IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

A Pharmacological Perspective On Tangeretin: Mechanistic Insights Into Its Multi-Target Anti-Obesity And Anticancer Activities

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Abstract

Tangeretin, a bioactive polymethoxylated flavone predominantly isolated from the peel of citrus fruits, has garnered considerable scientific interest owing to its astounding diverse pharmacological profile. Recent experimental evidences underscores its therapeutic potential as a multi-target agent in the management of obesity and cancer—two epidemiologically intertwined global health burdens of escalating concern. At the molecular level, tangeretin orchestrates the modulation of several pivotal signalling cascades, including the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), AMP-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, thereby exerting regulatory influence over chronic inflammation, lipid metabolism, oxidative stress, and tumour progression. The present review bring forth a critical and comprehensive appraisal of the anti-obesity and anticancer mechanisms attributable to tangeretin, while also addressing its current pharmacokinetic limitations and prospective avenues for clinical translation, including nanotechnology-based drug delivery strategies and combinatorial therapeutic approaches.

Keywords: *Anti-obesity; Anticancer; Phytochemical;Polymethoxylated flavones; Tangeretin.*

1. Introduction

The global burden of non-communicable diseases, particularly obesity and cancer, continues to escalate at an alarming rate, imposing profound socioeconomic and clinical challenges worldwide. Obesity, now recognised as a complex and heterogeneous metabolic disorder, is characterised by chronic low-grade inflammation, dysregulated lipid homeostasis, and insulin resistance—pathophysiological perturbations that collectively heighten susceptibility to malignant transformation [1]. The mechanistic overlap between adipose tissue dysfunction and oncogenic signalling has firmly established the obesity–cancer axis as a critical therapeutic target warranting rigorous investigation.

In recent decades, naturally occurring phytochemicals have emerged as a compelling class of therapeutic candidates, owing to their capacity to simultaneously modulate multiple molecular targets with favourable safety profiles [2]. Among these, tangeretin (5,6,7,8,4′-pentamethoxyflavone)—a structurally unique polymethoxylated flavone (PMF) abundantly present in the peel of *Citrus reticulata* and allied species—has attracted sustained scientific attention. Its distinctive polymethoxylated scaffold confers enhanced lipophilicity and superior membrane permeability relative to conventional hydroxylated flavonoids, thereby facilitating more efficient cellular uptake and broader biological activity [3].

Tangeretin has been reported to exert a wide spectrum of pharmacological activities, encompassing antioxidant, anti-inflammatory, anti-adipogenic, and antineoplastic properties. Notably, its ability to simultaneously target metabolic and oncogenic pathways positions it as a promising multi-target agent for the integrated management of obesity-associated cancers. The present review systematically examines the molecular mechanisms underpinning the anti-obesity and anticancer activities of tangeretin, critically evaluates its pharmacokinetic attributes and associated limitations, and delineates future perspectives for its therapeutic development.

2. Chemical Structure and Pharmacokinetics

2.1 Chemical Characteristics

Tangeretin (molecular formula: $C_{20}H_{20}O_7$; molecular weight: 372.37 g/mol) belongs to the PMF subclass of flavonoids, distinguished by the presence of five methoxy substituents at positions 5, 6, 7, 8, and 4′ of the flavone backbone (Figure 1). This extensive methoxylation substantially enhances molecular lipophilicity and promotes passive transcellular diffusion across biological membranes, facilitating intracellular bioavailability to a degree markedly superior to that observed with hydroxylated flavone counterparts [3]. The absence of hydroxyl groups also confers greater metabolic stability, reducing susceptibility to rapid conjugation and phase II biotransformation. The planar aromatic structure of tangeretin further enables intercalation into lipid bilayers and interaction with hydrophobic binding pockets of target proteins, contributing to its pleiotropic pharmacological activity.

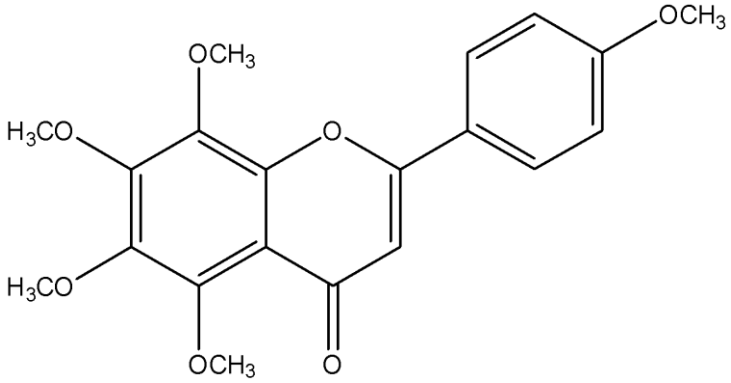


Figure 1: Chemical structure of Tangeritin

2.2 Pharmacokinetics and Bioavailability

Notwithstanding its structural advantages, tangeretin exhibits a number of pharmacokinetic limitations that constrain its therapeutic applicability. Its poor aqueous solubility impedes dissolution in the gastrointestinal milieu, resulting in restricted and variable oral bioavailability [4]. Following intestinal absorption, tangeretin undergoes hepatic first-pass metabolism, predominantly via cytochrome P450-mediated O-demethylation, yielding a series of partially demethylated metabolites with potentially altered pharmacological activities. Rapid systemic clearance further diminishes plasma drug concentrations below therapeutically efficacious thresholds. These pharmacokinetic constraints collectively highlight the imperative for advanced drug delivery platforms capable of augmenting solubility, protecting the molecule from premature metabolic degradation, and enabling targeted tissue distribution [4].

3. Anti-Obesity Mechanisms of Tangeretin

3.1 Regulation of Lipid Metabolism and Adipogenesis

A principal mechanism through which tangeretin exerts its anti-obesity effects is the suppression of adipogenesis—the differentiation of preadipocytes into mature lipid-laden adipocytes. Tangeretin has been demonstrated to attenuate the transcriptional activity of key adipogenic regulators, including peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα), thereby impeding lipid accumulation in adipose tissue [5]. Concurrently, it activates the AMPK signalling pathway, a central cellular energy sensor that promotes fatty acid oxidation, inhibits lipogenesis, and enhances mitochondrial biogenesis. Through coordinated modulation of these molecular targets, tangeretin effectively restrains *de novo* lipid synthesis while augmenting lipolytic activity.

3.2 Promotion of Adipose Tissue Browning and Thermogenesis

Beyond its inhibitory influence on adipogenesis, tangeretin promotes the phenotypic conversion of white adipose tissue (WAT) to beige adipose tissue—a process known as browning—which is accompanied by increased thermogenic capacity and enhanced energy expenditure [6]. This effect is mechanistically underpinned by the upregulation of uncoupling protein 1 (UCP1), the hallmark thermogenic effector localised in the inner mitochondrial membrane of brown and beige adipocytes. Elevated UCP1 expression dissociates oxidative phosphorylation from ATP synthesis, liberating stored chemical energy as heat. Tangeretin-mediated induction of browning thus represents a metabolically beneficial adaptation with substantial implications for the attenuation of diet-induced obesity and associated comorbidities.

3.3 Attenuation of Obesity-Associated Chronic Inflammation

Chronic low-grade inflammation within adipose tissue constitutes a pathological hallmark of obesity and a principal driver of its metabolic sequelae. Tangeretin has been shown to exert potent anti-inflammatory effects by suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway, a master transcriptional regulator of inflammatory gene expression [7]. This inhibition is accompanied by a significant reduction in the secretion of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), as well as decreased expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). By dismantling the inflammatory microenvironment within hypertrophic adipose depots, tangeretin mitigates insulin resistance and curtails systemic metabolic dysfunction.

3.4 Modulation of Gut Microbiota Composition

The gut microbiome has been increasingly recognised as a pivotal determinant of host metabolic phenotype, with dysbiosis contributing significantly to the pathogenesis of obesity [6]. Emerging preclinical evidence suggests that tangeretin exerts a prebiotic-like influence on intestinal microbial ecology, selectively promoting the proliferation of beneficial taxa such as Akkermansia muciniphila and Lactobacillus spp. while suppressing the abundance of obesity-associated pathobionts. These microbiome-mediated effects are associated with enhanced production of short-chain fatty acids (SCFAs), restoration of gut barrier integrity, and attenuation of endotoxaemia-driven metabolic inflammation. Such findings implicate the gut–metabolic axis as an important additional dimension of tangeretin's anti-obesity mechanism.

3.5 Mitigation of Oxidative Stress

Oxidative stress, characterised by an imbalance between reactive oxygen species (ROS) generation and antioxidant defence capacity, is a fundamental contributor to adipocyte dysfunction and obesity-related pathology [8]. Tangeretin has been documented to enhance the expression and enzymatic activity of endogenous antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), whilst simultaneously attenuating mitochondrial ROS production. Activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling axis by tangeretin further reinforces cellular antioxidant defences, thereby safeguarding adipose tissue against oxidative injury and preserving mitochondrial integrity.

4. Anticancer Mechanisms of Tangeretin

4.1 Inhibition of Cancer Cell Proliferation

Uncontrolled cellular proliferation, orchestrated through dysregulated cell cycle progression, is a defining hallmark of malignant transformation. Tangeretin has been shown to exert potent antiproliferative effects across a diverse array of cancer cell lines, including those of breast, colorectal, hepatocellular, and lung origin [9]. Mechanistically, this effect is mediated through the transcriptional downregulation of cyclin-dependent kinases (CDKs) and their cognate cyclin partners—particularly cyclin D1, cyclin E, CDK2, and CDK4—coupled with the concurrent upregulation of endogenous CDK inhibitors such as $p21^{WAT1}$ and $p27^{WAT1}$. The resultant impairment of cyclin–CDK complex formation arrests cells predominantly at the G_0/G_1 and G_2/M checkpoints, effectively decelerating tumour growth without inducing acute cytotoxicity in non-malignant cells.

4.2 Induction of Apoptosis

The capacity of tangeretin to reinstate programmed cell death in neoplastic cells constitutes one of its most therapeutically significant anticancer attributes. Tangeretin activates the intrinsic (mitochondrial) apoptotic pathway by disrupting the pro-survival/pro-apoptotic balance of the B-cell lymphoma-2 (Bcl-2) protein family, effecting a marked increase in the Bax/Bcl-2 expression ratio [10]. This molecular shift promotes mitochondrial outer membrane permeabilisation (MOMP), resulting in the release of cytochrome c into the cytosol, formation of the apoptosome complex, and sequential activation of caspase-9 and executioner caspases-3 and -7. In certain cancer types, tangeretin additionally engages the extrinsic (death receptor) pathway through upregulation of Fas and TNF-related apoptosis-inducing ligand (TRAIL) receptors. The capacity of tangeretin to restore apoptotic sensitivity in otherwise resistant cancer cells is of considerable therapeutic importance.

4.3 Inhibition of Tumour Invasion and Metastasis

Tumour invasion and distant metastasis represent the primary determinants of cancer-related mortality, and the suppression of these processes constitutes a crucial therapeutic objective. Tangeretin has been demonstrated to impede the metastatic cascade through multiple complementary mechanisms [2]. It potently inhibits the expression and proteolytic activity of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are indispensable for extracellular matrix (ECM) degradation and basal membrane breaching. Additionally, tangeretin interferes with epithelial-to-mesenchymal transition (EMT) by restoring E-cadherin expression and suppressing mesenchymal markers such as vimentin and N-cadherin. Anti-angiogenic activity has also been attributed to tangeretin through downregulation of vascular endothelial growth factor (VEGF) and its downstream signalling effectors, thereby restricting the formation of tumour-supporting neovasculature.

4.4 Modulation of Oncogenic Signalling Pathways

The therapeutic efficacy of tangeretin as an anticancer agent is substantially attributable to its capacity to simultaneously modulate multiple oncogenic signalling networks [11]. The PI3K/Akt/mTOR axis, frequently hyperactivated in human malignancies and central to the regulation of cell survival, growth, and metabolism, is effectively suppressed by tangeretin through inhibition of PI3K catalytic activity and consequent dephosphorylation of Akt and mTOR. Tangeretin additionally attenuates the MAPK/ERK signalling cascade, which governs mitogenic responses and is commonly deregulated in epithelial cancers. Furthermore, it inhibits constitutive JAK/STAT3 signalling—a pathway critically implicated in cancer cell survival, immune evasion, and tumour angiogenesis—through direct suppression of JAK2 phosphorylation and STAT3 nuclear translocation. The convergent inhibition of these interconnected pathways by a single phytochemical agent is particularly noteworthy, as it diminishes the probability of compensatory pathway activation that frequently undermines single-target therapies.

4.5 Chemosensitisation and Reversal of Drug Resistance

Acquired resistance to conventional chemotherapeutic agents remains among the most formidable obstacles in oncological management. Tangeretin has demonstrated a compelling ability to sensitize refractory cancer cells to standard-of-care chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel [11]. The molecular basis of this chemo sensitization is multifactorial, encompassing down regulation of ATP-binding cassette (ABC) drug efflux transporters, restoration of apoptotic pathway responsiveness, suppression of anti-apoptotic survival signals, and attenuation of NF-κB-mediated chemoresistance. These properties suggest that tangeretin may serve as a valuable adjunct in combination chemotherapeutic regimens, potentially enabling dose reduction of cytotoxic agents whilst maintaining or enhancing therapeutic efficacy.

5. The Obesity–Cancer Axis and the Dual Role of Tangeretin

The mechanistic interplay between obesity and cancer is multidimensional, encompassing chronic inflammation, hyperinsulinaemia and insulin-like growth factor (IGF) axis dysregulation, adipokine imbalance, and hypoxic tumour microenvironment formation [1]. Adipose tissue hypertrophy engenders a state of chronic paracrine and endocrine inflammatory signalling, in which elevated circulating concentrations of leptin, TNF-α, IL-6, and insulin collectively drive oncogenic transformation, tumour growth, and metastatic dissemination. Conversely, the adipokine adiponectin—characterised by tumour-suppressive and insulin-sensitising properties—is markedly suppressed in the obese state.

Tangeretin is uniquely positioned to simultaneously address multiple nodes within this obesity–cancer nexus. Its anti-inflammatory and insulin-sensitising properties attenuate the metabolic and hormonal milieu that promotes malignant transformation, whilst its direct anticancer activities curtail tumour progression through independent mechanisms. The convergence of these dual therapeutic modalities renders tangeretin a particularly attractive candidate for cancer chemoprevention in obese and metabolically dysregulated patient populations, where both the metabolic substrate and neoplastic progression require concurrent therapeutic targeting.

6. Multi-Target Pharmacological Profile

The polypharmacological nature of tangeretin—encompassing simultaneous modulation of lipid metabolic networks, inflammatory cascades, gut microbial ecology, oxidative stress pathways, and tumour-associated signalling axes—distinguishes it fundamentally from conventional single-target therapeutic agents. This multi-target pharmacological profile is particularly advantageous in the context of complex, polygenic diseases such as obesity and cancer, wherein targeting a single molecular node is frequently insufficient to achieve durable therapeutic benefit. The ability of tangeretin to modulate the PI3K/Akt, AMPK, MAPK, JAK/STAT, and NF-κB pathways in a concerted and context-dependent manner reflects the structural promiscuity inherent to its polymethoxylated scaffold, enabling simultaneous engagement with multiple protein binding domains across diverse cellular compartments.

7. Nanotechnology-Based Drug Delivery Strategies

To overcome the pharmacokinetic limitations inherent to tangeretin, substantial research efforts have been directed towards the development of advanced nanoformulation strategies. A variety of nanocarrier platforms have been investigated, including polymeric nanoparticles, lipid-based nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and self-emulsifying drug delivery systems (SEDDS) [12]. These systems collectively enhance the aqueous dispersibility and gastrointestinal solubility of tangeretin, protect the molecule against enzymatic degradation within the gut lumen, prolong systemic circulation half-life through evasion of reticuloendothelial clearance, and enable preferential accumulation within tumour tissues via the enhanced permeability and retention (EPR) effect.

Functionalised nanocarriers conjugated with tumour-targeting ligands—such as folate, transferrin, hyaluronic acid, and cancer-specific antibodies—offer the additional prospect of receptor-mediated active targeting, further refining the selectivity of tangeretin delivery to neoplastic tissue whilst minimising collateral exposure of healthy organs [12]. The integration of stimuli-responsive release mechanisms (pH-, redox-, or enzyme-triggered) into nanocarrier architectures represents a particularly promising frontier, enabling on-demand drug release within the characteristically acidic and oxidising tumour microenvironment.

8. Safety Profile and Toxicological Considerations

The preclinical safety profile of tangeretin is generally considered favourable. In vitro and in vivo toxicological studies have consistently demonstrated low systemic toxicity at pharmacologically relevant doses, with no significant hepatotoxic, nephrotoxic, or genotoxic effects reported in rodent models subjected to acute or subchronic exposure [13]. Tangeretin appears to exhibit a reasonable therapeutic index, exhibiting selective cytotoxicity towards malignant cells whilst largely sparing non-neoplastic tissues. However, it is important to acknowledge that high-dose or prolonged exposure may theoretically disrupt cytochrome P450 enzyme activity, potentially precipitating pharmacokinetic interactions with co-administered therapeutic agents. Furthermore, the preponderance of available safety data is derived exclusively from preclinical investigations, and the clinical translatability of these findings to human populations remains to be rigorously established through well-designed Phase I dose-escalation trials.

9. Limitations of Current Evidence

Despite the substantial body of preclinical evidence supporting the therapeutic potential of tangeretin, several critical limitations must be acknowledged. Foremost among these is the complete absence of clinical trial data evaluating its safety, tolerability, pharmacokinetics, and efficacy in human subjects—a deficiency that fundamentally precludes definitive conclusions regarding its clinical applicability. The challenges of poor aqueous solubility and limited oral bioavailability remain incompletely resolved, necessitating further optimisation of delivery systems. Further, the elucidation of tangeretin's metabolic fate and the

pharmacological contribution of its metabolites *in vivo* requires more rigorous investigation. Finally, the potential for off-target drug interactions, particularly in the context of polypharmacy prevalent in the target patient populations, warrants systematic evaluation.

10. Future Perspectives

The future trajectory of tangeretin research necessitates a strategic and coordinated translational effort spanning multiple scientific disciplines. Prioritisation of well-designed, prospective randomised controlled clinical trials—initially evaluating pharmacokinetics and safety in Phase I settings, followed by proof-of-concept efficacy studies in Phase II—is of paramount importance. The continued development and clinical validation of optimised nanoformulation platforms capable of surmounting the inherent pharmacokinetic limitations of tangeretin constitutes a critical research priority. Investigation of rationally designed combination therapies, wherein tangeretin is co-administered with existing chemotherapeutic agents, targeted molecular therapies, or immunotherapeutic agents, holds particular promise for synergistic efficacy and potential mitigation of drug resistance. The application of multi-omics approaches—encompassing transcriptomics, proteomics, metabolomics, and microbiomics—will be invaluable in comprehensively delineating the molecular landscape of tangeretin's pleiotropic pharmacological actions and in identifying predictive biomarkers of therapeutic response. Exploration of tangeretin's chemopreventive potential in high-risk obese populations represents a particularly compelling and under-investigated clinical application.

11. Conclusion

Tangeretin is an exceptionally versatile multi-target phytochemical endowed with a well-characterised capacity to modulate the molecular underpinnings of both obesity and cancer through mechanistically complementary and synergistic pathways. Its demonstrated ability to simultaneously suppress adipogenesis, restore metabolic homeostasis, attenuate chronic inflammation, induce cancer cell apoptosis, arrest cell cycle progression, and abrogate metastatic dissemination—mediated through coordinated regulation of the PI3K/Akt, AMPK, MAPK, JAK/STAT, and NF-κB signalling networks—underscores its remarkable pharmacological versatility. Whilst current evidence is predominantly derived from preclinical investigations, the cumulative mechanistic and safety data provide a robust scientific foundation for the clinical advancement of tangeretin. Concerted efforts in clinical trial design, nanoformulation optimisation, and mechanistic biomarker identification will be essential to realise the full therapeutic potential of this promising citrus-derived natural product.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This review work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

[1] Han, G. et al. 2026. Obesity-associated cancer risk: mechanisms and therapeutic targets. *Metabolites.*

[2] de Luna, F.C.F. et al. 2023. Tangeretin: pharmacological properties and therapeutic applications. *Pharmaceuticals.*

[3] Li, S. et al. 2023. Polymethoxylated flavones: structural basis of enhanced bioavailability. *Nutrients.*

[4] Wang, Y. et al. 2024. Pharmacokinetic challenges of citrus-derived flavones. *Frontiers in Pharmacology.*

[5] Chen, Q. et al. 2022. AMPK and PI3K/Akt regulation by tangeretin in adipogenesis. *Journal of Nutritional Biochemistry.*

[6] Chen, Q. et al. 2022. Gut microbiota modulation and adipose browning by tangeretin. *Journal of Nutritional Biochemistry.*

[7] Zhang, H. et al. 2023. NF-κB inhibition and cytokine suppression by tangeretin. *International Journal of Molecular Sciences.*

[8] Gao, Y. et al. 2024. Nrf2/ARE activation and antioxidant enzyme induction by tangeretin. *Antioxidants.*

[9] Ahn, S. and Choi, K.C. 2026. Tangeretin-mediated cell cycle arrest in cancer cells. *Biomolecules & Therapeutics.*

[10] Xu, Y. et al. 2025. Apoptotic pathway activation by tangeretin: Bax/Bcl-2 modulation. *Molecules.*

[11] Kumar, A. et al. 2024. Tangeretin as a chemosensitiser targeting PI3K/Akt, MAPK, and JAK/STAT. *Phytomedicine.*

[12] Yang, X. et al. 2024. Nanoformulation strategies for tangeretin delivery. *Pharmaceutics.*

[13] Zhao, Y. et al. 2023. Safety and toxicological profile of tangeretin in preclinical models. *Drug Delivery.*

[14] Liu, J. et al. 2024. Tangeretin modulates mitochondrial ROS and apoptosis. *Biomedicine & Pharmacotherapy.*

[15] Singh, R. et al. 2024. Anti-metastatic mechanisms of polymethoxylated flavones. *Cancer Letters.*

[16] Patel, K. et al. 2023. Ethnopharmacological relevance of citrus flavonoids in oncology. *Journal of Ethnopharmacology.*

[17] Gupta, S.C. et al. 2023. Phytochemicals in the management of obesity-associated malignancies. *Pharmacological Research.*

[18] Sharma, P. et al. 2024. Regulation of Bcl-2 family proteins by dietary flavonoids. *Biochemical Pharmacology.*

[19] Sun, Y. et al. 2024. VEGF suppression and anti-angiogenic activity of tangeretin. *Frontiers in Oncology.*

[20] Zhou, Z. et al. 2023. Metabolic effects of citrus PMFs in diet-induced obesity. *Nutrition Research.*

[21] Kim, H. et al. 2024. Adipokine regulation and tangeretin in metabolic inflammation. *International Journal of Obesity.*

[22] Park, J. et al. 2023. EMT suppression by tangeretin in invasive cancer models. *Cells.*

[23] He, L. et al. 2023. Oxidative stress and obesity: phytochemical interventions. *Oxidative Medicine and Cellular Longevity.*

[24] Wu, D. et al. 2024. Insulin sensitisation by tangeretin in high-fat diet models. *Clinical Science.*

[25] Tang, Y. et al. 2023. Bioavailability enhancement strategies for flavonoid phytochemicals. *Journal of Agricultural and Food Chemistry.*

[26] Liu, Z. et al. 2024. Gut microbiome-flavonoid interactions and systemic metabolism. *Food & Function.*

[27] Chen, L. et al. 2024. Tangeretin in colorectal cancer: mechanistic and therapeutic insights. *Cancers.*

[28] Wang, J. et al. 2024. Dietary flavones and nutrient-sensing pathway regulation. *Frontiers in Nutrition.*

[29] Li, X. et al. 2024. Mitochondrial pathway modulation by polymethoxylated flavones. *Nutrients.*

[30] Xu, H. et al. 2023. Structural activity relationships of citrus PMFs. *Molecules.*

[31] Deng, S. et al. 2024. STAT3 inhibition and tumour microenvironment remodelling by tangeretin. *International Journal of Biological Sciences.*

[32] Zhou, Y. et al. 2024. MMP inhibition and invasion suppression by flavonoid phytochemicals. *Cancer Science.*

[33] Huang, Q. et al. 2023. Cyclin–CDK complex disruption and G_2/M arrest by tangeretin. *Journal of Cellular and Molecular Medicine.*

[34] Luo, M. et al. 2023. Nanoparticle-encapsulated tangeretin: pharmacokinetic optimisation. *Frontiers in Pharmacology.*

[35] Tian, R. et al. 2024. Liposomal delivery of citrus flavones for anticancer application. *Biochimica et Biophysica Acta.*

[36] Fan, J. et al. 2023. Short-chain fatty acid production and metabolic homeostasis. *Nutrition & Metabolism.*

[37] Zhang, Y. et al. 2024. Ageing, metabolic dysfunction, and phytochemical intervention. *Aging and Disease.*

[38] Chen, W. et al. 2023. Translational oncology and natural product combination therapies. *Journal of Translational Medicine.*

[39] Li, Q. et al. 2024. Dietary flavonoids and chemoprevention in obesity-related cancers. *Nutrition and Cancer.*

[40] Zhao, L. et al. 2023. Flavone stability and bioactivity in food matrices. *Food Chemistry.*