

The Role of Oxidative Stress and Mitochondrial Dysfunction in Obesity-Induced Diabetes and Carcinogenesis

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ABSTRACT

Obesity has emerged as a global health crisis, intricately linked to the pathogenesis of type 2 diabetes mellitus (T2DM) and various malignancies. Central to this pathological nexus is the interplay between oxidative stress and mitochondrial dysfunction. Adipose tissue expansion in obesity induces chronic inflammation, leading to the overproduction of reactive oxygen species (ROS) and impairment of mitochondrial function. This redox imbalance disrupts insulin signaling, impairs glucose homeostasis, and fosters a metabolic environment conducive to DNA damage, mutagenesis, and cancer development. Moreover, mitochondrial dysfunction exacerbates adipocyte insulin resistance and contributes to the metabolic reprogramming characteristic of cancer cells. This review critically examines the molecular and biochemical mechanisms by which oxidative stress and mitochondrial dysfunction bridge obesity to both diabetes and carcinogenesis. We explore the roles of key mediators such as NADPH oxidase, mitochondrial respiratory chain complexes, and redox-sensitive transcription factors, including NF- κ B and HIF-1 α . Understanding these interconnected pathways opens avenues for novel therapeutic strategies targeting redox homeostasis and mitochondrial health to mitigate obesity-driven metabolic diseases and cancer progression.

Keywords: Oxidative stress, Mitochondrial dysfunction, Obesity, Type 2 diabetes mellitus, Carcinogenesis

INTRODUCTION

Obesity is a complex, chronic, and multifactorial metabolic disorder defined by an abnormal or excessive accumulation of adipose tissue that presents a significant risk to health [1–4]. According to the World Health Organization (WHO), the global prevalence of obesity has more than tripled since 1975, now affecting over 650 million adults worldwide [5–7]. This increase has serious health implications, as obesity is a major risk factor for numerous non-communicable diseases, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, and various types of cancers, such as breast, colorectal, endometrial, and pancreatic cancer [8, 9]. While sedentary lifestyles and calorie-dense diets are commonly implicated in the rising prevalence of obesity, a deeper understanding of its pathophysiology reveals a complex interplay of genetic predispositions, hormonal imbalances, environmental exposures, and psychosocial factors [10, 11]. The metabolic dysregulation associated with obesity extends beyond fat accumulation and includes insulin resistance, chronic inflammation, altered adipokine secretion, and endothelial dysfunction. At the molecular level, obesity induces profound changes in cellular metabolism and signaling pathways [12, 13]. Among these, oxidative stress and mitochondrial dysfunction have emerged as pivotal mechanisms linking excess adiposity to both insulin resistance and carcinogenesis. Oxidative stress, characterized by the excessive generation of reactive oxygen species (ROS), disrupts normal cellular function by damaging proteins, lipids, and nucleic acids [14]. This redox imbalance interferes with insulin signaling and contributes to β -cell dysfunction, thereby promoting T2DM. Concurrently, chronic oxidative stress can induce DNA mutations and genomic instability, which are critical events in the initiation and progression of cancer [15]. Mitochondria, often referred to as the "powerhouses" of the cell, are central to cellular energy metabolism and play a vital role in redox homeostasis [16, 17]. In obese individuals, nutrient excess leads to mitochondrial overload, impaired oxidative phosphorylation, and further ROS production. This feedback loop contributes to cellular stress, energy failure, and inflammation, all of which exacerbate insulin resistance and create a tumor-promoting microenvironment [16, 18, 19]. Understanding the

dual impact of oxidative stress and mitochondrial dysfunction in obesity provides critical insights into the pathogenesis of obesity-related diseases. This knowledge is especially important in the context of the growing global burden of obesity-linked T2DM and cancer. With these diseases often co-occurring and influencing each other's outcomes, a mechanistic understanding is vital for identifying novel therapeutic targets and developing effective intervention strategies. As the scientific community continues to unravel the intricate molecular networks driving obesity-related complications, targeting oxidative stress and mitochondrial dysfunction offers promising avenues for mitigating the health risks associated with obesity[20]. Therapies aimed at enhancing mitochondrial function, restoring redox balance, and modulating metabolic inflammation could revolutionize the management of metabolic and oncologic complications in obese individuals[20]. This review aims to elucidate the critical roles of oxidative stress and mitochondrial dysfunction in bridging obesity with insulin resistance and cancer, ultimately paving the way for integrated and targeted treatment approaches.

2. Oxidative Stress in Obesity

Oxidative stress refers to a physiological state in which the production of reactive oxygen species (ROS) exceeds the body's ability to neutralize them using antioxidant defenses[20–23]. ROS include molecules such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\bullet OH$). Although low levels of ROS serve essential roles in cell signaling and immune defense, excessive ROS can inflict significant damage on cellular macromolecules, contributing to the onset and progression of various diseases[24]. In the context of obesity, oxidative stress is markedly elevated. Adipose tissue expansion during obesity is accompanied by increased infiltration of pro-inflammatory immune cells, particularly macrophages. These cells, along with hypertrophic adipocytes, upregulate enzymes such as NADPH oxidase, xanthine oxidase, and inducible nitric oxide synthase (iNOS), all of which contribute to ROS generation[25–27]. Mitochondrial dysfunction within adipocytes further exacerbates ROS production, especially under conditions of nutrient overload and hypoxia—a common feature of rapidly expanding adipose tissue.

Chronic inflammation in obesity plays a critical role in promoting oxidative stress. Pro-inflammatory cytokines such as tumor necrosis factor-alpha ($TNF-\alpha$), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) activate signaling pathways that stimulate ROS-producing enzymes while simultaneously downregulating endogenous antioxidant defenses, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase[28–30]. This results in a systemic redox imbalance that affects multiple tissues, including the liver, muscle, and pancreas.

One of the primary consequences of oxidative stress in obesity is its detrimental impact on insulin signaling. ROS can oxidize key signaling molecules and promote serine phosphorylation of insulin receptor substrate-1 (IRS-1), impairing its function. Furthermore, stress kinases such as c-Jun N-terminal kinase (JNK), p38 MAPK, and I κ B kinase (IKK β) are activated by oxidative stress, leading to further inhibition of insulin receptor signaling[31]. This cascade of events contributes to systemic insulin resistance, a defining feature of T2DM. In addition to metabolic dysfunction, oxidative stress promotes genomic instability by inducing DNA strand breaks, base modifications, and chromosomal rearrangements[31]. These genotoxic effects may lead to activation of oncogenes and inactivation of tumor suppressor genes, providing a fertile ground for carcinogenesis. For instance, ROS-induced DNA damage can trigger mutations in the p53 gene, a critical guardian of genomic integrity. Moreover, chronic oxidative stress can stimulate cell proliferation, angiogenesis, and evasion of apoptosis, hallmarks of cancer development[32]. Beyond its direct effects, oxidative stress also perpetuates a vicious cycle by promoting mitochondrial dysfunction and sustaining inflammation. Damaged mitochondria produce more ROS, which in turn exacerbate mitochondrial injury and further impair cellular energy metabolism. This feedback loop reinforces the pathological changes associated with obesity and its complications[27]. In sum, oxidative stress serves as a central molecular mechanism linking obesity to both insulin resistance and cancer. Its role in disrupting insulin signaling, inducing genomic instability, and promoting inflammation makes it a key therapeutic target. Strategies aimed at restoring redox homeostasis—through dietary antioxidants, pharmacologic agents, or lifestyle interventions—hold promise in mitigating the metabolic and oncologic consequences of obesity.

3. Mitochondrial Dysfunction in Obesity

Mitochondria are dynamic organelles that perform essential functions in cellular energy production, redox balance, and apoptosis[19, 20, 33]. They generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) and regulate cellular responses to metabolic stress. In obesity, mitochondrial dysfunction emerges as a critical driver of metabolic impairment and inflammation, ultimately contributing to insulin resistance and increased cancer risk[34]. Under conditions of nutrient excess, a hallmark of obesity, mitochondria are subjected to metabolic overload. Elevated levels of circulating glucose and free fatty acids increase substrate influx into mitochondria, overwhelming the electron transport chain (ETC). This results in incomplete electron transfer, leading to the leakage of electrons and excessive production of ROS[34]. While mitochondria naturally generate ROS as a byproduct of respiration, their overproduction in obesity contributes to oxidative damage to mitochondrial and cellular components.

Mitochondrial dysfunction in obesity is characterized by impaired OXPHOS, reduced ATP generation, and altered mitochondrial dynamics (i.e., fission and fusion processes). These disruptions impair cellular energy metabolism and render tissues such as skeletal muscle, liver, and adipose tissue less responsive to insulin [35]. For example, in skeletal muscle, diminished mitochondrial capacity impairs fatty acid oxidation, leading to lipid accumulation and insulin resistance. In addition to bioenergetic failure, mitochondrial DNA (mtDNA) is particularly vulnerable to oxidative damage due to its proximity to the ETC and lack of protective histones [35]. ROS-induced mtDNA mutations impair the synthesis of ETC proteins, further reducing mitochondrial efficiency and propagating a cycle of dysfunction. Damaged mtDNA can also be released into the cytosol, where it acts as a damage-associated molecular pattern (DAMP) that activates innate immune responses and promotes chronic inflammation [36].

The regulation of mitochondrial biogenesis is also compromised in obesity. Transcriptional coactivators like peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α) and sirtuin 1 (SIRT1) play essential roles in maintaining mitochondrial function by promoting the transcription of genes involved in mitochondrial replication, respiration, and antioxidant defense. In obesity, these regulatory pathways are downregulated, leading to reduced mitochondrial content and function [37]. Mitochondrial dysfunction is closely intertwined with inflammation in obesity. Dysfunctional mitochondria release ROS and mitochondrial components that activate the NLRP3 inflammasome, a multiprotein complex that triggers the production of pro-inflammatory cytokines such as IL-1 β and IL-18. This inflammasome activation exacerbates adipose tissue inflammation, perpetuating insulin resistance and creating a microenvironment conducive to cancer development [37].

Moreover, impaired mitochondrial function influences cancer progression by promoting metabolic reprogramming, a hallmark of cancer cells. Tumor cells often exhibit the Warburg effect, a shift from oxidative phosphorylation to aerobic glycolysis even in the presence of oxygen [38]. Mitochondrial dysfunction in obesity may facilitate this metabolic shift, thereby supporting rapid cell proliferation and survival in hypoxic tumor environments [38]. Therapeutic strategies aimed at improving mitochondrial function are gaining attention in the management of obesity-related diseases. These include exercise, which enhances mitochondrial biogenesis and function; caloric restriction; and pharmacologic agents such as metformin and resveratrol that activate PGC-1 α and SIRT1 pathways. Additionally, mitochondrial-targeted antioxidants like MitoQ have shown potential in reducing oxidative damage and improving insulin sensitivity [39]. Mitochondrial dysfunction plays a central role in the pathophysiology of obesity, bridging the gap between metabolic disturbances and increased cancer risk. By disrupting energy production, amplifying oxidative stress, and driving inflammation, dysfunctional mitochondria contribute to the onset and progression of insulin resistance and tumorigenesis. Restoring mitochondrial health represents a promising approach for reducing the burden of obesity-related diseases [39].

4. Oxidative Stress and Mitochondrial Dysfunction in Diabetes

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder marked by chronic hyperglycemia arising from both insulin resistance in peripheral tissues and progressive pancreatic β -cell dysfunction [40–42]. Among the diverse pathogenic mechanisms implicated, oxidative stress and mitochondrial dysfunction have emerged as central contributors to the onset and progression of the disease. In insulin-sensitive tissues such as skeletal muscle, adipose tissue, and the liver, oxidative stress impairs insulin signaling pathways primarily by generating excessive reactive oxygen species (ROS). These ROS interfere with insulin receptor substrate (IRS) activation and downstream PI3K-Akt signaling, ultimately reducing glucose transporter 4 (GLUT4) translocation and inhibiting glucose uptake [43, 44].

In pancreatic β -cells, prolonged exposure to high glucose (glucotoxicity) and elevated free fatty acids (lipotoxicity) further exacerbate oxidative stress. This stress is particularly damaging due to the inherently low antioxidant enzyme expression in β -cells, rendering them highly susceptible to ROS-induced damage [45]. Excessive oxidative stress leads to β -cell apoptosis through mitochondrial-mediated pathways involving cytochrome c release, activation of caspases, and upregulation of pro-apoptotic proteins such as Bax [45]. Concurrently, mitochondrial dysfunction limits ATP production, which is essential for insulin granule exocytosis in response to glucose stimulation. Impaired mitochondrial biogenesis and alterations in mitochondrial DNA (mtDNA) integrity also contribute to the declining insulin secretory capacity over time.

The resulting combination of impaired insulin secretion and peripheral insulin resistance contributes to sustained hyperglycemia, forming a vicious cycle that further amplifies oxidative stress. Evidence from both animal models and clinical studies indicates that antioxidant therapies, such as vitamin E, N-acetylcysteine (NAC), and coenzyme Q10, can reduce oxidative stress markers and improve glucose metabolism [46]. Similarly, agents targeting mitochondrial health, such as AMPK activators, SIRT1 modulators, and mitochondrial uncouplers, have demonstrated partial efficacy in improving insulin sensitivity and β -cell function [47]. While these interventions have not achieved universal success in reversing diabetes, their benefits highlight the therapeutic potential of targeting oxidative stress and mitochondrial dysfunction to halt or slow disease progression.

5. Oxidative Stress and Carcinogenesis in Obesity

Obesity is now recognized not only as a metabolic disorder but also as a major risk factor for several types of cancer, including colorectal, breast, liver, endometrial, and pancreatic cancers[48]. A central link between obesity and cancer is the chronic oxidative stress and inflammation generated by excessive adipose tissue. In obese individuals, the expansion of white adipose tissue leads to hypoxia, macrophage infiltration, and the release of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β [49]. These inflammatory signals stimulate the production of ROS, which in turn cause direct damage to DNA, proteins, and lipids, setting the stage for genetic mutations and genomic instability, key initiators of carcinogenesis[49]. Furthermore, sustained oxidative stress activates multiple redox-sensitive transcription factors, including NF- κ B, STAT3, and AP-1. These transcription factors modulate the expression of genes involved in cell proliferation, anti-apoptotic mechanisms, angiogenesis, and immune suppression[50]. The activation of these pathways fosters an environment conducive to tumor initiation and progression. Additionally, ROS stabilizes hypoxia-inducible factor-1 α (HIF-1 α), which is typically degraded under normoxic conditions. Stabilized HIF-1 α promotes angiogenesis and metabolic reprogramming by enhancing glycolytic enzyme expression, a hallmark of cancer metabolism known as the Warburg effect[51–54]. This shift supports rapid energy production and biomass synthesis, facilitating tumor growth even under hypoxic conditions.

Mitochondrial dysfunction in obesity further amplifies this carcinogenic potential. Mitochondria are both sources and targets of ROS, and their impaired function leads to altered energy metabolism and increased oxidative damage[33, 43]. Dysfunctional mitochondria favor aerobic glycolysis over oxidative phosphorylation, reinforcing the Warburg phenotype common in malignant cells. Additionally, adipokines and metabolic hormones elevated in obesity, such as leptin and insulin-like growth factor-1 (IGF-1), act synergistically with ROS to promote oncogenic signaling[20, 55]. Leptin, for instance, activates the JAK/STAT and MAPK pathways, contributing to increased cell proliferation and reduced apoptosis. IGF-1 enhances mitogenic and anti-apoptotic pathways, further increasing cancer risk[56–58]. Collectively, these interconnected mechanisms underscore how oxidative stress and mitochondrial alterations in obesity not only compromise metabolic health but also contribute substantially to cancer initiation and progression. Targeting oxidative stress pathways and restoring mitochondrial function thus represents a promising strategy in mitigating obesity-associated cancer risk.

6. Crosstalk Between Diabetes and Cancer: A Shared Redox Landscape

An increasing body of epidemiological and mechanistic evidence supports a strong link between diabetes, particularly type 2 diabetes mellitus (T2DM), and heightened cancer incidence and mortality[59]. This relationship is underpinned by shared molecular mechanisms, notably oxidative stress and mitochondrial dysfunction, which play critical roles in both disease pathogenesis. In diabetes, chronic hyperglycemia leads to excessive production of reactive oxygen species (ROS) through various pathways, including glucose autooxidation, activation of NADPH oxidase, and mitochondrial electron transport chain leakage[60]. Elevated ROS levels induce oxidative DNA damage, lipid peroxidation, and protein modifications, all of which can promote genetic mutations and genomic instability—hallmarks of cancer initiation and progression. Additionally, hyperglycemia contributes to the formation of advanced glycation end products (AGEs), which activate the receptor for AGEs (RAGE) signaling, triggering pro-inflammatory cascades and further ROS generation[61, 62]. This chronic inflammatory state fosters a tumor-promoting microenvironment. Insulin resistance, another hallmark of T2DM, results in compensatory hyperinsulinemia. High circulating insulin levels amplify insulin-like growth factor 1 (IGF-1) signaling, activating mitogenic pathways such as PI3K/AKT and MAPK, thereby enhancing cellular proliferation, inhibiting apoptosis, and favoring oncogenesis[61]. Mitochondrial dysfunction compounds this redox imbalance. Impaired oxidative phosphorylation and reduced ATP generation compromise cellular energy homeostasis and further elevate ROS production. In both diabetes and cancer, altered mitochondrial dynamics (e.g., fission, fusion, and mitophagy) disturb metabolic flexibility, fueling disease progression. Notably, obesity, a common precursor to T2DM, also contributes to this redox landscape[63]. Adipose tissue dysfunction leads to elevated pro-inflammatory cytokines like TNF- α and IL-6, which synergize with oxidative stress to support tumorigenesis. The redox imbalance caused by oxidative stress and mitochondrial dysfunction forms a central, overlapping nexus linking diabetes and cancer[63]. Understanding this shared redox landscape is vital for developing dual-targeted interventions that could mitigate both metabolic and oncologic outcomes.

7. Therapeutic Strategies Targeting Oxidative Stress and Mitochondrial Dysfunction.

Given the central role of oxidative stress and mitochondrial dysfunction in the pathophysiology of both diabetes and cancer, targeted therapeutic interventions aimed at modulating redox balance and restoring mitochondrial health offer significant promise[64]. A wide range of antioxidants has been explored for their ability to reduce ROS levels, improve mitochondrial function, and halt the progression of metabolic and oncogenic pathways. Natural antioxidants such as *resveratrol*, *N-acetylcysteine (NAC)*, *alpha-lipoic acid*, and *coenzyme Q10* have shown efficacy in improving insulin sensitivity, lowering blood glucose levels, and reducing systemic inflammation in

preclinical studies. These compounds neutralize ROS, protect mitochondrial integrity, and modulate redox-sensitive signaling pathways[64]. More advanced therapies involve mitochondrial-targeted antioxidants such as *mitoTEMPO* and *SS-31*, which are engineered to localize within mitochondria and directly scavenge superoxide radicals. These agents help stabilize the mitochondrial membrane potential, improve ATP production, and reduce apoptosis in metabolic and cancer models. In addition, agents like *melatonin* have demonstrated dual roles as antioxidants and mitochondrial protectants[65]. Lifestyle interventions are equally crucial. Regular aerobic and resistance exercise promotes mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), thereby enhancing oxidative metabolism and redox homeostasis[66]. Intermittent fasting and caloric restriction also stimulate autophagy and mitophagy, facilitating the removal of dysfunctional mitochondria and promoting metabolic resilience. Pharmacologic agents with pleiotropic effects, such as *metformin*, are gaining recognition for their dual impact[67–69]. Metformin not only improves insulin sensitivity by activating AMP-activated protein kinase (AMPK) but also modulates mitochondrial respiration and exhibits anti-cancer activity by inhibiting mTOR signaling[70]. Overall, these therapeutic strategies—ranging from pharmacological agents to lifestyle interventions underscore the translational potential of targeting oxidative stress and mitochondrial dysfunction in managing obesity-associated diseases, particularly diabetes and cancer. This integrated approach may offer a powerful avenue for disease prevention and improved long-term outcomes.

CONCLUSION

Oxidative stress and mitochondrial dysfunction are fundamental to the pathophysiology of obesity-induced diabetes and carcinogenesis. They orchestrate a cascade of molecular events that disrupt cellular homeostasis, promote inflammation, and initiate genetic and epigenetic changes favoring disease progression. A deeper understanding of these mechanisms provides a valuable framework for the development of integrated therapeutic strategies. Targeting redox imbalances and mitochondrial health represents a promising avenue for preventing and managing obesity-related metabolic and neoplastic diseases.

REFERENCES

1. Abdulla, A., Sadida, H.Q., Jerobin, J., Elfaki, I., Mir, R., Mirza, S., Singh, M., Macha, M.A., Uddin, S., Fakhro, K., Bhat, A.A., Akil, A.S.A.-S.: Unraveling molecular interconnections and identifying potential therapeutic targets of significance in obesity-cancer link. *J Natl Cancer Cent.* 5, 8–27 (2024). <https://doi.org/10.1016/j.jncc.2024.11.001>
2. Abdulla, A., Sadida, H.Q., Jerobin, J., Elfaki, I., Mir, R., Mirza, S., Singh, M., Macha, M.A., Uddin, S., Fakhro, K., Bhat, A.A., Akil, A.S.A.-S.: Unraveling molecular interconnections and identifying potential therapeutic targets of significance in obesity-cancer link. *Journal of the National Cancer Center.* 5, 8–27 (2025). <https://doi.org/10.1016/j.jncc.2024.11.001>
3. Akter, R., Awais, M., Boopathi, V., Ahn, J.C., Yang, D.C., Kang, S.C., Yang, D.U., Jung, S.-K.: Inversion of the Warburg Effect: Unraveling the Metabolic Nexus between Obesity and Cancer. *ACS Pharmacology & Translational Science.* 7, 560 (2024). <https://doi.org/10.1021/acsptsci.3c00301>
4. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. *Obesity Medicine.* 56, 100623 (2025). <https://doi.org/10.1016/j.obmed.2025.100623>
5. Anand, S., Patel, T.N.: Integrating the metabolic and molecular circuits in diabetes, obesity and cancer: a comprehensive review. *Discov Onc.* 15, 779 (2024). <https://doi.org/10.1007/s12672-024-01662-1>
6. Basso, P.J., Schcolnik-Cabrera, A., Zhu, M., Strachan, E., Clemente-Casares, X., Tsai, S.: Weight Loss-Associated Remodeling of Adipose Tissue Immunometabolism. *Obesity Reviews.* n/a, e13975. <https://doi.org/10.1111/obr.13975>
7. Bays, H.E., Kirkpatrick, C., Maki, K.C., Toth, P.P., Morgan, R.T., Tondt, J., Christensen, S.M., Dixon, D., Jacobson, T.A.: Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association 2024. *Obesity Pillars.* 10, 100108 (2024). <https://doi.org/10.1016/j.obpill.2024.100108>
8. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. *International Journal of Molecular Sciences.* 25, 1882 (2024). <https://doi.org/10.3390/ijms25031882>
9. Collins, K.H., Herzog, W., MacDonald, G.Z., Reimer, R.A., Rios, J.L., Smith, I.C., Zernicke, R.F., Hart, D.A.: Obesity, Metabolic Syndrome, and Musculoskeletal Disease: Common Inflammatory Pathways Suggest a Central Role for Loss of Muscle Integrity. *Front. Physiol.* 9, (2018). <https://doi.org/10.3389/fphys.2018.00112>
10. Chan, Y., Ng, S.W., Tan, J.Z.X., Gupta, G., Negi, P., Thangavelu, L., Balusamy, S.R., Perumalsamy, H., Yap, W.H., Singh, S.K., Caruso, V., Dua, K., Chellappan, D.K.: Natural products in the management of obesity: Fundamental mechanisms and pharmacotherapy. *South African Journal of Botany.* 143, 176–197 (2021). <https://doi.org/10.1016/j.sajb.2021.07.026>

11. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? *Obesity Medicine*. 55, 100610 (2025). <https://doi.org/10.1016/j.obmed.2025.100610>
12. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR- γ expressions with reciprocal suppression of TNF- α gene in obesity. *J Cell Mol Med*. 28, e70086 (2024). <https://doi.org/10.1111/jcmm.70086>
13. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. *Natural Product Communications*. 20, 1934578X251344035 (2025). <https://doi.org/10.1177/1934578X251344035>
14. Alum, E.U.: Antioxidant Effect of *Buchholzia coriacea* Ethanol Leaf-Extract and Fractions on Freund's Adjuvant-Induced Arthritis In Albino Rats: A Comparative Study. *Slovenian Veterinary Research*. 59, (2022). <https://doi.org/10.26873/SVR-1150-2022>
15. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Nna, V.U., Udeozor, P.A.: African walnuts attenuate ectopic fat accumulation and associated peroxidation and oxidative stress in monosodium glutamate-obese Wistar rats. *Biomedicine & Pharmacotherapy*. 124, 109879 (2020). <https://doi.org/10.1016/j.biopha.2020.109879>
16. Gonzalez-Franquesa, A., Gama-Perez, P., Kulis, M., Szczepanowska, K., Dahdah, N., Moreno-Gomez, S., Latorre-Pellicer, A., Fernández-Ruiz, R., Aguilar-Mogas, A., Hoffman, A., Monelli, E., Samino, S., Miró-Blanch, J., Oemer, G., Duran, X., Sanchez-Reboredo, E., Schneeberger, M., Obach, M., Montane, J., Castellano, G., Chapaprieta, V., Sun, W., Navarro, L., Prieto, I., Castaño, C., Novials, A., Gomis, R., Monsalve, M., Claret, M., Graupera, M., Soria, G., Wolfrum, C., Vendrell, J., Fernández-Veledo, S., Enríquez, J.A., Carracedo, A., Perales, J.C., Nogueiras, R., Herrero, L., Trifunovic, A., Keller, M.A., Yanes, O., Sales-Pardo, M., Guimerà, R., Blüher, M., Martín-Subero, J.I., Garcia-Roves, P.M.: Remission of obesity and insulin resistance is not sufficient to restore mitochondrial homeostasis in visceral adipose tissue. *Redox Biology*. 54, 102353 (2022). <https://doi.org/10.1016/j.redox.2022.102353>
17. Koh, Y.-C., Lin, S.-J., Hsu, K.-Y., Nagabhushanam, K., Ho, C.-T., Pan, M.-H.: Pterostilbene Enhances Thermogenesis and Mitochondrial Biogenesis by Activating the SIRT1/PGC-1 α /SIRT3 Pathway to Prevent Western Diet-Induced Obesity. *Mol Nutr Food Res*. 67, e2300370 (2023). <https://doi.org/10.1002/mnfr.202300370>
18. Kuo, C.-L., Ponneri Babuharisankar, A., Lin, Y.-C., Lien, H.-W., Lo, Y.K., Chou, H.-Y., Tangeda, V., Cheng, L.-C., Cheng, A.N., Lee, A.Y.-L.: Mitochondrial oxidative stress in the tumor microenvironment and cancer immunoescape: foe or friend? *Journal of Biomedical Science*. 29, 74 (2022). <https://doi.org/10.1186/s12929-022-00859-2>
19. Zaied, H., Ashmawy, M.I., Abdel Karim, A.E., Ghareeb, D.A., El Wakil, A.: Berberine-loaded albumin nanoparticles alleviate liver damage in rats by modulating mitochondrial biogenesis and mitochondria-endoplasmic reticulum interactions. *Biochem Biophys Res Commun*. 754, 151555 (2025). <https://doi.org/10.1016/j.bbrc.2025.151555>
20. Balan, A.I., Halațiu, V.B., Scridon, A.: Oxidative Stress, Inflammation, and Mitochondrial Dysfunction: A Link between Obesity and Atrial Fibrillation. *Antioxidants (Basel)*. 13, 117 (2024). <https://doi.org/10.3390/antiox13010117>
21. Alharbi, H.O.A., Alshebremi, M., Babiker, A.Y., Rahmani, A.H.: The Role of Quercetin, a Flavonoid in the Management of Pathogenesis Through Regulation of Oxidative Stress, Inflammation, and Biological Activities. *Biomolecules*. 15, 151 (2025). <https://doi.org/10.3390/biom15010151>
22. Aloo, S.O., Barathikannan, K., Oh, D.-H.: Polyphenol-rich fermented hempseed ethanol extracts improve obesity, oxidative stress, and neural health in high-glucose diet-induced *Caenorhabditis elegans*. *Food Chemistry: X*. 21, 101233 (2024). <https://doi.org/10.1016/j.fochx.2024.101233>
23. Feng, J., Zheng, Y., Guo, M., Ares, I., Martínez, M., Lopez-Torres, B., Martínez-Larrañaga, M.-R., Wang, X., Anadón, A., Martínez, M.-A.: Oxidative stress, the blood-brain barrier and neurodegenerative diseases: The critical beneficial role of dietary antioxidants. *Acta Pharmaceutica Sinica B*. 13, 3988–4024 (2023). <https://doi.org/10.1016/j.apsb.2023.07.010>
24. Owczarek, A., Kołodziejczyk-Czepas, J., Marczuk, P., Siwek, J., Wąsowicz, K., Olszewska, M.A.: Bioactivity Potential of Aesculus hippocastanum L. Flower: Phytochemical Profile, Antiradical Capacity and Protective Effects on Human Plasma Components under Oxidative/Nitrative Stress In Vitro. *Pharmaceuticals*. 14, 1301 (2021). <https://doi.org/10.3390/ph14121301>
25. Mokra, D., Joskova, M., Mokry, J.: Therapeutic Effects of Green Tea Polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) in Relation to Molecular Pathways Controlling Inflammation, Oxidative Stress, and Apoptosis. *Int J Mol Sci*. 24, 340 (2022). <https://doi.org/10.3390/ijms24010340>

26. Li, K., Deng, Z., Lei, C., Ding, X., Li, J., Wang, C.: The Role of Oxidative Stress in Tumorigenesis and Progression. *Cells*. 13, 441 (2024). <https://doi.org/10.3390/cells13050441>
27. Sharifi-Rad, M., Anil Kumar, N.V., Zucca, P., Varoni, E.M., Dini, L., Panzarini, E., Rajkovic, J., Tsouh Fokou, P.V., Azzini, E., Peluso, I., Prakash Mishra, A., Nigam, M., El Rayess, Y., Beyrouthy, M.E., Polito, L., Iriti, M., Martins, N., Martorell, M., Docea, A.O., Setzer, W.N., Calina, D., Cho, W.C., Sharifi-Rad, J.: Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. *Front Physiol*. 11, 694 (2020). <https://doi.org/10.3389/fphys.2020.00694>
28. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. *Obesity Medicine*. 54, 100585 (2025). <https://doi.org/10.1016/j.obmed.2025.100585>
29. Sharma, D., Arora, S., Banerjee, A., Singh, J.: Improved insulin sensitivity in obese-diabetic mice via chitosan Nanomicelles mediated silencing of pro-inflammatory Adipocytokines. *Nanomedicine: Nanotechnology, Biology and Medicine*. 33, 102357 (2021). <https://doi.org/10.1016/j.nano.2020.102357>
30. Esquivel-Velázquez, M., Ostoa-Saloma, P., Palacios-Arreola, M.I., Nava-Castro, K.E., Castro, J.I., Morales-Montor, J.: The Role of Cytokines in Breast Cancer Development and Progression. *J Interferon Cytokine Res*. 35, 1–16 (2015). <https://doi.org/10.1089/jir.2014.0026>
31. Čolak, E., Pap, D.: The role of oxidative stress in the development of obesity and obesity-related metabolic disorders. *J Med Biochem*. 40, 1–9 (2021). <https://doi.org/10.5937/jomb0-24652>
32. Arfin, S., Jha, N.K., Jha, S.K., Kesari, K.K., Ruokolainen, J., Roychoudhury, S., Rathi, B., Kumar, D.: Oxidative Stress in Cancer Cell Metabolism. *Antioxidants (Basel)*. 10, 642 (2021). <https://doi.org/10.3390/antiox10050642>
33. Sushma, Sahu, M.R., Murugan, N.A., Mondal, A.C.: Amelioration of Amyloid- β Induced Alzheimer's Disease by *Bacopa monnieri* through Modulation of Mitochondrial Dysfunction and GSK-3 β /Wnt/ β -Catenin Signaling. *Molecular Nutrition Food Res*. 68, 2300245 (2024). <https://doi.org/10.1002/mnfr.202300245>
34. Liu, H., Pan, M., Li, Y., Huang, Z., Li, H., Zhang, C., Guo, C., Wang, H.: Recent advances and applications of mitochondria in tumors and inflammation. *J Transl Med*. 23, 764 (2025). <https://doi.org/10.1186/s12967-025-06722-w>
35. López-Lluch, G.: Mitochondrial activity and dynamics changes regarding metabolism in ageing and obesity. *Mechanisms of Ageing and Development*. 162, 108–121 (2017). <https://doi.org/10.1016/j.mad.2016.12.005>
36. Nissanka, N., Moraes, C.T.: Mitochondrial DNA damage and reactive oxygen species in neurodegenerative disease. *FEBS Lett*. 592, 728–742 (2018). <https://doi.org/10.1002/1873-3468.12956>
37. Abu Shelbayeh, O., Arroum, T., Morris, S., Busch, K.B.: PGC-1 α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. *Antioxidants (Basel)*. 12, 1075 (2023). <https://doi.org/10.3390/antiox12051075>
38. Mao, Y., Xia, Z., Xia, W., Jiang, P.: Metabolic reprogramming, sensing, and cancer therapy. *Cell Reports*. 43, 115064 (2024). <https://doi.org/10.1016/j.celrep.2024.115064>
39. Jun, L., Tao, Y.-X., Geetha, T., Babu, J.R.: Mitochondrial Adaptation in Skeletal Muscle: Impact of Obesity, Caloric Restriction, and Dietary Compounds. *Curr Nutr Rep*. 13, 500–515 (2024). <https://doi.org/10.1007/s13668-024-00555-7>
40. Fernandez, C.J., George, A.S., Subrahmanyam, N.A., Pappachan, J.M.: Epidemiological link between obesity, type 2 diabetes mellitus and cancer. *World Journal of Methodology*. 11, 23–45 (2021). <https://doi.org/10.5662/wjm.v11.i3.23>
41. Berbudi, A., Khairani, S., Tjahjadi, A.I.: Interplay Between Insulin Resistance and Immune Dysregulation in Type 2 Diabetes Mellitus: Implications for Therapeutic Interventions. *Immunotargets Ther*. 14, 359–382 (2025). <https://doi.org/10.2147/ITT.S499605>
42. 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>
43. Veluthakal, R., Esparza, D., Hoolachan, J.M., Balakrishnan, R., Ahn, M., Oh, E., Jayasena, C.S., Thurmond, D.C.: Mitochondrial Dysfunction, Oxidative Stress, and Inter-Organ Miscommunications in T2D Progression. *Int J Mol Sci*. 25, 1504 (2024). <https://doi.org/10.3390/ijms25031504>
44. Xiao Liang, K.: Interplay of mitochondria and diabetes: Unveiling novel therapeutic strategies. *Mitochondrion*. 75, 101850 (2024). <https://doi.org/10.1016/j.mito.2024.101850>
45. Vilas-Boas, E.A., Almeida, D.C., Roma, L.P., Ortis, F., Carpinelli, A.R.: Lipotoxicity and β -Cell Failure in Type 2 Diabetes: Oxidative Stress Linked to NADPH Oxidase and ER Stress. *Cells*. 10, 3328 (2021). <https://doi.org/10.3390/cells10123328>
46. Heimes, F., Berendes, L.-S., Hannibal, L., Park, J.: Antioxidant therapy in inborn metabolic diseases. *Molecular Genetics and Metabolism*. 145, 109176 (2025). <https://doi.org/10.1016/j.ymgme.2025.109176>

47. Chen, X., Xie, N., Feng, L., Huang, Y., Wu, Y., Zhu, H., Tang, J., Zhang, Y.: Oxidative stress in diabetes mellitus and its complications: From pathophysiology to therapeutic strategies. *Chinese Medical Journal*. 138, 15 (2025). <https://doi.org/10.1097/CM9.00000000000003230>
48. Zou, Y., Pitchumoni, C.S.: Obesity, obesities and gastrointestinal cancers. *Disease-a-Month*. 69, 101592 (2023). <https://doi.org/10.1016/j.disamonth.2023.101592>
49. Solsona-Vilarrasa, E., Vousden, K.H.: Obesity, white adipose tissue and cancer. *The FEBS Journal*. 292, 2189–2207 (2025). <https://doi.org/10.1111/febs.17312>
50. Tiwari, R., Mondal, Y., Bharadwaj, K., Mahajan, M., Mondal, S., Sarkar, A.: Reactive Oxygen Species (ROS) and Their Profound Influence on Regulating Diverse Aspects of Cancer: A Concise Review. *Drug Development Research*. 86, e70107 (2025). <https://doi.org/10.1002/ddr.70107>
51. Basheeruddin, M., Qausain, S.: Hypoxia-Inducible Factor 1-Alpha (HIF-1 α) and Cancer: Mechanisms of Tumor Hypoxia and Therapeutic Targeting. *Cureus*. 16, e70700. <https://doi.org/10.7759/cureus.70700>
52. Li, Y., Zhang, M.-Z., Zhang, S.-J., Sun, X., Zhou, C., Li, J., Liu, J., Feng, J., Lu, S.-Y., Pei-Jun, L., Wang, J.-C.: HIF-1 α inhibitor YC-1 suppresses triple-negative breast cancer growth and angiogenesis by targeting PIGF/VEGFR1-induced macrophage polarization. *Biomed Pharmacother*. 161, 114423 (2023). <https://doi.org/10.1016/j.biopha.2023.114423>
53. Magar, A.G., Morya, V.K., Kwak, M.K., Oh, J.U., Noh, K.C.: A Molecular Perspective on HIF-1 α and Angiogenic Stimulator Networks and Their Role in Solid Tumors: An Update. *Int J Mol Sci*. 25, 3313 (2024). <https://doi.org/10.3390/ijms25063313>
54. Ruan, H., Zhang, Q., Zhang, Y., Li, S., Ran, X.: Unraveling the role of HIF-1 α in sepsis: from pathophysiology to potential therapeutics—a narrative review. *Critical Care*. 28, 100 (2024). <https://doi.org/10.1186/s13054-024-04885-4>
55. Rodríguez-Hernández, M.A., Cruz-Ojeda, P. de la, López-Grueso, M.J., Navarro-Villarán, E., Requejo-Aguilar, R., Castejón-Vega, B., Negrete, M., Gallego, P., Vega-Ochoa, Á., Victor, V.M., Cordero, M.D., Del Campo, J.A., Bárcena, J.A., Padilla, C.A., Muntané, J.: Integrated molecular signaling involving mitochondrial dysfunction and alteration of cell metabolism induced by tyrosine kinase inhibitors in cancer. *Redox Biol*. 36, 101510 (2020). <https://doi.org/10.1016/j.redox.2020.101510>
56. Andò, S., Gelsomino, L., Panza, S., Giordano, C., Bonfiglio, D., Barone, I., Catalano, S.: Obesity, Leptin and Breast Cancer: Epidemiological Evidence and Proposed Mechanisms. *Cancers (Basel)*. 11, 62 (2019). <https://doi.org/10.3390/cancers11010062>
57. Bocian-Jastrzębska, A., Malczewska-Herman, A., Kos-Kudła, B.: Role of Leptin and Adiponectin in Carcinogenesis. *Cancers (Basel)*. 15, 4250 (2023). <https://doi.org/10.3390/cancers15174250>
58. Lin, T.-C., Hsiao, M.: Leptin and Cancer: Updated Functional Roles in Carcinogenesis, Therapeutic Niches, and Developments. *Int J Mol Sci*. 22, 2870 (2021). <https://doi.org/10.3390/ijms22062870>
59. Wang, M., Yang, Y., Liao, Z.: Diabetes and cancer: Epidemiological and biological links. *World J Diabetes*. 11, 227–238 (2020). <https://doi.org/10.4239/wjd.v11.i6.227>
60. Zhu, B., Qu, S.: The Relationship Between Diabetes Mellitus and Cancers and Its Underlying Mechanisms. *Front. Endocrinol*. 13, (2022). <https://doi.org/10.3389/fendo.2022.800995>
61. Khalid, M., Petroianu, G., Adem, A.: Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. *Biomolecules*. 12, 542 (2022). <https://doi.org/10.3390/biom12040542>
62. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. *Diabetes & Vascular Disease Research*. 22, 14791641251334726 (2025). <https://doi.org/10.1177/14791641251334726>
63. Clemente-Suárez, V.J., Redondo-Flórez, L., Beltrán-Velasco, A.I., Ramos-Campo, D.J., Belinchón-deMiguel, P., Martínez-Guardado, I., Dalamitros, A.A., Yáñez-Sepúlveda, R., Martín-Rodríguez, A., Tornero-Aguilera, J.F.: Mitochondria and Brain Disease: A Comprehensive Review of Pathological Mechanisms and Therapeutic Opportunities. *Biomedicines*. 11, 2488 (2023). <https://doi.org/10.3390/biomedicines11092488>
64. Chen, S., Li, Q., Shi, H., Li, F., Duan, Y., Guo, Q.: New insights into the role of mitochondrial dynamics in oxidative stress-induced diseases. *Biomedicine & Pharmacotherapy*. 178, 117084 (2024). <https://doi.org/10.1016/j.biopha.2024.117084>
65. Clemente-Suárez, V.J., Martín-Rodríguez, A., Beltrán-Velasco, A.I., Rubio-Zarapuz, A., Martínez-Guardado, I., Valcárcel-Martín, R., Tornero-Aguilera, J.F.: Functional and Therapeutic Roles of Plant-Derived Antioxidants in Type 2 Diabetes Mellitus: Mechanisms, Challenges, and Considerations for Special Populations. *Antioxidants*. 14, 725 (2025). <https://doi.org/10.3390/antiox14060725>
66. Zhang, H., Zhang, Y., Zhang, J., Jia, D.: Exercise Alleviates Cardiovascular Diseases by Improving Mitochondrial Homeostasis. *J Am Heart Assoc*. 13, e036555 (2024). <https://doi.org/10.1161/JAHA.124.036555>

67. Chen, D., Wang, Y., Wu, K., Wang, X.: Dual Effects of Metformin on Adipogenic Differentiation of 3T3-L1 Preadipocyte in AMPK-Dependent and Independent Manners. *Int J Mol Sci.* 19, 1547 (2018). <https://doi.org/10.3390/ijms19061547>
68. Dutta, S., Shah, R.B., Singhal, S., Dutta, S.B., Bansal, S., Sinha, S., Haque, M.: Metformin: A Review of Potential Mechanism and Therapeutic Utility Beyond Diabetes. *Drug Des Devel Ther.* 17, 1907–1932 (2023). <https://doi.org/10.2147/DDDT.S409373>
69. Vancura, A., Bu, P., Bhagwat, M., Zeng, J., Vancurova, I.: Metformin as an Anticancer Agent. *Trends Pharmacol Sci.* 39, 867–878 (2018). <https://doi.org/10.1016/j.tips.2018.07.006>
70. Foretz, M., Guigas, B., Viollet, B.: Metformin: update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol.* 1–17 (2023). <https://doi.org/10.1038/s41574-023-00833-4>

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