Flavones as Emerging Modulators of Obesity-Associated Inflammation: Mechanistic Insights, Clinical Perspectives, and Therapeutic Strategies

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ABSTRACT

Obesity is a chronic metabolic disorder characterized by systemic low-grade inflammation, immune dysregulation, and metabolic impairment. The need for safe, multi-targeted interventions has fueled increased interest in dietary bioactives such as flavones, naturally occurring polyphenolic compounds abundant in fruits, vegetables, and herbs. This manuscript highlights insights from recent mechanistic and translational research, which delineates how flavones such as apigenin mitigate obesity-induced inflammation through modulation of macrophage polarization, inhibition of NF-κB and STAT signaling pathways, and activation of AMPK and Nrf2-dependent antioxidant responses. Unlike conventional pharmacotherapies and bariatric surgery, which primarily target weight loss and often carry adverse effects, flavones address underlying immunometabolic dysfunction and exhibit safe profiles in preclinical and early human studies. Evidence in diet-induced obese mice shows improvements in lipid homeostasis, insulin sensitivity, hepatic steatosis, and inflammatory cytokines at physiologically relevant dietary doses. Emerging human studies with flavonoid-rich preparations reveal favorable effects on inflammatory biomarkers and metabolic risk factors. Together, these data highlight significant translational potential for flavones as complementary or alternative approaches to existing obesity treatments, warranting well-designed clinical trials focused on efficacy, bioavailability optimization, and long-term safety.

1. Introduction

Obesity prevalence continues to escalate globally and remains a primary driver of type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD) (Heymsfield and Wadden, 2017). While traditionally viewed as an energy imbalance, obesity is now recognized as a state of chronic low-grade inflammation, driven predominantly by immune dysregulation within expanding adipose tissue (Hotamisligil, 2017). Macrophage infiltration and pro-inflammatory cytokine secretion (e.g., TNF-α, IL-6) impair insulin signaling, promote lipotoxicity, and contribute to systemic metabolic dysfunction (Lumeng and Saltiel, 2011). Several anti-obesity medications are currently available, including GLP-1 (Glucagon-like peptide-1) receptor agonists, phentermine-topiramate, and orlistat. However, these pharmacotherapies often come with significant limitations. These include gastrointestinal intolerance, high costs, limited accessibility, and only modest effectiveness in restoring metabolic health without side effects. Additionally, these medications do not prevent the recurrence of obesity and require the need for lifelong use in many cases, since once they are stopped, the condition often returns (Gudzune and Kushner, 2024). Bariatric surgery provides durable weight loss for severe obesity; however, it is invasive, costly, and associated with surgical risks and micronutrient

deficiencies (Kim et al., 2023). Importantly, these interventions do not directly target inflammation, a core driver of metabolic disease progression. Consequently, there is strong scientific and clinical interest in dietary bioactive compounds that can modulate inflammation and metabolic disease with minimal toxicity.

Flavonoids, a large class of polyphenolic compounds, and specifically the flavone subclass (including apigenin, luteolin, and chrysin), have emerged as promising candidates due to their ability to reduce inflammation, improve mitochondrial and metabolic function, protect liver and adipose tissue from obesity-induced stress, and by achieving these effects with minimal toxicity at dietary intake levels (Jiang et al., 2016; Kariagina and Doseff, 2022). These compounds are found at high levels in parsley (*Petroselinum crispum*), celery (*Apium graveolens*), chamomile (*Matricaria chamomilla*) tea, grapefruit (*Citrus x paradisi*), orange (*Citrus × sinensis)* and tangerine (*Citrus tangerina)* peels, and some non-GMO maize (*Zea mays*) lines (Casas et al., 2014; Hostetler et al., 2017; Bhagwat and Haytowitz, 2018; Crawford, 2024). This commentary integrates mechanistic, preclinical, and emerging clinical evidence to evaluate the therapeutic potential of flavones in obesity-associated inflammation, fatty liver, and metabolic disease.

2. Flavones and Obesity-Associated Inflammation

Obesity increases innate and adaptive immune activation within the adipose tissue, liver, and gut, leading to persistent secretion of inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (Hotamisligil, 2017). This immunometabolic imbalance promotes insulin resistance and hepatic steatosis while amplifying systemic inflammation (Xu et al., 2003). Flavones help restore homeostasis by directly suppressing inflammatory signaling and improving metabolic function (Kwon et al., 2015).

Among dietary flavones, apigenin, luteolin, and chrysin have demonstrated consistent efficacy in diet-induced obese (DIO) mouse models. Daily intake of apigenin (10–50 mg/kg) reduces adipose tissue macrophage infiltration, suppresses hepatic triglyceride accumulation, and improves glucose tolerance without signs of liver or kidney toxicity (Jung et al., 2016). Luteolin decreases expression of TNF-α and IL-1β in adipose tissue and enhances insulin sensitivity by preserving adipocyte mitochondrial function (Zhang et al., 2016). Chrysin (50 and 100 mg/kg) mitigated obesity in rats fed with a high fat diet (HFD), reducing serum triglycerides, adiposity index, and inflammation (Pai et al., 2020). These effects seem to be dependent of the effect of chrysin in pancreatic lipase. In mice chrysin improved glucose and lipid metabolism, resulting in a reduction of liver injury, suggesting its role as a potential treatment of glucose and lipid metabolic disorders (Zhou et al., 2021).

Flavones counteract these processes through multiple complementary mechanisms, including attenuation of NF-κB and JAK/STAT signaling, enhancement of antioxidant defenses, and modulation of gut microbiota (Rezai-Zadeh et al., 2008). Several preclinical studies using DIO mouse models have demonstrated that apigenin administered orally at doses in the range of 10–50 mg/kg/day (and in diet supplemented studies at ~80-125 mg/kg/day given at 0.005% w/w) reduces hepatic steatosis, macrophage infiltration, serum triglycerides, and inflammatory cytokine levels while restoring insulin sensitivity (Jung et al., 2016; Gentile et al., 2018; Wu et al., 2021; Lu et al., 2023; Lu et al., 2024) . Similarly, luteolin suppresses obesity-induced macrophage infiltration into mouse adipose tissue and downregulates expression of TNF-α, IL-1β, and MCP-1 (Baek et al., 2019) HFD with 0.005% luteolin (or 4.75 mg/kg body weight/day). Chrysin (10-30 mg/kg for five weeks), structurally similar to apigenin, improves glucose and lipid metabolism activating AMP-activated protein kinase (AMPK) in DIO mouse model (Zhou et al., 2021). These effects are achieved at physiologically relevant concentrations, with no observable toxicity or behavioral changes in treated animals.

This immunometabolic reprogramming aligns with reduced adipocyte hypertrophy and improved

insulin signaling. The dual role of flavones in modulating immune cell metabolism and gene expression, particularly via PPARγ activation and inhibition of NLRP3 inflammasome assembly has been previously noted (Kariagina and Doseff, 2022). Collectively, these findings support the concept that flavones address the inflammatory roots of obesity rather than its symptomatic manifestations.

3. Mechanistic Insights: Molecular Targets of Flavones

Flavones act on key molecular targets that integrate metabolic and inflammatory signaling pathways. NF-κB is a critical master regulator of inflammation targeted by flavones. Flavones inhibit IKK phosphorylation, prevent IκB degradation, and suppress NF-κB nuclear translocation, leading to decreased expression of IL-6, COX-2, and iNOS (Nicholas et al., 2007; Cardenas et al., 2016; Yeo et al., 2020; Caporali et al., 2022; Kurkiewicz et al., 2025). Additionally, apigenin (given by subcutaneous injection at doses ~15 to 30 mg/kg/day for 13 days) interfered with the phosphorylation of the transcription factor STAT3 in fat tissues, reducing visceral obesity (Su et al., 2020). AMPK serves as a central energy sensor regulating lipid and glucose metabolism. Apigenin and chrysin activate AMPK, promoting fatty acid oxidation and glucose uptake while inhibiting hepatic lipogenesis (Ono and Fujimori, 2011; Lu et al., 2019; Hsu et al., 2021; Zhou et al., 2021). In parallel, activation of PPARγ by apigenin mirrors the insulin-sensitizing effect of thiazolidinediones but without their adverse cardiovascular outcomes (Wang et al., 2014; Jung et al., 2016). Furthermore, apigenin (at concentrations ranging from 10 to 50 mg/kg/day) in a DIO mouse model decreases macrophage polarization and activates PPARγ, resulting in reduced obesity-induced inflammation (Feng et al., 2016). This convergence of metabolic and inflammatory control distinguishes flavones from conventional pharmacologic agents.

Flavones also induce nuclear translocation of Nrf2 and subsequent upregulation of phase II detoxifying enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1) (Xu et al., 2016; Zhang et al., 2020; Huang et al., 2023). This pathway reduces reactive oxygen species (ROS) accumulation and lipid peroxidation, both key contributors to insulin resistance and mitochondrial dysfunction in obesity (Li et al., 2020; Fiorenza et al., 2024).

Emerging evidence indicates that flavonoids can alter the gut microbiota, helping to counteract dysbiosis caused by obesity (Li et al., 2025b). Apigenin and luteolin favorably remodel gut microbiota composition, enriching *Bacteroidetes* and *Akkermansia* spp., which are associated with improved glucose tolerance and reduced adiposity (Qiao et al., 2021; Rodríguez-Daza and de Vos, 2022). Furthermore, dietary compounds remodeled gut microbiota-derived metabolites (Feng et al., 2022). These effects may synergize with their direct anti-inflammatory actions in the intestine and liver.

4. Comparison with Current Anti-Obesity Treatments

Modern anti-obesity pharmacotherapy primarily targets appetite suppression, nutrient absorption, or hormonal regulation. GLP-1 receptor agonists (semaglutide, liraglutide) enhance insulin secretion and promote satiety, yielding weight reductions of 10–15% but often cause gastrointestinal side effects and require chronic administration (Pi-Sunyer et al., 2015). Orlistat, a tetrahydrolipstatin derivative of lipstatin, is a potent inhibitor pancreatic and intestinal lipase, reducing fat absorption but causing steatorrhea and fat-soluble vitamin deficiency. Other agents such as phentermine/topiramate (Qsymia) and bupropion/naltrexone (Contrave) work by reducing appetite but have been associated with cardiovascular or psychiatric adverse effects (Cosentino et al., 2013). While these therapies effectively lower body weight, they rarely target the inflammatory and oxidative processes driving metabolic deterioration.

Surgical interventions such as Roux-en-Y gastric bypass and sleeve gastrectomy induce profound metabolic changes and remission of type 2 diabetes in many patients (Adams et al., 2017). However, they are invasive, costly, and associated with risks of micronutrient deficiency and postoperative

complications (Saarinen et al., 2025). Moreover, they do not directly correct underlying immune dysregulation or inflammatory signaling.

Flavones offer a fundamentally different approach from pharmacologic and surgical interventions: rather than imposing energy restriction or blocking nutrient absorption, they modulate intracellular signaling networks governing metabolism, lipid homeostasis, and inflammation. For example, apigenin activates PPARγ, promoting a shift toward anti-inflammatory macrophage polarization and improving metabolic and inflammatory parameters in HFD mouse models, without the weight gain or other adverse effects associated with classical thiazolidinediones (Feng et al., 2016). Similarly, luteolin improves insulin sensitivity in adipocytes via PPARγ modulation and reduces inflammatory cytokine expression (Ding et al., 2010). In hepatocytes, flavones such as chrysin, apigenin, and luteolin, activate antioxidant and detoxification pathways, including Nrf2-driven enzymes such as HO-1, which reduce oxidative stress and lipid peroxidation (Huang et al., 2013). Importantly, in preclinical models, chronic administration of these flavones at pharmacological doses produced no overt hepatotoxicity, nephrotoxicity, or behavioral abnormalities, supporting a favorable safety profile at doses used for metabolic and inflammatory modulation. Thus, flavones may complement or in selective setting substitute pharmacologic therapies, particularly in individuals with limited tolerant to standard drugs or with chronic metabolic-inflammatory conditions.

5. Clinical and Translational Perspectives

Although most evidence stems from preclinical studies, a growing number of human trials support the metabolic benefits of flavonoid-rich diets or supplements. In a randomized controlled trial, quercetin supplementation (500 mg/day for 8 weeks) reduced blood pressure and plasma oxidized LDL in hypertensive subjects (Egert et al., 2009). Green tea catechins, structurally related to flavones, have demonstrated modest reductions in body weight and LDL cholesterol (Chen et al., 2016). While direct human clinical data on pure apigenin or luteolin remain scarce, animal, and *in vitro* evidence suggests favorable safety at physiologic and pharmacologic doses sufficient to modulate inflammation. We showed that mice fed with a diet supplemented with Chinese celery (*Apium graveolens*, a diet rich in apigenin aglycone corresponding to 50 mg/kg/day) for seven-days resulted in 1 μM apigenin in serum (Hostetler et al., 2012) without any noted adverse effects. Additionally, this dose of apigenin reduced NF-κB-dependent inflammation and microRNAs altered in inflammation *in vivo* (Cardenas et al., 2016).

The limited bioavailability of flavones represents a challenge for translation. However, novel delivery systems such as nanoemulsions, phospholipid complexes, and self-nanoemulsifying drug delivery systems (SNEDDS), have markedly improved oral absorption and systemic exposure in experimental models (Sato et al., 2024). For example, Bio-SNEDDS formulations of apigenin increased plasma concentrations nearly 100% in rats compared with unformulated compound (Kazi et al., 2020). Such advances could bridge the gap between preclinical efficacy and clinical application. Furthermore, enhancing the bioavailability of flavonoids through agricultural engineering and targeted food design offers benefits that are only beginning to be recognized (Casas et al., 2014; Ahn-Jarvis et al., 2019).

Beyond favorable pharmacokinetics, flavones generally show good safety profiles *in vivo* and *in vitro*. In rodent oral administration studies (diet or gavage), doses up to 50-200 mg/kg/day for several weeks showed no indication of hepatoxicity, nephrotoxicity, behavioral changes, or weight loss (Li et al., 2025a). In contrast, an intraperitoneal high-single dose (100-200 mg/kg) has been associated with elevation of liver enzymes (ALT, AST and ALP) (Singh et al., 2012), suggesting the dose and route of administration-dependent effect in hepatic stress. Importantly, typical human dietary intake of flavone from foods such as parsley (*Petroselinum crispum)*, celery (*Apium graveolens*), or chamomile corresponds to low milligrams per day ranges (~0.5-5 mg/day in their glycoside forms), which are far below pharmacologic doses tested in animals (Chun

et al., 2007; Allemailem et al., 2024). At the cellular level, flavones have demonstrated protective, antioxidant, and anti-inflammatory activities without cytotoxicity in primary hepatocytes or immune cells at physiologically relevant concentrations (Huang et al., 2013). Collectively, these data suggest that flavone consumption at a range of doses is compatible with long-term safety and supports their potential as candidates for chronic prevention or therapy of obesity-related metabolic inflammation.

6. Translational Integration and Future Directions

Translating flavone research into therapeutic practice requires addressing several challenges. For example, flavones undergo extensive phase II metabolism (glucuronidation and sulfation) in the intestine and liver, limiting free aglycone levels (Manach et al., 2005). Co-administration of other flavonoids with bioenhancers such as piperine, which inhibits drug-metabolizing enzymes (phase I and II) or encapsulation in lipophilic carriers showed increased systemic exposure (Shoba et al., 1998; Johnson et al., 2011). Identifying active metabolites and understanding their tissue distribution will be critical for dosing optimization. Flavones act on multiple signaling pathways simultaneously. Integrative transcriptomic and metabolomic approaches are needed to map their pleiotropic effects and identify biomarkers of response. Systems-level analyses may also uncover synergistic combinations of flavones with existing therapies. Future trials should adopt randomized, placebo-controlled designs assessing metabolic endpoints (lipid profile, transcriptomics, and inflammatory cytokines) and tissue-specific markers (adipose, hepatic) over extended durations. Some flavones (e.g., hispidulin, apigenin, luteolin) have been shown, in preclinical studies to stimulate GLP-1 secretion, raising the possibility that they could serve as adjuvants in combination with GLP-1 agonists or metformin, potentially allowing lower drug doses or mitigating side effects (Hira et al., 2021). Inter-individual differences in gut microbiota composition influence flavone metabolism and efficacy. Personalized interventions combining flavone-rich foods with prebiotics or probiotics could enhance their therapeutic impact.

7. Conclusions

Flavones represent a promising class of natural dietary compounds capable of addressing obesity at its immunometabolic roots. Through coordinated modulation of critical pathways, flavones reduce inflammation, improve insulin sensitivity, and restore metabolic balance. Preclinical studies demonstrate efficacy comparable to pharmacologic agents but without adverse effects. Early human data support safety and bioactivity, though larger clinical trials are needed to confirm metabolic benefits. Compared with current anti-obesity treatments, flavones offer a multi-targeted, low-toxicity strategy that could complement or enhance existing therapeutic paradigms. Continued translational research, focusing on bioavailability, biomarker validation, clinical efficacy, and potential interactions with other medications, will determine whether flavones can bridge the gap between nutrition and pharmacotherapy in combating obesity-associated diseases.

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