EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES (EEJMMS)
ISSN: 2992-4103
©EEJMMS Publications Volume 6 Issue 3 2025

The Interplay between Inflammation, Oxidative Stress, and Cancer in Diabesity: Natural Compounds and Nanoscale Interventions

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ABSTRACT

Diabesity, a synergistic manifestation of obesity and type 2 diabetes mellitus, presents a chronic metabolic condition characterized by persistent inflammation and oxidative stress. These underlying factors significantly contribute to carcinogenesis, establishing diabesity as a major risk factor for several cancers. The intricate pathophysiological connections linking chronic low-grade inflammation and excessive reactive oxygen species with tumor initiation, promotion, and progression underscore the urgency to explore targeted therapies. Natural compounds with potent antioxidant and anti-inflammatory properties have shown promise in modulating these molecular pathways. Moreover, nanoscale drug delivery systems are being increasingly harnessed to enhance the bioavailability, specificity, and therapeutic efficacy of these bioactive compounds. This review comprehensively examines the molecular interplay between inflammation, oxidative stress, and cancer within the context of diabesity. It also highlights emerging research on natural phytochemicals and advanced nanomedicine strategies as potential interventions to mitigate this multifactorial health burden.

Keywords: Diabesity, Inflammation, Oxidative Stress, Cancer, Nanomedicine

INTRODUCTION

The global prevalence of diabesity, a term coined to describe the coexistence and interrelationship between type 2 diabetes mellitus (T2DM) and obesity has escalated alarmingly in recent decades[1–4]. With over 650 million obese individuals and more than 450 million diabetes patients worldwide, the convergence of these two metabolic disorders is no longer viewed as independent epidemics but rather as a dual pandemic[5–7]. This convergence profoundly alters systemic physiology, particularly through the amplification of low-grade chronic inflammation and heightened oxidative stress, both of which serve as principal mediators in the pathogenesis of various malignancies[8–10].

Obesity and T2DM individually contribute to the onset and progression of cancer; however, their combined presence in diabesity creates a unique metabolic milieu conducive to neoplastic transformation[11, 12]. Adipose tissue, especially in excess, acts not only as an energy reservoir but also as an active endocrine organ. It secretes a myriad of bioactive substances, including adipokines, cytokines, and chemokines, that influence systemic metabolism, immune function, and cellular proliferation[13, 14]. In the diabesity state, this secretory profile shifts towards a pro-inflammatory pattern, with elevated levels of tumor necrosis factor-alpha (TNF-\u03b1), interleukin-6 (IL-6), leptin, and resistin, along with decreased adiponectin. These inflammatory mediators promote insulin resistance, further exacerbating hyperglycemia and creating a feedback loop of metabolic dysregulation[8].

Parallel to this, oxidative stress a condition resulting from the imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms is markedly elevated in individuals with diabesity[15, 16]. Persistent hyperglycemia and excess free fatty acids, common in this condition, enhance mitochondrial dysfunction and promote ROS generation. Oxidative stress not only damages cellular macromolecules such as DNA, proteins, and lipids but also activates various redox-sensitive transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-\u03baB) and activator protein-1 (AP-1), both of which are pivotal in regulating genes involved in inflammation and carcinogenesis[17–19].

The bidirectional relationship between inflammation and oxidative stress compounds the risk of oncogenesis. Inflammatory cells such as macrophages and neutrophils produce[17, 20, 21] ROS and reactive nitrogen species

(RNS) during the respiratory burst, which can induce DNA mutations and genomic instability. Simultaneously, oxidative stress enhances the expression of pro-inflammatory cytokines, sustaining a tumor-friendly microenvironment. Furthermore, insulin resistance and hyperinsulinemia associated with diabesity promote increased insulin-like growth factor-1 (IGF-1) signaling, which enhances mitogenic and anti-apoptotic pathways, further contributing to cancer development[22–24].

Given the multifaceted pathophysiology of diabesity-induced carcinogenesis, there is growing interest in multi-targeted therapeutic approaches that can simultaneously modulate inflammation, oxidative stress, and metabolic dysfunction[25–27]. Natural compounds derived from medicinal plants have emerged as promising candidates due to their pleiotropic effects and minimal toxicity. Polyphenols such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) exhibit potent antioxidant, anti-inflammatory, and anti-cancer properties. These compounds modulate key signaling pathways such as NF-\u03baB, PI3K/Akt, and MAPK, thereby interfering with the molecular events underpinning diabesity and cancer[19].

Despite their therapeutic promise, the clinical application of natural compounds is often hampered by poor solubility, limited bioavailability, and rapid metabolism[28]. This challenge has spurred the development of nanotechnology-based delivery systems that can encapsulate bioactive molecules, protect them from degradation, and facilitate targeted delivery to diseased tissues[27, 29, 30]. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles have demonstrated considerable success in enhancing the pharmacokinetics and pharmacodynamics of phytochemicals. Moreover, the functionalization of these nanosystems with ligands specific to cancer or inflamed tissues enhances their specificity and reduces off-target effects[31].

In this review, we delve into the molecular crosstalk between inflammation, oxidative stress, and cancer in the context of diabesity. We also evaluate the therapeutic landscape focusing on natural compounds and nanoscale drug delivery strategies, emphasizing their synergistic potential in addressing this complex pathological triad. Understanding these intricate mechanisms and exploring innovative interventions could pave the way for more effective prevention and treatment strategies for cancer in patients suffering from diabesity.

Molecular Mechanisms Linking Diabesity to Cancer

The link between diabesity and cancer is underpinned by a complex network of molecular and cellular interactions, primarily orchestrated by chronic inflammation and oxidative stress. In the diabesity milieu, adipose tissue expansion is accompanied by immune cell infiltration, particularly of M1 macrophages, which secrete pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β[32]. These mediators perpetuate a state of systemic inflammation and insulin resistance, which not only exacerbates hyperglycemia but also establishes a tumor-promoting environment[33].

Insulin resistance leads to compensatory hyperinsulinemia, which activates insulin and IGF-1 receptors on various cells, stimulating downstream signaling cascades like the PI3K/Akt and MAPK pathways[34–36]. These pathways are known for their roles in promoting cell survival, proliferation, and angiogenesis, while inhibiting apoptosis—hallmarks of cancer development. Moreover, hyperglycemia and elevated free fatty acids further stimulate ROS production through mitochondrial dysfunction, activation of NADPH oxidase, and glycation reactions that form advanced glycation end-products (AGEs). AGEs interact with their receptor (RAGE), enhancing NF-κB activation and thus further propagating inflammation and ROS generation in a vicious cycle[37].

Oxidative stress damages cellular components, including DNA, leading to mutations, chromosomal instability, and altered gene expression. Additionally, oxidative stress activates transcription factors such as AP-1 and STAT3, both of which are implicated in inflammation-driven tumorigenesis[16, 38]. The tumor microenvironment in diabesity is also rich in leptin, a pro-inflammatory adipokine that promotes angiogenesis, cell proliferation, and metastasis through the JAK/STAT and PI3K pathways[39–41]. Conversely, adiponectin levels are reduced, depriving cells of its protective anti-inflammatory and anti-proliferative effects.

Hypoxia in hypertrophic adipose tissue further compounds the oncogenic process by stabilizing hypoxia-inducible factor-1α (HIF-1α), which upregulates VEGF and other angiogenic factors. Together, these molecular events not only foster a conducive environment for cancer initiation but also support its progression and resistance to therapy[42, 43]. Thus, understanding these intricate mechanisms is vital for developing targeted interventions aimed at disrupting the diabesity-cancer continuum.

Role of Natural Compounds in Modulating Inflammation and Oxidative Stress

Natural compounds have long served as therapeutic agents for managing various diseases, including cancer and metabolic disorders[25, 26]. Their role in diabesity-associated carcinogenesis is garnering increasing attention due to their multi-targeted actions, low toxicity, and ability to modulate critical molecular pathways involved in inflammation and oxidative stress.

Polyphenols, flavonoids, alkaloids, terpenoids, and other phytochemicals exert anti-inflammatory effects by inhibiting the activity of key transcription factors such as NF-κB, which regulates the expression of pro-inflammatory cytokines and enzymes like COX-2 and iNOS[20, 44, 45]. For example, curcumin from turmeric

suppresses NF-κB signaling, downregulates IL-6 and TNF-α, and inhibits COX-2 expression, thereby reducing systemic inflammation. Resveratrol, a stilbene found in grapes and berries, inhibits the activation of NF-κB and STAT3 while enhancing antioxidant enzyme activities like superoxide dismutase (SOD) and catalase[37, 46].
Antioxidant activity of natural compounds is crucial in neutralizing ROS and protecting cellular structures from oxidative damage. Epigallocatechin gallate (EGCG), a major catechin in green tea, scavenges free radicals, chelates transition metals, and upregulates endogenous antioxidant defenses. Similarly, quercetin and kaempferol reduce oxidative stress by enhancing the nuclear translocation of Nrf2, a master regulator of the antioxidant response element (ARE)-driven gene expression[47–49]. These compounds also interfere with tumorigenic signaling pathways. For instance, apigenin and luteolin inhibit the PI3K/Akt and MAPK pathways, leading to the suppression of cancer cell proliferation and the induction of apoptosis. Berberine, an isoquinoline alkaloid, has demonstrated significant anti-diabetic and anti-cancer properties through AMPK activation and modulation of mitochondrial function[50–52].

Furthermore, dietary natural compounds regulate adipokine expression and secretion, which play pivotal roles in modulating inflammation and cancer risk in diabesity. For example, genistein, a soy isoflavone, enhances adiponectin secretion while reducing leptin and inflammatory cytokines, improving insulin sensitivity and attenuating pro-cancerous pathways[5, 53]. Importantly, the synergistic use of these compounds with conventional therapies has shown improved outcomes in preclinical models, highlighting their potential in integrative oncology and metabolic disease management. However, limitations such as low solubility, poor bioavailability, and rapid metabolism in the gastrointestinal tract necessitate advanced strategies to maximize their therapeutic utility[53, 54].
Continued research is essential to uncover new bioactive compounds from plants, fungi, and marine organisms with strong anti-inflammatory and antioxidant properties. Pharmacokinetic optimization and structural modifications can help overcome delivery challenges. In parallel, mechanistic studies are crucial to elucidate their molecular targets and interactions within cellular networks.

Nanoscale Interventions for Targeted Therapy

Nanotechnology offers innovative solutions to the limitations of natural compounds by enhancing their delivery, stability, and therapeutic efficacy[31, 55, 56]. Nanoscale drug delivery systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and nanomicelles have shown great promise in addressing the pathophysiological complexities of diabesity-associated cancer[57, 58].
These nanocarriers can encapsulate natural compounds, protecting them from degradation and enhancing their solubility and systemic circulation time. For example, curcumin-loaded liposomes and resveratrol-encapsulated polymeric nanoparticles have demonstrated significantly improved bioavailability and anti-tumor effects in experimental models[59–61]. By modifying the surface of these nanocarriers with ligands or antibodies specific to cancer biomarkers or inflammatory cells, targeted delivery to the tumor or inflamed adipose tissue is achieved, thereby reducing off-target effects and enhancing therapeutic index. Smart nanosystems that respond to specific stimuli in the tumor microenvironment such as pH, temperature, enzymes, or redox status further improve drug release kinetics and site-specific activation. Additionally, co-delivery platforms that transport a combination of natural compounds and chemotherapeutics enable synergistic action while minimizing toxicity and resistance[37].
Beyond drug delivery, nanotechnology also plays a role in diagnostics and imaging. Theranostic nanoparticles combine therapeutic and diagnostic functions, allowing real-time monitoring of drug distribution, tumor targeting, and therapeutic response[37]. This is particularly valuable in managing complex diseases like diabesity-linked cancers, where early detection and personalized treatment strategies are crucial[8]. Emerging developments in nanomedicine include the use of exosomes and biomimetic nanoparticles, which leverage natural biological systems for targeted and immune-evasive delivery. Integration with microRNA or gene editing technologies, such as CRISPR/Cas9-loaded nanoparticles, offers potential avenues for correcting molecular derangements at the genetic level in diabesity and cancer[8].
Nevertheless, challenges such as biocompatibility, immune reactions, long-term toxicity, and regulatory hurdles must be addressed before widespread clinical adoption. Ongoing research is focused on optimizing nanomaterials, improving scalable production, and ensuring their safety and efficacy through rigorous preclinical and clinical evaluations.

Challenges and Future Perspectives

Despite significant advances in understanding the interplay between diabesity, inflammation, oxidative stress, and cancer, several challenges hinder the development and implementation of effective interventions. One major obstacle is the heterogeneity of patient populations and disease manifestations, which complicates the development of one-size-fits-all therapies. The inter-individual variability in genetic background, gut microbiome composition, lifestyle factors, and comorbidities necessitates personalized approaches.
The limited bioavailability and pharmacokinetic profiles of many promising natural compounds also present a barrier. Although nanotechnology has provided effective delivery solutions, translating these into clinical

practice requires overcoming technical and regulatory constraints. Additionally, long-term safety data on nanomedicine applications remain scarce, necessitating cautious and comprehensive evaluation.
Another challenge lies in the integration of multi-targeted therapies into standard care protocols. Current healthcare systems are often structured around mono-therapeutic approaches and may not be equipped to handle complex interventions involving combinations of natural compounds, nanocarriers, and conventional drugs. This calls for a paradigm shift in treatment design and implementation, emphasizing systems biology and network pharmacology.

Furthermore, the regulatory framework for natural compounds and nanomedicines often lags behind scientific innovation. Clear guidelines on manufacturing, quality control, and clinical evaluation are essential to ensure consistent and safe therapeutic products. Equally important is the education of healthcare professionals and the public about the benefits and limitations of these novel interventions.
Future research should focus on identifying specific molecular signatures of diabesity-related cancers to enable early diagnosis and precision therapy. High-throughput omics technologies, artificial intelligence, and machine learning can be harnessed to uncover novel biomarkers and predictive models. Furthermore, clinical trials assessing the efficacy and safety of phytochemical-loaded nanocarriers must be prioritized to validate their potential in real-world settings.
Collaboration between academic researchers, clinicians, regulatory agencies, and the pharmaceutical industry is essential to translate laboratory findings into accessible therapies. Public health strategies must also emphasize lifestyle interventions, nutritional education, and early screening programs to curb the rising incidence of diabesity and its complications.

CONCLUSION

In conclusion, addressing the intertwined pathologies of inflammation, oxidative stress, and cancer in diabesity requires a holistic and multi-pronged approach. Natural compounds, when effectively delivered through nanotechnology, hold significant promise as part of an integrative strategy to combat this global health challenge. Innovations in targeted delivery systems, systems biology, and precision medicine will pave the way for more effective interventions. Ultimately, a collaborative effort that bridges scientific discovery, clinical practice, and public health policy is necessary to mitigate the burden of diabesity-associated cancers.

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CITE AS: Kato Jumba K. (2025). The Interplay between Inflammation, Oxidative Stress, and Cancer in Diabesity: Natural Compounds and Nanoscale Interventions. EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES, 6(3):52-55