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Therapeutic Potential of Citrus Flavonoids in Metabolic Inflammation and Insulin Resistance

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ABSTRACT

Metabolic inflammation, or meta-inflammation, is a low-grade chronic inflammatory state associated with metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), and insulin resistance (IR). Recent evidence highlights the role of bioactive compounds, particularly citrus flavonoids, in modulating metabolic pathways and inflammatory responses. Citrus flavonoids, such as hesperidin, naringenin, nobiletin, and tangeretin, exhibit diverse biological properties including antioxidant, anti-inflammatory, and insulin-sensitizing effects. This review consolidates current findings on the molecular mechanisms through which citrus flavonoids exert protective effects against metabolic inflammation and insulin resistance. These compounds target multiple signaling pathways including NF-κB, AMPK, PI3K/Akt, and PPARγ, thereby regulating cytokine expression, glucose uptake, lipid metabolism, and oxidative stress. Clinical and preclinical studies are also discussed, providing insight into the translational potential of citrus flavonoids as adjuncts in the management of metabolic diseases. Furthermore, challenges in bioavailability and future research directions aimed at enhancing the efficacy of these natural compounds are highlighted. Overall, citrus flavonoids represent a promising therapeutic avenue for alleviating metabolic inflammation and improving insulin sensitivity.

Keywords: Citrus flavonoids, metabolic inflammation, insulin resistance, hesperidin, naringenin, NF-κB, AMPK, oxidative stress, type 2 diabetes mellitus

INTRODUCTION

Metabolic diseases, particularly obesity and type 2 diabetes mellitus (T2DM), have become significant global health challenges due to their increasing prevalence and their association with a multitude of comorbidities, including cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and certain types of cancer[1–3]. These conditions are characterized by complex pathophysiological mechanisms, with chronic low-grade inflammation playing a central role[3]. Unlike acute inflammation, which serves a protective role in host defense, chronic metabolic inflammation is subtle, persistent, and often goes unnoticed until it contributes significantly to disease progression[4–6]. One of the hallmark features of metabolic diseases is the infiltration of immune cells into metabolic tissues such as adipose tissue, liver, and skeletal muscle, where they release a variety of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1)[7–9]. These cytokines impair insulin signaling pathways by promoting serine phosphorylation of insulin receptor substrate (IRS) proteins and inhibiting downstream insulin signaling cascades. The result is insulin resistance, a condition in which cells fail to respond adequately to insulin, leading to elevated blood glucose levels and compensatory hyperinsulinemia. Over time, insulin resistance can progress to overt diabetes and contribute to systemic metabolic dysregulation[10–12].

In recent years, considerable attention has been directed toward the role of diet and nutritional interventions in managing and potentially reversing metabolic inflammation and insulin resistance. Among these, dietary flavonoids have emerged as promising bioactive compounds. Flavonoids are a diverse group of polyphenolic compounds found abundantly in fruits, vegetables, and plant-derived beverages[13–16]. Within the flavonoid family, citrus flavonoids, which are primarily found in oranges, lemons, grapefruits, and other citrus fruits, have gained interest due to their potent antioxidant, anti-inflammatory, and insulin-sensitizing properties[17, 18].

Citrus flavonoids such as hesperidin, naringenin, narirutin, and eriocitrin have been shown to exert multiple beneficial effects on metabolic health[19–21]. These compounds can modulate signaling pathways involved in

inflammation and oxidative stress, improve lipid and glucose metabolism, enhance mitochondrial function, and restore insulin sensitivity[22–25]. Experimental studies in animal models and cell cultures have demonstrated that citrus flavonoids can attenuate the expression of pro-inflammatory cytokines, reduce macrophage infiltration into adipose tissue, and inhibit the activation of key inflammatory transcription factors such as nuclear factor-kappa B (NF-κB)[26, 27]. Furthermore, clinical trials and observational studies suggest that regular consumption of citrus fruits or their extracts may correlate with improved metabolic parameters, including reduced fasting blood glucose, improved lipid profiles, and decreased markers of systemic inflammation[28]. Despite the growing body of evidence supporting the health benefits of citrus flavonoids, their precise mechanisms of action in the context of metabolic inflammation and insulin resistance remain an active area of research. Various molecular targets, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and the insulin signaling cascade itself, are believed to be modulated by these compounds. Additionally, factors such as bioavailability, dosage, duration of intake, and individual metabolic responses can influence their efficacy[29, 30]. This review aims to provide a comprehensive overview of the therapeutic potential of citrus flavonoids in addressing metabolic inflammation and insulin resistance. By examining both preclinical and clinical evidence, we seek to highlight the mechanisms through which these natural compounds may contribute to the prevention and management of metabolic disorders. Understanding the interplay between dietary flavonoids and metabolic health not only advances our knowledge of nutritional interventions in chronic disease management but also opens new avenues for the development of flavonoid-based therapeutics.

Overview of Citrus Flavonoids

Classification and Sources

Citrus flavonoids are a diverse group of naturally occurring polyphenolic compounds primarily found in the peels, pulps, and juices of citrus fruits. These bioactive molecules can be broadly classified into three main subgroups based on their chemical structures: flavanones, polymethoxylated flavones, and flavones.

Flavanones are the most abundant class of flavonoids in citrus fruits. Key examples include *hesperidin*, commonly found in oranges and tangerines, and *naringenin*, prevalent in grapefruits. These compounds are known for their potent antioxidant, anti-inflammatory, and cardiovascular-protective properties[31, 32].

Polymethoxylated flavones (PMFs) such as *nobiletin* and *tangeretin* are unique to citrus fruits, particularly in the peels. They are distinguished by multiple methoxy groups attached to their flavone backbone, which confer enhanced lipophilicity and potential for better biological activity. PMFs have attracted attention for their strong anti-cancer, anti-inflammatory, and neuroprotective effects[33, 34].

Flavones, including *diosmetin* and *apigenin*, are less prevalent but still contribute to the overall health-promoting effects of citrus. They are primarily found in citrus peels and are being studied for their roles in improving blood flow, reducing oxidative stress, and modulating enzymatic activities[35, 36].

Common citrus sources rich in these flavonoids include oranges (*Citrus sinensis*), grapefruits (*Citrus paradisi*), lemons (*Citrus limon*), limes (*Citrus aurantiifolia*), and mandarins (*Citrus reticulata*)[37, 38]. The concentration of flavonoids varies significantly among species, cultivars, and even plant parts, with peels generally containing higher amounts than pulps or juices. Beyond fresh fruits, citrus flavonoids are also present in processed products such as juices, jams, marmalades, and dietary supplements. The growing interest in citrus flavonoids as functional food components and nutraceuticals has spurred research into their extraction, characterization, and therapeutic applications.

Bioavailability and Metabolism

Despite the promising biological activities of citrus flavonoids, their clinical efficacy is often hindered by poor bioavailability. Bioavailability refers to the proportion of a compound that enters systemic circulation in an active form after oral administration[39–41]. The low bioavailability of citrus flavonoids can be attributed to several factors, including limited intestinal absorption, rapid metabolism, and poor water solubility [40, 42]. Once ingested, these compounds undergo extensive transformation in the gastrointestinal tract and liver. Initially, flavonoid glycosides are hydrolyzed by intestinal enzymes or gut microbiota into aglycones, which may then be absorbed. However, they often undergo first-pass metabolism in the liver, where they are conjugated into glucuronides, sulfates, or methylated derivatives[43]. These metabolic processes can significantly alter the structure and reduce the biological activity of the parent compounds.

To overcome these limitations, several strategies are being explored. Nanoencapsulation involves incorporating flavonoids into nanoparticles, liposomes, or micelles to enhance solubility, protect against degradation, and facilitate intestinal absorption[44]. Co-administration with absorption enhancers, such as piperine or phospholipids, can inhibit metabolizing enzymes or improve membrane permeability, increasing systemic availability. Structural modification, including methylation or glycosylation, can improve stability and facilitate targeted delivery[45].

Emerging technologies such as solid lipid nanoparticles, self-emulsifying drug delivery systems (SEDDS), and polymeric micelles are being optimized for citrus flavonoid delivery[46–48]. These innovations aim to maintain the integrity of bioactive compounds through the digestive system and release them effectively at target sites.

Understanding the metabolism and pharmacokinetics of citrus flavonoids is essential for developing effective therapeutic agents. Current research continues to investigate the complex interplay between flavonoid structure, gut microbiota, and host metabolism to improve their functional use in disease prevention and treatment.

Metabolic Inflammation and Insulin Resistance

Pathophysiology: The pathophysiology of obesity-induced insulin resistance and metabolic disorders is driven largely by chronic overnutrition, which promotes excessive accumulation of adipose tissue[49, 50]. This state of overnutrition leads to adipocyte hypertrophy and dysfunction, initiating a cascade of inflammatory responses. Enlarged adipocytes secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as various chemokines that attract immune cells, particularly macrophages, into adipose tissue[3]. These infiltrating immune cells further amplify local and systemic inflammation by producing additional cytokines and reactive oxygen species (ROS), which create a sustained pro-inflammatory microenvironment[3]. One of the central consequences of this inflammation is the disruption of insulin signaling pathways. Specifically, cytokines like TNF-α activate serine kinases, which in turn phosphorylate insulin receptor substrates (IRS) on serine residues rather than tyrosine residues[51]. This abnormal phosphorylation inhibits the ability of IRS proteins to propagate downstream insulin signals, thereby impairing glucose uptake and promoting insulin resistance. Additionally, lipotoxicity from elevated free fatty acids in circulation further exacerbates cellular stress and inflammation[52]. These pathophysiological changes collectively disrupt metabolic homeostasis, contributing to the development of type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease. Understanding this chronic low-grade inflammatory state and its molecular mediators is crucial for identifying therapeutic targets aimed at restoring insulin sensitivity and metabolic balance. Hence, therapeutic strategies often aim to attenuate inflammatory signaling and improve insulin action by targeting specific molecules involved in these pathways.

Key Molecular Pathways: Several key molecular pathways regulate the intricate balance between metabolism, inflammation, and insulin sensitivity in the context of obesity. The nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways are central to the inflammatory response. Upon activation by inflammatory stimuli such as cytokines or lipid metabolites, these pathways induce the transcription of genes encoding pro-inflammatory cytokines like TNF-α and IL-6[53]. Their chronic activation in obesity sustains a state of systemic inflammation, which interferes with insulin signaling and promotes insulin resistance. On the other hand, AMP-activated protein kinase (AMPK) functions as an energy sensor that is activated under low-energy conditions. AMPK inhibits inflammatory pathways and promotes catabolic processes such as fatty acid oxidation and glucose uptake, thereby enhancing insulin sensitivity[54]. Pharmacological activation of AMPK has emerged as a promising strategy for metabolic disease management. The phosphoinositide 3-kinase (PI3K)/Akt pathway is a critical mediator of insulin signal transduction. Upon insulin binding to its receptor, PI3K is activated, leading to downstream activation of Akt, which facilitates glucose transporter (GLUT4) translocation to the plasma membrane and glucose uptake. Dysregulation of this pathway is a hallmark of insulin resistance[55]. Lastly, peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor that plays a pivotal role in lipid metabolism and adipocyte differentiation. It also exerts anti-inflammatory effects by antagonizing pro-inflammatory transcription factors like NF-κB. Activation of PPARγ enhances insulin sensitivity, which is the basis for the therapeutic use of thiazolidinediones in diabetes treatment[56]. Together, these molecular pathways offer valuable insights into potential therapeutic targets for metabolic diseases.

Mechanisms of Action of Citrus Flavonoids

Antioxidant Effects: Citrus flavonoids exhibit potent antioxidant properties by neutralizing harmful reactive oxygen species (ROS), which are known to damage cellular components such as lipids, proteins, and DNA[57]. These natural compounds enhance the body's own antioxidant defense mechanisms by upregulating enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase. By reducing oxidative stress, they help mitigate cellular dysfunction, a major underlying factor in the development of metabolic disorders including insulin resistance and chronic inflammation[58]. The antioxidant capabilities of citrus flavonoids not only protect tissues from oxidative damage but also contribute to the maintenance of redox homeostasis and overall metabolic health.

Anti-inflammatory Effects: Citrus flavonoids exert strong anti-inflammatory effects by targeting key signaling pathways involved in the inflammatory response[23]. Notably, they inhibit the activation of nuclear factor kappa B (NF-κB), a central transcription factor that drives the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1)[23]. This suppression results in reduced infiltration of macrophages into adipose tissue, which is a hallmark of chronic low-grade inflammation in metabolic disorders. By dampening these inflammatory signals, citrus flavonoids help attenuate systemic inflammation, improve insulin sensitivity, and offer protection against obesity-related metabolic complications.

Modulation of Insulin Signalling: Citrus flavonoids significantly influence insulin signalling pathways, contributing to improved glucose homeostasis[59]. They enhance the activity of insulin receptors and facilitate

the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, promoting efficient glucose uptake by peripheral tissues such as muscle and adipose tissue. These effects are largely mediated through activation of AMP-activated protein kinase (AMPK), a critical energy sensor, and the inhibition of protein tyrosine phosphatase 1B (PTP1B), an enzyme that negatively regulates insulin signalling[59]. Through these molecular actions, citrus flavonoids help to restore insulin sensitivity and reduce the risk of insulin resistance and type 2 diabetes.

Regulation of Lipid Metabolism: Citrus flavonoids play an essential role in lipid metabolism by modulating key enzymes and transcription factors involved in fat synthesis and breakdown[60]. They inhibit hepatic lipogenesis by downregulating enzymes like fatty acid synthase and acetyl-CoA carboxylase, thereby reducing the accumulation of triglycerides in the liver. Simultaneously, they enhance the oxidation of fatty acids through upregulation of mitochondrial β-oxidation pathways[60]. This dual action leads to improved lipid profiles, including lower blood triglycerides and cholesterol levels, and reduced ectopic fat deposition in organs such as the liver and muscle. Overall, these effects contribute to enhanced metabolic efficiency and insulin sensitivity.

Challenges and Future Directions

Low bioavailability remains a significant challenge in the effective use of citrus flavonoids for therapeutic purposes. These compounds often exhibit poor absorption in the gastrointestinal tract and limited distribution to target tissues, which significantly reduces their biological efficacy. To overcome this limitation, the development of innovative delivery systems, such as nano-formulations, liposomes, and polymer-based carriers, is essential to enhance their solubility, stability, and overall bioavailability.

Standardization poses another critical hurdle in the clinical application of citrus flavonoids. There is considerable variability in the flavonoid content across different citrus products due to differences in species, growing conditions, harvesting methods, and processing techniques. This inconsistency complicates the accurate determination of dosing regimens and affects reproducibility in research and clinical settings. Therefore, establishing standardized extraction methods and quantification protocols is vital to ensure uniformity in flavonoid composition and potency.

Long-term safety and efficacy of citrus flavonoids remain areas that require more robust scientific validation. While preliminary studies have shown promising health benefits, comprehensive randomized controlled trials are still limited. More long-duration, high-quality clinical studies are needed to evaluate potential side effects, optimal dosages, and therapeutic outcomes over extended periods to confidently establish the safety profile and effectiveness of these compounds in chronic disease prevention and treatment.

Synergistic effects of citrus flavonoids with other bioactive compounds or pharmaceutical agents represent a promising area for further exploration. Preliminary evidence suggests that combining flavonoids with other natural or synthetic substances may produce enhanced biological activity through additive or synergistic mechanisms. Investigating these interactions could uncover new therapeutic strategies and improve the overall efficacy of treatment regimens, particularly in the management of complex or multifactorial health conditions.

CONCLUSION

Citrus flavonoids offer a promising natural strategy to combat metabolic inflammation and insulin resistance through multi-targeted mechanisms involving antioxidant, anti-inflammatory, and insulin-sensitizing pathways. Although further studies are warranted to address challenges in bioavailability and standardization, current evidence supports their potential as adjuncts in the prevention and management of metabolic diseases.

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