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Adaptogenic and Antioxidant Properties of Herbal Compounds in Combatting Oxidative Stress in Obesity-Linked Diabetes

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ABSTRACT

Obesity-linked diabetes, also known as diabesity, is a growing global health concern characterized by insulin resistance, chronic inflammation, and oxidative stress. Oxidative stress plays a pivotal role in the pathogenesis of obesity-induced insulin resistance by disrupting cellular homeostasis, impairing pancreatic β-cell function, and promoting pro-inflammatory pathways. Recent evidence suggests that plant-derived bioactive compounds with adaptogenic and antioxidant properties offer promising therapeutic potential in mitigating oxidative stress and its associated metabolic dysfunctions. This review explores the role of oxidative stress in obesity-linked diabetes, highlighting the molecular mechanisms through which herbal compounds exert their adaptogenic and antioxidant effects. Key bioactive phytochemicals, including polyphenols, flavonoids, alkaloids, terpenoids, and saponins, are discussed in the context of their ability to enhance insulin sensitivity, modulate inflammatory responses, and regulate glucose metabolism. Additionally, we examine preclinical and clinical studies demonstrating the efficacy of medicinal plants such as Curcuma longa, Withania somnifera, Panax ginseng, and Camellia sinensis in reducing oxidative damage and improving metabolic outcomes. Understanding the synergistic interactions of these herbal compounds may provide new insights into integrative therapeutic approaches for managing obesity-linked diabetes.

Keywords: Adaptogens, Antioxidants, Obesity-Linked Diabetes, Oxidative Stress, Insulin Resistance, Herbal Medicine, Phytochemicals

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are closely interrelated metabolic disorders, collectively referred to as "diabesity"[1–4]. They are driven by a complex interplay of genetic, environmental, and lifestyle factors, with chronic low-grade inflammation and oxidative stress playing central roles in their pathogenesis [5–7]. The excessive accumulation of adipose tissue in obesity is not merely a passive energy reservoir but an active endocrine organ that secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and resisting [4]. These inflammatory mediators contribute to insulin resistance by interfering with insulin receptor signaling, impairing glucose uptake, and exacerbating metabolic dysfunction [8, 9]. Additionally, obesity is associated with mitochondrial dysfunction and increased production of reactive oxygen species (ROS), which further aggravate oxidative stress and disrupt insulin homeostasis [10–12]. Oxidative stress arises when the balance between ROS production and antioxidant defense mechanisms is disrupted, leading to cellular damage[13, 14]. In the context of diabesity, ROS overproduction not only damages pancreatic β-cells but also affects key insulin-signaling pathways in peripheral tissues, including skeletal muscle, liver, and adipose tissue. β-cells are particularly vulnerable to oxidative stress due to their relatively low expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase[15]. This oxidative burden accelerates β-cell apoptosis, impairs insulin secretion, and worsens hyperglycemia, creating a vicious cycle of metabolic deterioration.

Given the pivotal role of oxidative stress in the onset and progression of diabesity, considerable research has focused on developing therapeutic strategies to counteract ROS-induced damage[16]. While conventional antidiabetic medications such as metformin, thiazolidinediones, and insulin therapy offer glycemic control, they do not specifically target oxidative stress. As a result, there has been growing interest in plant-based

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antioxidants and adaptogens—naturally occurring bioactive compounds with potent antioxidative, anti-inflammatory, and insulin-sensitizing properties[17]. Herbal antioxidants such as polyphenols, flavonoids, carotenoids, and alkaloids exert their beneficial effects by scavenging free radicals, upregulating endogenous antioxidant defense systems, and modulating key signaling pathways involved in glucose and lipid metabolism. For example, curcumin, a polyphenol derived from *Curcuma longa*, has been shown to reduce oxidative stress by activating nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that enhances the expression of antioxidant enzymes. Similarly, resveratrol, a stilbenoid found in grapes and berries, improves insulin sensitivity and mitochondrial function while reducing oxidative stress and inflammation [18].

Preclinical and clinical studies have provided compelling evidence supporting the therapeutic potential of plant-derived antioxidants in diabesity management[18]. Animal models of diet-induced obesity and diabetes have demonstrated that supplementation with polyphenols improves glucose homeostasis, reduces lipid accumulation, and protects pancreatic β-cells from oxidative damage[2, 19]. Clinical trials have also reported that dietary interventions rich in antioxidants, such as green tea catechins and berberine, significantly improve insulin sensitivity and lipid profiles in patients with T2DM[18]. This review explores the molecular underpinnings of oxidative stress in diabesity, highlighting the pathophysiological mechanisms involved, the role of herbal antioxidants in alleviating oxidative damage, and emerging evidence from both experimental and clinical studies. Understanding these mechanisms could pave the way for the development of novel antioxidant-based interventions to mitigate the burden of obesity-linked diabetes and improve metabolic health outcomes.

Oxidative Stress and Its Role in Obesity-Linked Diabetes

Oxidative stress is a condition that arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms[16, 20, 21]. Under normal physiological conditions, ROS play essential roles in cell signaling and homeostasis. However, when their levels become excessive, they can cause cellular damage, leading to a cascade of metabolic disturbances. In obesity, chronic overnutrition results in increased metabolic activity and mitochondrial dysfunction, leading to excessive ROS generation[22, 23]. This oxidative burden triggers inflammatory pathways that further compromise cellular function, creating a vicious cycle that contributes to the pathogenesis of metabolic disorders such as diabesity—a combination of obesity and type 2 diabetes. One of the major mechanisms through which oxidative stress contributes to diabesity is pancreatic β-cell dysfunction[23, 24]. The pancreatic β-cells are responsible for insulin secretion in response to glucose levels, but they are particularly susceptible to oxidative damage due to their low antioxidant capacity. Elevated ROS levels can induce β-cell apoptosis, reducing the overall number of functional insulin-secreting cells. Additionally, oxidative stress impairs insulin synthesis and secretion, leading to inadequate glycemic control[24, 25]. As β-cell function deteriorates, the body struggles to maintain normal blood glucose levels, ultimately progressing toward type 2 diabetes. Another significant effect of oxidative stress in diabesity is the development of insulin resistance[26]. Insulin signaling relies on a complex network of molecular interactions, including the activation of insulin receptor substrates (IRS) and the translocation of glucose transporter 4 (GLUT4) to the cell membrane for glucose uptake.[27, 28]. However, oxidative stress disrupts these pathways by inducing post-translational modifications, such as phosphorylation of IRS proteins at inhibitory sites, which attenuates insulin signaling[29]. Additionally, ROS interfere with GLUT4 expression and function, reducing glucose uptake in muscle and adipose tissues. As a result, cells become resistant to insulin, leading to hyperglycemia and further exacerbation of metabolic dysfunction[29]. Chronic inflammation is another critical link between oxidative stress and diabesity. ROS act as key mediators of inflammation by activating nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These inflammatory mediators contribute to the progression of insulin resistance by interfering with insulin signaling pathways. Moreover, oxidative stress promotes the infiltration of immune cells, such as macrophages, into adipose tissue, further amplifying inflammation[30, 31]. This sustained inflammatory state not only worsens insulin resistance but also increases the risk of developing complications such as cardiovascular disease and non-alcoholic fatty liver disease. In sum, oxidative stress plays a pivotal role in the development of diabesity by impairing pancreatic β-cell function, promoting insulin resistance, and triggering chronic inflammation. The interplay between excessive ROS production and metabolic dysfunction underscores the importance of antioxidant defense mechanisms in preventing and managing obesity-related diabetes. Future therapeutic strategies aimed at reducing oxidative stress, either through lifestyle modifications or pharmacological interventions, may offer promising approaches to mitigate the impact of diabesity and improve metabolic health.

Herbal Adaptogens and Antioxidants in Diabesity Management

Plants synthesize a diverse array of bioactive compounds with adaptogenic and antioxidant properties. These phytochemicals counteract oxidative stress through multiple mechanisms, including scavenging free radicals, upregulating endogenous antioxidant enzymes, and modulating inflammatory signaling pathways[18].

Polyphenols: Polyphenols are bioactive compounds found in fruits, vegetables, and medicinal plants, renowned for their potent antioxidant and anti-inflammatory properties[32, 33]. Among them, curcumin, derived from *Curcuma longa*, exhibits strong antioxidant effects by inhibiting nuclear factor-kappa B (NF-κB), a key regulator

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of inflammation, while simultaneously activating nuclear factor erythroid 2-related factor 2 (Nrf2), which enhances cellular defense mechanisms against oxidative stress[34, 35]. Similarly, epigallocatechin gallate (EGCG), the predominant polyphenol in *Camellia sinensis* (green tea), plays a crucial role in mitochondrial function by reducing oxidative damage and improving cellular energy metabolism[36, 37,38,39,40,41,42]. Another significant polyphenol, resveratrol, found in *Vitis vinifera* (grapes), is known for its ability to modulate AMP-activated protein kinase (AMPK) signaling, thereby promoting glucose homeostasis and enhancing insulin sensitivity[43,44,45,46,47,48,49]. These polyphenols collectively contribute to reducing the risk of chronic diseases such as diabetes, cardiovascular disorders, and neurodegenerative conditions by counteracting oxidative stress and inflammation at the molecular level. Their diverse mechanisms of action make them promising candidates for therapeutic interventions aimed at improving metabolic and cellular health. Ongoing research continues to explore their potential applications in drug development, reinforcing their significance in nutrition, medicine, and preventive healthcare strategies.

Flavonoids: Flavonoids, a subclass of polyphenols, are known for their potent antioxidant properties and significant roles in metabolic regulation[50,51,52,53,54,55,56,57,58]. Among them, quercetin has demonstrated the ability to lower blood glucose levels and enhance insulin sensitivity by modulating key inflammatory markers, thereby reducing oxidative stress and improving glucose homeostasis[42]. This flavonoid interacts with various signaling pathways involved in inflammation and insulin resistance, making it a promising candidate for managing metabolic disorders such as diabetes. Similarly, kaempferol exerts beneficial effects on glucose metabolism by enhancing the expression of glucose transporter type 4 (GLUT4) and promoting glucose uptake in skeletal muscle cells. By facilitating GLUT4 translocation to the cell membrane, kaempferol improves cellular glucose absorption, which is essential for maintaining energy balance and preventing hyperglycemia[59,60,61,62,63,64,65]. These flavonoids contribute to metabolic health not only through their direct effects on glucose regulation but also by mitigating oxidative stress and inflammation, which are key contributors to insulin resistance and metabolic dysfunction. Their bioactive properties make them valuable in dietary interventions and potential therapeutic agents for diabetes management. Overall, quercetin and kaempferol exemplify the therapeutic potential of flavonoids in modulating key metabolic pathways, offering promising avenues for improving insulin sensitivity and glucose homeostasis.

Alkaloids: Berberine, a bioactive alkaloid derived from *Berberis* species, exhibits potent antidiabetic properties by mimicking metformin-like effects. It primarily activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis, thereby enhancing insulin sensitivity and promoting glucose uptake in peripheral tissues[66,67,68,69,70]. Additionally, berberine reduces oxidative stress by modulating reactive oxygen species (ROS) levels and improving mitochondrial function. Its ability to lower blood glucose levels through multiple pathways, including inhibition of gluconeogenesis and enhancement of glycolysis, makes it a promising natural compound for diabetes management.

Terpenoids and Saponins: Ginsenosides, the primary bioactive compounds in *Panax ginseng*, regulate glucose metabolism by enhancing insulin secretion from pancreatic β-cells and mitigating oxidative damage[66,67,68,69,70]. These triterpenoid saponins also improve insulin sensitivity in target tissues, reducing hyperglycemia-related complications. Similarly, withanolides, derived from *Withania somnifera*, exert protective effects by enhancing mitochondrial function and reducing ROS-induced cellular stress.[71,72,73,74,75,76,77,78] Their antioxidant and anti-inflammatory properties contribute to improved metabolic homeostasis, making them valuable candidates for therapeutic intervention in metabolic disorders.

Evidence from Preclinical and Clinical Studies

Several experimental and clinical studies have validated the antioxidant and adaptogenic properties of herbal compounds, highlighting their potential in managing metabolic disorders. Curcumin, a bioactive component of turmeric, has been extensively studied for its therapeutic effects. Research has shown that curcumin supplementation lowers oxidative stress biomarkers, which are crucial indicators of cellular damage[80,81]. Additionally, curcumin improves insulin sensitivity in diabetic patients, thereby helping regulate blood glucose levels and reducing complications associated with diabetes.

Another well-known herbal compound, ginseng, has demonstrated significant benefits in metabolic health. Ginseng extracts are known to enhance mitochondrial function, which plays a pivotal role in energy metabolism. Moreover, ginseng exhibits anti-inflammatory properties that help mitigate obesity-related metabolic dysfunction, reducing the risk of insulin resistance and other metabolic complications[52, 53]. These effects make ginseng a promising natural remedy for individuals struggling with obesity and metabolic syndrome.

Green tea polyphenols further contribute to metabolic health through their potent antioxidant effects. Studies have shown that these bioactive compounds help lower fasting glucose levels, making them beneficial for diabetes management[36, 54]. Additionally, green tea polyphenols improve lipid profiles by reducing cholesterol levels and promoting cardiovascular health. The cumulative evidence supporting these herbal compounds underscores their potential as complementary interventions for metabolic disorders, providing a natural and effective approach to disease prevention and management.

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Synergistic Effects and Future Perspectives

The combined effects of multiple herbal compounds may enhance their therapeutic efficacy through synergistic interactions, offering a promising approach to managing complex metabolic disorders like diabesity. Herbal adaptogens, rich in bioactive phytochemicals, have shown potential in modulating key metabolic pathways, including insulin signaling, lipid metabolism, and inflammatory responses. Understanding these mechanisms at a molecular level is essential for optimizing their therapeutic benefits. Future research should focus on mechanistic studies to unravel the precise pathways influenced by these compounds, providing a scientific basis for their use in diabetes and obesity management. Furthermore, clinical trials are crucial to validating the long-term efficacy and safety of herbal adaptogens in diabesity treatment. While preclinical studies have demonstrated promising results, robust clinical evidence is needed to assess their effectiveness in diverse patient populations. Well-designed randomized controlled trials can help determine optimal dosages, potential drug-herb interactions, and overall safety profiles. These studies will be instrumental in gaining regulatory approval and integrating herbal formulations into mainstream medical practice for metabolic disorders. In addition to clinical validation, personalized medicine approaches should be explored to optimize treatment outcomes. The integration of herbal compounds with conventional diabetes therapies can be tailored based on an individual's genetic makeup, metabolic profile, and disease progression. Advances in pharmacogenomics and precision medicine can help identify patients who are most likely to benefit from specific herbal interventions. This holistic approach will pave the way for more effective and patient-centric diabesity management, leveraging the complementary benefits of both traditional and modern therapeutic strategies.

CONCLUSION

Oxidative stress is a key driver of obesity-linked diabetes, necessitating effective interventions that restore redox balance. Herbal adaptogens and antioxidants offer a promising natural alternative for mitigating oxidative damage and improving metabolic outcomes. While preclinical and clinical evidence supports their role in enhancing insulin sensitivity and reducing inflammation, further research is needed to optimize their therapeutic applications in diabesity management.

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