCRESAHA.110.217117
12. Paneque A, Fortus H, Zheng J, Werlen G, Jacinto E. The Hexosamine Biosynthesis Pathway: Regulation and Function. Genes. 2023;14(4):933. doi:10.3390/genes14040933
13. Giri B, Dey S, Das T, Sarkar M, Banerjee J, Dash SK. Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. Biomedicine & Pharmacotherapy. 2018;107:306–28. doi:10.1016/j.biopha.2018.07.157
14. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.A. Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine, 2025; 100622. https://doi.org/10.1016/j.obmed.2025.100622
15. Wang J, Wang H. Oxidative stress in pancreatic beta cell regeneration. Oxidative Medicine and Cellular Longevity. 2017;2017(1). doi:10.1155/2017/1930261
16. Ogugua Victor Nwadiogbu., Agu Obiora Uroko., Egba, Simeon Ikechukwu and Robert Ikechukwu. Modulation of Blood Glucose Concentration, Lipid Profile and Haematological Parameters in Alloxan Induced Diabetic Rats Using Methanol Extract of *Nauclea latifolia* Root Bark. *Asian Journal of Biological Sciences*, 2017; 10(1): 1-8
17. Hurrle S, Hsu WH. The etiology of oxidative stress in insulin resistance. Biomedical Journal. 2017;40(5):257–62. doi:10.1016/j.bj.2017.06.007
18. Afanas'Ev I. Signaling of reactive oxygen and nitrogen species in diabetes mellitus. Oxidative Medicine and Cellular Longevity. 2010;3(6):361–73. doi:10.4161/oxim.3.6.14415
19. Magenta A, Greco S, Capogrossi MC, Gaetano C, Martelli F. Nitric oxide, oxidative stress, ANdP66SHCInterplay in diabetic endothelial dysfunction. BioMed Research International. 2014;2014:1–16. doi:10.1155/2014/193095
20. Münzel T, Daiber A. Vascular Redox Signaling, Endothelial Nitric Oxide Synthase Uncoupling, and Endothelial Dysfunction in the Setting of Transportation Noise Exposure or Chronic Treatment with Organic Nitrates. Antioxidants and Redox Signaling. 2023;38(13–15):1001–21. doi:10.1089/ars.2023.0006
21. Famurewa AC, Orji OU, Aja PM, Nwite F, Ohuche SE, Ukasoanya SC, Nnaji LO, Joshua D, Igwe KU, Chima SF. Nephroprotective effects of *Datura stramonium* leaves against methotrexate nephrotoxicity via attenuation of oxidative stress-mediated inflammation and apoptosis in rats. Avicenna J Phytomed. 2023 Jul-Aug;13(4):377-387. doi: 10.22038/AJP.2023.21903. PMID: 37663387; PMCID: PMC10474919.
22. Diabetic neuropathy. Nature Reviews Disease Primers. 2019;5(1). doi:10.1038/s41572-019-0097-9
23. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-Hydroxy-2-Nonenal. Oxidative Medicine and Cellular Longevity. 2014;2014:1–31. doi:10.1155/2014/360438
24. Miller MA, Zachary JF. Mechanisms and morphology of cellular injury, adaptation, and death. In: Elsevier eBooks. 2017. p. 2–43.e19. doi:10.1016/B978-0-323-35775-3.00001-1
25. Zheng M, Liu Y, Zhang G, Yang Z, Xu W, Chen Q. The applications and mechanisms of superoxide dismutase in medicine, food, and cosmetics. Antioxidants. 2023;12(9):1675. doi:10.3390/antiox12091675
26. Pascual-Ahuir A, Manzanares-Estreder S, Proft M. Pro- and antioxidant functions of the Peroxisome-Mitochondria connection and its impact on aging and disease. Oxidative Medicine and Cellular Longevity. 2017;2017(1). doi:10.1155/2017/9860841
27. AlOkda A, Van Raamsdonk JM. Evolutionarily conserved role of thioredoxin systems in determining longevity. Antioxidants. 2023;12(4):944. doi:10.3390/antiox12040944
28. Aoyama K, Nakaki T. Glutathione in Cellular Redox Homeostasis: Association with the Excitatory Amino Acid Carrier 1 (EAAC1). Molecules. 2015;20(5):8742–58. doi:10.3390/molecules20058742
29. 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
30. Jomova K, Alomar SY, Valko R, Nepovimova E, Kuca K, Valko M. The role of redox-active iron, copper, manganese, and redox-inactive zinc in toxicity, oxidative stress, and human diseases. PubMed. 2025;24:880–954. Available from: https://pubmed.ncbi.nlm.nih.gov/40933952
31. Ngo V, Duennwald ML. NRF2 and Oxidative Stress: A General Overview of Mechanisms and implications in human disease. Antioxidants. 2022;11(12):2345. doi:10.3390/antiox11122345
32. Tan SM, De Haan JB. Combating oxidative stress in diabetic complications with Nrf2 activators: How much is too much? Redox Report. 2014;19(3):107–17. doi:10.1179/1351000214y.0000000087

33. 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
34. 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
35. 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
36. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Science. 2015;8(3):143–52. doi:10.1016/j.slsci.2015.09.002
37. Wang Y, An H, Liu T, Qin C, Sesaki H, Guo S, et al. Metformin Improves Mitochondrial Respiratory Activity through Activation of AMPK. Cell Reports. 2019;29(6):1511–1523.e5. doi:10.1016/j.celrep.2019.09.070
38. Luna-Marco C, Iannantuoni F, Hermo-Argibay A, Devos D, Salazar JD, Víctor VM, et al. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists through effects on mitochondrial function and oxidative stress. Free Radical Biology and Medicine. 2024;213:19–35. doi:10.1016/j.freeradbiomed.2024.01.015
39. Di Marzio D. Peroxisome proliferator-activated receptor-γ agonists and diabetes: Current evidence and future perspectives. Vascular Health and Risk Management. 2008;4:297–304. doi:10.2147/VHRM.S993
40. Sahasrabudhe SA, Terluk MR, Kartha RV. N-acetylcysteine Pharmacology and Applications in Rare Diseases—Repurposing an old antioxidant. Antioxidants. 2023;12(7):1316. doi:10.3390/antiox12071316
41. Alum, E. U., Aja, W., Ugwu, O. P. C., Obeagu, E. I., Okon, M. B. Assessment of vitamin composition of ethanol leaf and seed extracts of *Datura stramonium*. *Avicenna J Med Biochem*. 2023; 11(1):92-97. doi:10.34172/ajmb.2023.2421.
42. Robledinos-Antón N, Fernández-Ginés R, Manda G, Cuadrado A. Activators and inhibitors of NRF2: A review of their Potential for Clinical development. Oxidative Medicine and Cellular Longevity. 2019;2019:1–20. doi:10.1155/2019/9372182
43. Broome SC, Woodhead JST, Merry TL. Mitochondria-Targeted antioxidants and skeletal muscle function. Antioxidants. 2018;7(8):107. doi:10.3390/antiox7080107
44. Vermot A, Petit-Härtlein I, Smith SME, Fieschi F. NADPH Oxidases (NOX): An Overview from Discovery, Molecular Mechanisms to Physiology and Pathology. Antioxidants. 2021;10(6):890. doi:10.3390/antiox10060890
45. Hass DT, Barnstable CJ. Uncoupling proteins in the mitochondrial defense against oxidative stress. Progress in Retinal and Eye Research. 2021;83:100941. doi:10.1016/j.preteyeres.2021.100941
46. Isaac Edyedu PMA, Ugwu OPC, Ugwu CN, Alum EU, et al. The role of pharmacological interventions in managing urological complications during pregnancy and childbirth: A review. Medicine. 2025;104(7):e41381.
47. Alum EU, Ugwu OPC, Obeagu EI, et al. Nutritional care in diabetes mellitus: A comprehensive guide. Int J Innov Appl Res. 2023;11(12):16-25.
48. Obeagu EI, Ahmed YA, Obeagu GU, Bunu UO, Ugwu OPC, Alum EU. Biomarkers of breast cancer: Overview. Int J Curr Res Biol Med. 2023;1:8-16.
49. Uti DE, Alum EU, Atangwho IJ, Ugwu OPC, et al. Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: Advances in targeted delivery and precision therapeutics. J Nanobiotechnol. 2025;23:336.
50. Ugwu CN, Ugwu OPC, Alum EU, Eze VHU, Basajja M, Ugwu JN, Ogenyi FC, et al. Medical preparedness for bioterrorism and chemical warfare: A public health integration review. Medicine. 2025;104(18):e42289.
51. Obeagu EI, Scott GY, Amekpor F, Ugwu OPC, Alum EU. COVID-19 infection and diabetes: A current issue. Int J Innov Appl Res. 2023;11(1):25-30.
52. Offor CE, Ugwu OPC, Alum EU. Anti-diabetic effect of ethanol leaf extract of *Allium sativum* on albino rats. Int J Pharm Med Sci. 2014;4(1):1-3.
53. Asogwa FC, Okechukwu PCU, Esther UA, Chinedu OE, Nzubechukwu E. Hygienic and sanitary assessment of street food vendors in selected towns of Enugu North District, Nigeria. Am-Eurasian J Sci Res. 2015;10(1):22-26.
54. Alum EU, Uti DE, Agah VM, Orji OU, Nkeiru N, et al. Physico-chemical and bacteriological analysis of water used for drinking and domestic purposes in Amaozara Ozizza, Afikpo North, Nigeria. Niger J Biochem Mol Biol. 2023;38(1):1-8.
55. Ugwu OPC, Alum EU, Okon MB, Obeagu EI. Mechanisms of microbiota modulation: Implications for health, disease, and therapeutic interventions. Medicine. 2024;103(19):e38088.
56. Ezekwe CI, Uzomba CR, Ugwu OPC. Effect of methanol extract of *Talinum triangulare* on hematology and liver parameters in rats. Glob J Biotechnol Biochem. 2013;8(2):51-60.

57. Alum EU, Inya JE, Ugwu OPC, Obeagu EI, Aloke C, Aja PM, Okpata MG, et al. Ethanolic leaf extract of *Datura stramonium* attenuates methotrexate-induced biochemical alterations in Wistar rats. RPS Pharmacol Rep. 2023;2(1):1-6.
58. Ugwu OPC, Erisa K, Inyangat R, Obeagu EI, et al. Indigenous medicinal plants for managing diabetes in Uganda: Ethnobotanical and pharmacotherapeutic insights. INOSR Exp Sci. 2023;12(2):214-224.
59. Alum EU, Aja W, Ugwu OPC. Vitamin composition of ethanol leaf and seed extracts of *Datura stramonium*. Avicenna J Med Biochem. 2023;11(1):92-97.
60. Ezenwaji CO, Alum EU, Ugwu OPC. Digital health in pandemic preparedness and response: Securing global health? Glob Health Action. 2024;17(1):2419694.
61. Adonu CC, Ugwu OP, Bawa A, Ossai EC, Nwaka AC. Intrinsic blood coagulation studies in patients with diabetes and hypertension. Int J Pharm Med Bio Sci. 2013;2(2):36-45.
62. Offor CE, Ugwu PC, Okechukwu PM, Igwenyi IO. Proximate and phytochemical analyses of *Terminalia catappa* leaves. Eur J Appl Sci. 2015;7(1):9-11.
63. Enechi YS, Ugwu OC, Ugwu KK, Ugwu OPC, Omeh N. Evaluation of antinutrient levels of *Ceiba pentandra* leaves. IJRRPAS. 2013;3(3):394-400.
64. Alum EU, Uti DE, Ugwu OPC, Alum BN, Edeh FO, Ainebyoona C. Microbiota in cancer development and treatment. Discov Oncol. 2025;16(1):646.
65. Asogwa FC, Okoye COB, Ugwu OPC, Edwin N, Alum EU, Egwu CO. Phytochemistry and antimicrobial assay of *Jatropha curcas* extracts. Eur J Appl Sci. 2015;7(1):12-16.
66. Enechi OC, Oluka HI, Ugwu PCO. Acute toxicity and ameliorative properties of *Alstonia boonei* leaf extract on diabetic rats. Afr J Biotechnol. 2014;13(5).
67. Alum EU, Obeagu EI, Ugwu OPC. Enhancing water, sanitation, and hygiene for diarrhoea control and SDGs: A review. Medicine. 2024;103(38):e39578.
68. Odo CE, Nwodo OFC, Joshua PE, Ugwu OPC, Okonkwo CC. Anti-diarrhoeal effect of chloroform–methanol extract of *Persea americana* seeds in rats. J Pharm Res. 2013;6(3):331-335.
69. Ugwu OPC, Obeagu EI, Alum EU, Michael M, et al. Effect of ethanol leaf extract of *Chromolaena odorata* on hepatic markers in diabetic rats. IAA J Appl Sci. 2023;9(1):46-56.
70. Ibiam UA, Alum EU, Orji OU, Aja PM, Nwamaka EN, Ugwu OPC, et al. Anti-inflammatory effects of *Buchholzia coriacea* leaf extract in arthritic rats. Indo Am J Pharm Sci. 2018;5(7):6341-6357.
71. Obeagu EI, Obeagu GU, Odo EO, Alum EU. Nutritional approaches for enhancing immune competence in HIV-positive individuals. IDOSR J Appl Sci. 2024;9(1):40-50.
72. Obeagu EI, Alum EU, Ugwu OPC. Hepcidin: Gatekeeper of iron in malaria resistance. Newport Int J Res Med Sci. 2023;4(2):1-8.
73. Nyamboga TO, Ugwu OPC, Ugwu JN, et al. Biotechnological innovations in soil health management: a systematic review of integrating microbiome engineering, bioinformatics, and sustainable practices. Cogent Food Agric. 2025;11(1):2519811.
74. Madu ANB, Alum EU, Aloh HE, Ugwu OPC, Obeagu EI, Uti DE, Egba SI, Ukaidi CUA. The price of progress: Assessing the financial costs of HIV/AIDS management in East Africa. Medicine. 2025;104(18):e42300.
75. Alum EU, Ugwu OPC. Beyond pregnancy: Understanding long-term implications of gestational diabetes mellitus. INOSR Sci Res. 2024;11(1):63-71.
76. Ugwu OPC, Alum EU, Okon MB, Aja PM, Obeagu EI, Onyeneke EC. Anti-nutritional and GC-MS analysis of ethanol root extract and fractions of *Sphenocentrum jollyanum*. RPS Pharmacol Pharm Rep. 2023;2(2):rqad007.
77. Eze VHU, Eze CE, Mbabazi A, Ugwu CN, Ugwu PO, Ogenyi CF, Ugwu JN, et al. Qualities and characteristics of a good scientific research writing: Step-by-step approaches. IAA J Appl Sci. 2023;9(2):71-76.
78. Igwenyi IO, Nchi PO, Okechukwu UPC, Igwenyi IP, Obasi DC, Edwin N. Nutritional potential of *Azadirachta indica* seeds. Indo Am J Pharm Sci. 2017;4(2):477-482.
79. Enechi OC, Oluka IH, Ugwu OPC, Omeh YS. Effect of ethanol leaf extract of *Alstonia boonei* on lipid profile of alloxan-induced diabetic rats. Afr J Biotechnol. 2013;24.
80. Ugwu OPC. Anti-malaria effect of ethanol extract of *Moringa oleifera* leaves on malaria-induced mice. University of Nigeria Nsukka; 2011:39.
81. Alum EU, Ugwu OPC, Obeagu EI. Nutritional interventions for cervical cancer patients: Beyond conventional therapies. J Cancer Res Cell Ther. 2024;8(1):1-6.
82. Obeagu EI, Obeagu GU. Advancements in immune augmentation strategies for HIV patients. IAA J Biol Sci. 2024;11(1):1-11.
83. Okechukwu PU, Nzubechukwu E, Ogbanshi ME, Ezeani N, Nworie MO. Effect of ethanol leaf extract of *Jatropha curcas* on chloroform-induced hepatotoxicity in albino rats. Glob J Biotech Biochem. 2015;10:11-15.

84. Ilozue NM, Ikezu UP, Okechukwu PCU. Antimicrobial and phytochemical screening of *Persea americana* seed extracts. IOSR J Pharm Biol Sci. 2014;9(2):23-25.
85. Onyeze R, Udeh SM, Akachi B, Ugwu OP. Isolation and characterization of fungi associated with spoilage of corn (*Zea mays*). Int J Pharm Med Biol Sci. 2013;2(3):86-91.
86. Obeagu EI, Alum EU, Ugwu OPC. Hepcidin: The gatekeeper of iron in malaria resistance. Newport Int J Res Med Sci. 2023;4:1-8.
87. Obeagu EI, Alum EU, Obeagu GU, Ugwu OPC. Prostate cancer: Review on risk factors. Eurasian Exp J Public Health. 2023;4(1):4-7.
88. Offor CE, Okaka ANC, Ogbugo SO, Egwu CO, Okechukwu PC. Effects of ethanol leaf extract of *Pterocarpus santalinoides* on haemoglobin, packed cell volume and platelets. IOSR J Nurs Health Sci. 2015;4:108-112, 93.
89. Offor C, Aja PC, Ugwu O, Agbafor KN. Effects of ethanol leaf extract of *Gmelina arborea* on serum proteins in albino rats. Glob J Environ Res. 2015;9(1):1-4.
90. Alum EU, Uti DE, Obeagu EI, Ugwu OPC, Alum BN. Cancer's psychosocial aspects: Impact on patient outcomes. Elite J Med. 2024;2(6):32-42.
91. Alum EU, Ugwu OPC, Egba SI, Uti DE, Alum BN. Climate variability and malaria transmission: Unravelling the complex relationship. INOSR Sci Res. 2024;11(2):16-22.
92. Alum EU, Obeagu EI, Ugwu OPC, Egba SI, EjimUti DE, Ukaidi CUA, et al. Confronting dual challenges: Substance abuse and HIV/AIDS. Elite J HIV. 2024;2(5):1-8.

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