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Targeting NF-κB and NLRP3 Inflammasome Pathways with Flavonoids in Obesity-Related Diabetes

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ABSTRACT

Obesity-related diabetes, often referred to as type 2 diabetes (T2D), is a growing global health concern with complex pathophysiological mechanisms involving inflammation, insulin resistance, and metabolic dysregulation. The nuclear factor kappa B (NF-κB) and NLRP3 inflammasome pathways are central to the chronic inflammation seen in obesity and T2D. Both pathways play pivotal roles in the activation of inflammatory cytokines that impair insulin signaling and contribute to systemic metabolic dysfunction. Flavonoids, a diverse group of polyphenolic compounds abundant in fruits, vegetables, and medicinal plants, have shown promising anti-inflammatory, antioxidant, and metabolic-modulating properties. Recent research has revealed that flavonoids can modulate the NF-κB and NLRP3 inflammasome pathways, thereby alleviating inflammation and improving insulin sensitivity. This review explores the molecular mechanisms by which flavonoids target these pathways, emphasizing their potential therapeutic role in managing obesity-related diabetes. Additionally, we examine the available preclinical and clinical evidence supporting the use of flavonoids as adjuncts in the treatment of T2D and discuss the challenges and future directions in translating flavonoid-based therapies into clinical practice.

Keywords: Obesity-related diabetes, type 2 diabetes, NF-κB, NLRP3 inflammasome, flavonoids, inflammation, insulin resistance, metabolic dysregulation

INTRODUCTION

Obesity-related type 2 diabetes (T2D) is a prevalent and serious metabolic disorder that affects millions of people worldwide[1–3]. It is primarily characterized by insulin resistance, chronic low-grade systemic inflammation, and disrupted glucose metabolism[4–7]. These interconnected pathophysiological features contribute to the development and progression of T2D and are influenced by a complex interplay of genetic predisposition, environmental factors, and lifestyle choices such as poor diet and physical inactivity. As obesity rates continue to rise globally, the incidence of T2D has reached alarming levels, prompting a critical need to understand its underlying mechanisms and identify effective therapeutic strategies[8–10].

At the heart of T2D pathogenesis is insulin resistance, a condition in which cells in muscles, fat, and the liver become less responsive to the actions of insulin, a hormone essential for regulating blood glucose levels[11, 12]. This impaired response leads to elevated blood glucose and compensatory increases in insulin secretion by pancreatic β-cells. Over time, this compensatory mechanism fails, resulting in overt hyperglycemia and the clinical onset of diabetes[13, 14]. Among the numerous contributors to insulin resistance, chronic inflammation has emerged as a key driver.

Inflammatory signaling pathways play a significant role in mediating the metabolic dysfunction observed in T2D. In particular, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathways have gained considerable attention[15–17]. Both are integral to the body's innate immune response and have been shown to be hyperactivated in the context of obesity. Adipose tissue, especially in obese individuals, becomes infiltrated with immune cells such as macrophages, which release pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These cytokines activate the NF-κB signaling cascade and stimulate the assembly and activation of the NLRP3 inflammasome complex, perpetuating inflammation and further impairing insulin signaling[18–20].

Given the central role of inflammation in obesity-induced insulin resistance, targeting these inflammatory pathways offers a promising avenue for therapeutic intervention. One area of growing interest is the use of dietary bioactive compounds, particularly flavonoids, for their anti-inflammatory and insulin-sensitizing effects[21–23]. Flavonoids are a diverse group of polyphenolic compounds naturally found in fruits, vegetables, tea, cocoa, and other plant-derived foods[24, 25]. They exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, and anti-diabetic effects [26]. Research has demonstrated that flavonoids can effectively modulate key molecular targets involved in inflammation and metabolic dysfunction. For example, several flavonoids have been shown to inhibit the activation of NF-κB by preventing the degradation of its inhibitory protein IκB, thereby reducing the transcription of pro-inflammatory genes. Additionally, flavonoids can suppress the activation of the NLRP3 inflammasome, limiting the maturation and release of IL-1β and IL-18, two key cytokines involved in the progression of insulin resistance and β-cell dysfunction[24, 27].

Beyond their molecular effects, flavonoids may also improve insulin sensitivity and glucose uptake in peripheral tissues, enhance lipid metabolism, and reduce oxidative stress, which collectively contribute to restoring metabolic balance[28, 29]. These properties make flavonoids attractive candidates for the development of nutraceuticals or complementary therapies aimed at managing or preventing obesity-related diabetes. In sum, the NF-κB and NLRP3 inflammasome pathways are critical mediators of the chronic inflammation observed in obesity-associated T2D. Flavonoids, through their ability to modulate these inflammatory cascades and improve metabolic parameters, represent a promising strategy for combating insulin resistance and restoring glucose homeostasis. Continued research into the specific mechanisms of flavonoid action and their clinical efficacy will be essential for translating these findings into practical therapeutic applications for patients with T2D.

NF-κB Pathway in Obesity-Related Diabetes

The NF-κB pathway is a crucial signaling cascade involved in regulating immune responses and inflammation[30]. This pathway is particularly significant in the context of obesity, where its activation plays a central role in the development of insulin resistance and the progression of type 2 diabetes (T2D). Adipose tissue, when in excess due to obesity, undergoes significant alterations. One of the major changes is the secretion of adipokines, which are signaling molecules released by adipocytes (fat cells). These adipokines, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), trigger the activation of the NF-κB pathway[12, 31, 32].

In healthy individuals, NF-κB activation is tightly regulated to ensure proper immune responses. However, in obesity, the overabundance of adipose tissue leads to the persistent activation of NF-κB[33]. This chronic activation results in an ongoing inflammatory state that affects not only the adipose tissue itself but also peripheral organs involved in metabolism, such as the liver and skeletal muscle. One of the primary consequences of NF-κB activation is the disruption of insulin signaling. Normally, insulin binds to its receptor on the surface of target cells, triggering a cascade of signals that promote glucose uptake and storage[33, 34]. However, when NF-κB is activated, it interferes with this signaling pathway by promoting the expression of inflammatory cytokines, which inhibit insulin receptor signaling. As a result, muscle and liver cells become less responsive to insulin, a condition known as insulin resistance[34].

The role of NF-κB in obesity-induced insulin resistance is further compounded by its impact on pancreatic β-cells, which are responsible for producing insulin. Chronic inflammation, driven by persistent NF-κB activation, leads to β-cell dysfunction, impairing their ability to secrete insulin properly[35]. This dysfunction exacerbates the hyperglycemia (high blood sugar) that is characteristic of T2D, creating a vicious cycle where insulin resistance and β-cell dysfunction perpetuate the disease. Given the central role of NF-κB in the pathogenesis of obesity-related insulin resistance and T2D, targeting this pathway has become an attractive therapeutic strategy. One promising approach involves the use of natural compounds, particularly flavonoids, which have been shown to modulate the NF-κB signaling pathway[35]. Flavonoids, a group of polyphenolic compounds found in fruits, vegetables, and tea, have demonstrated potent anti-inflammatory and antioxidant properties. Among these flavonoids, quercetin, kaempferol, and epigallocatechin gallate (EGCG) stand out for their ability to inhibit NF-κB activation[36–38]. The mechanisms by which flavonoids inhibit NF-κB are diverse. For example, quercetin and kaempferol can suppress the activity of upstream kinases, such as IκB kinase (IKK), which play a pivotal role in the activation of NF-κB. IKK phosphorylates IκB proteins, leading to their degradation and allowing NF-κB dimers (such as p65/p50) to translocate into the nucleus, where they activate the expression of inflammatory genes[39–41]. By inhibiting IKK, flavonoids prevent the degradation of IκB and thus block the activation of NF-κB[42].

Flavonoids can also modulate the production of pro-inflammatory cytokines, further dampening the inflammatory response. For instance, EGCG, a major polyphenol in green tea, has been shown to reduce the expression of TNF-α, IL-6, and IL-1β, cytokines that are upregulated by NF-κB activation in obesity[43]. By decreasing the levels of these cytokines, flavonoids help to reduce the inflammatory burden within adipose tissue and other metabolic organs, which in turn can reverse or mitigate the development of insulin resistance. In

addition to their effects on insulin sensitivity, flavonoids may also have beneficial effects on glucose metabolism. By downregulating NF-κB activity and reducing inflammation, flavonoids can help restore normal glucose homeostasis.[43] This suggests that flavonoid-rich diets or supplementation may provide a complementary approach to managing obesity-related metabolic dysfunction and improving glycemic control in individuals with T2D.

In sum, the NF-κB pathway is a key mediator of the inflammatory responses that drive insulin resistance and β-cell dysfunction in obesity. Flavonoids such as quercetin, kaempferol, and EGCG offer promising therapeutic potential by inhibiting NF-κB activation and reducing systemic inflammation. Through these mechanisms, flavonoids can help improve insulin sensitivity, restore glucose homeostasis, and potentially prevent or reverse the development of T2D. Further research is needed to explore the clinical applicability of flavonoids in the management of obesity-related metabolic disorders, but the evidence thus far is promising.

NLRP3 Inflammasome in Obesity-Related Diabetes

The NLRP3 inflammasome is a crucial component of the innate immune system, playing an essential role in the regulation of inflammatory responses[44]. It is responsible for the activation of caspase-1, which in turn initiates the release of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β) and interleukin-18 (IL-18). These cytokines are pivotal in driving systemic inflammation, a central feature in the pathogenesis of several metabolic disorders, including obesity, type 2 diabetes (T2D), and insulin resistance[45]. Under normal conditions, the NLRP3 inflammasome remains inactive but can be triggered by a variety of stressors, including pathogens, damage-associated molecular patterns (DAMPs), and metabolic imbalances such as excessive nutrient accumulation and oxidative stress.

In the context of obesity, the NLRP3 inflammasome is often activated in key tissues such as adipocytes (fat cells) and macrophages, contributing to chronic low-grade inflammation[46]. This inflammation impairs normal metabolic processes, exacerbating insulin resistance and promoting β-cell dysfunction in the pancreas, which are both hallmark features of T2D. Adipocytes, particularly in obese individuals, become dysfunctional, secreting pro-inflammatory cytokines like IL-6 and TNF-α, which further activate the NLRP3 inflammasome[46]. The chronic activation of the NLRP3 inflammasome, especially in adipose tissue, worsens systemic inflammation and leads to impaired insulin signaling pathways. This results in reduced glucose uptake, increased glucose production by the liver, and eventually the development of insulin resistance[47].

The impact of NLRP3 inflammasome activation extends beyond insulin resistance, as it also contributes to β-cell dysfunction. β-cells in the pancreas are responsible for insulin production, and under conditions of chronic inflammation, they are particularly vulnerable to cytokine-induced apoptosis, which significantly impairs insulin secretion. Furthermore, the activation of NLRP3 inflammasome contributes to the formation of reactive oxygen species (ROS), which are known to damage cellular components, further exacerbating metabolic dysfunction. In this way, the NLRP3 inflammasome is a central mediator of the metabolic dysregulation observed in obesity and T2D[48, 49].

Given the critical role of the NLRP3 inflammasome in the pathogenesis of insulin resistance and T2D, identifying potential therapeutic targets to inhibit its activation has become a priority in metabolic disease research[50]. Flavonoids, a diverse group of polyphenolic compounds found in fruits, vegetables, and herbs, have emerged as potent inhibitors of NLRP3 inflammasome activation. Several studies have demonstrated the ability of flavonoids such as luteolin and apigenin to suppress NLRP3 inflammasome activation by inhibiting ROS production and the subsequent assembly of the inflammasome complex. By preventing this activation, flavonoids can reduce the inflammatory response and its associated metabolic consequences[24, 50].

In addition to their inhibitory effects on the NLRP3 inflammasome, flavonoids have been shown to improve insulin sensitivity and glucose metabolism in both preclinical and clinical studies[28, 51]. One of the mechanisms through which flavonoids exert these effects is by reducing oxidative stress, a key driver of insulin resistance. Flavonoids such as quercetin and epigallocatechin gallate (EGCG) have been found to decrease the levels of ROS in tissues, which, in turn, reduces oxidative damage to insulin signaling pathways. These compounds can enhance insulin signaling by modulating the activity of various enzymes and transcription factors involved in glucose metabolism, including AMPK, PI3K, and Akt[37]. Moreover, flavonoids have been shown to positively influence adipocyte function. In obesity, dysfunctional adipocytes contribute to the development of insulin resistance and systemic inflammation.[47] Flavonoids like kaempferol and catechins have been shown to improve adipocyte metabolism, enhance lipid storage, and reduce inflammation within adipose tissue. By improving the function of adipocytes, flavonoids help maintain proper lipid homeostasis and mitigate the adverse metabolic effects of obesity [52].

Flavonoids also exert direct effects on β-cell function. The chronic inflammation associated with obesity and T2D can lead to β-cell apoptosis and impaired insulin secretion. However, certain flavonoids, such as curcumin and resveratrol, have demonstrated protective effects on β-cells by modulating inflammatory pathways [21, 23]. These compounds help protect β-cells from the harmful effects of cytokines like IL-1β and TNF-α, thereby reducing β-cell apoptosis. Additionally, flavonoids such as resveratrol have been shown to promote insulin

secretion and improve β-cell proliferation, potentially enhancing the capacity of the pancreas to produce insulin in response to glucose[24]. This effect is crucial in the context of T2D, where β-cell dysfunction is a key factor in disease progression.

In sum, the NLRP3 inflammasome plays a central role in the inflammatory processes that drive insulin resistance and β-cell dysfunction in obesity and T2D. Flavonoids, with their ability to inhibit NLRP3 inflammasome activation, reduce oxidative stress, and modulate insulin signaling, represent a promising class of natural compounds for the management of metabolic disorders. By targeting the inflammasome and improving insulin sensitivity, flavonoids offer a multifaceted approach to mitigating the effects of obesity and T2D, highlighting their potential as therapeutic agents in the prevention and treatment of these conditions.

Preclinical and Clinical Evidence

Numerous preclinical studies have demonstrated the beneficial effects of flavonoids in animal models of obesity and diabetes. For example, quercetin supplementation has been shown to improve insulin sensitivity, reduce fasting blood glucose levels, and attenuate inflammatory cytokine production in obese rats[40, 53]. Similar findings have been observed with other flavonoids such as catechins, apigenin, and genistein[54–56].

Clinical studies also support the potential of flavonoids in managing obesity-related diabetes. Clinical trials investigating the effects of flavonoid-rich foods and supplements have reported improvements in glucose control, insulin sensitivity, and inflammatory biomarkers in individuals with T2D[57]. However, the results have been somewhat variable, and more large-scale, randomized controlled trials are needed to confirm the efficacy of flavonoid-based interventions in human populations.

Challenges and Future Directions

Despite the promising preclinical and clinical evidence, several challenges remain in translating flavonoid-based therapies into clinical practice. The bioavailability of flavonoids is a major limiting factor, as these compounds are often poorly absorbed and rapidly metabolized in the body. Strategies to enhance the bioavailability of flavonoids, such as the use of nanoparticles or co-administration with bioenhancers, may improve their therapeutic potential.

Additionally, the complex nature of flavonoid action, with multiple molecular targets and pathways involved, makes it difficult to pinpoint the most effective compounds and dosages for clinical use. Future research should focus on identifying specific flavonoid derivatives with enhanced bioavailability and selectivity for NF-κB and NLRP3 inflammasome inhibition.

CONCLUSION

Flavonoids represent a promising class of compounds for targeting NF-κB and NLRP3 inflammasome pathways in obesity-related diabetes. By modulating these inflammatory pathways, flavonoids can reduce insulin resistance, improve metabolic function, and protect against β-cell dysfunction. While preclinical and clinical evidence supports their potential therapeutic role, further studies are needed to optimize their use and establish their clinical efficacy. Given their safety profile and widespread availability, flavonoids may become an important adjunct in the management of obesity-related diabetes, offering a natural and cost-effective approach to controlling inflammation and improving insulin sensitivity.

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