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Flavonoids as Natural Therapeutics for Metabolic Syndrome: Targeting Inflammation, Obesity, and Diabetes

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ABSTRACT

Metabolic syndrome (MetS) is a multifactorial disorder characterized by a cluster of metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension. These interrelated conditions significantly elevate the risk of type 2 diabetes mellitus (T2DM), cardiovascular diseases, and other chronic disorders. Inflammation and oxidative stress are now recognized as pivotal mechanisms underlying the pathogenesis of MetS. Flavonoids, a diverse class of polyphenolic compounds found abundantly in fruits, vegetables, tea, and other plant-derived products, have garnered considerable attention for their broad-spectrum biological activities. This review provides an in-depth analysis of the current evidence supporting the therapeutic potential of flavonoids in managing MetS, focusing on their anti-inflammatory, anti-obesity, and antidiabetic mechanisms. We highlight the molecular pathways modulated by flavonoids, including AMP-activated protein kinase (AMPK), nuclear factor-kappa B (NF-κB), phosphoinositide 3-kinase (PI3K)/Akt, and peroxisome proliferator-activated receptors (PPARs). Additionally, we discuss human clinical trials, bioavailability challenges, and future prospects for flavonoid-based interventions in metabolic health.

Keywords: Flavonoids; Metabolic syndrome; Inflammation; Obesity; Diabetes; AMPK; Oxidative stress; Natural therapeutics; Polyphenols; Insulin resistance

INTRODUCTION

Metabolic syndrome (MetS) is a growing global health concern that has garnered significant attention from healthcare professionals and researchers due to its increasing prevalence and profound implications on public health[1, 2]. Affecting approximately one-quarter of the global adult population, MetS represents a constellation of interconnected metabolic abnormalities that collectively increase the risk for developing chronic non-communicable diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and certain types of cancer[3–5]. The primary components of MetS include central obesity, insulin resistance, dyslipidemia (elevated triglycerides and reduced high-density lipoprotein cholesterol), hypertension, and impaired glucose tolerance. These risk factors often co-occur and synergistically heighten the likelihood of adverse cardiovascular outcomes and premature mortality[5].

The alarming rise in the incidence of MetS has been attributed to a combination of genetic predisposition and environmental influences, with lifestyle factors such as sedentary behavior, poor dietary habits, and chronic stress playing pivotal roles[6, 7]. Urbanization, globalization, and the proliferation of energy-dense, nutrient-poor diets have further compounded the burden of metabolic disorders worldwide. Despite the availability of pharmacological interventions aimed at controlling individual components of MetS—such as antihypertensives, statins, and insulin-sensitizing agents—the overall management of the syndrome remains suboptimal. This is primarily due to the complex, multifactorial nature of the syndrome and the inability of monotherapies to address the underlying pathophysiological mechanisms holistically[8]. Emerging evidence suggests that chronic low-grade inflammation and oxidative stress are key contributors to the pathogenesis of MetS[5, 9]. These processes disrupt metabolic homeostasis, exacerbate insulin resistance, and impair endothelial function, thereby accelerating disease progression. Inflammatory mediators such as tumor necrosis factor-alpha (TNF-α),

interleukin-6 (IL-6), and C-reactive protein (CRP), as well as elevated reactive oxygen species (ROS), have been implicated in the dysregulation of lipid and glucose metabolism. As such, therapeutic strategies that can target these fundamental processes offer a promising avenue for the prevention and management of MetS[10]. In recent years, considerable interest has turned toward the role of dietary bioactive compounds in mitigating metabolic dysfunctions[4]. Among these, flavonoids—a diverse group of naturally occurring polyphenolic compounds found abundantly in fruits, vegetables, tea, cocoa, and wine—have attracted substantial scientific attention[11]. Flavonoids are classified into several subgroups, including flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanins, each possessing unique chemical structures and biological activities. These compounds have demonstrated a wide range of beneficial effects on human health, particularly in the context of metabolic diseases[12, 13]. Flavonoids exhibit potent antioxidant properties that enable them to scavenge free radicals, chelate metal ions, and modulate the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase[14, 15]. This antioxidant capacity plays a crucial role in reducing oxidative damage to cellular components, including lipids, proteins, and DNA[16, 17]. In addition, flavonoids exert anti-inflammatory effects by downregulating pro-inflammatory cytokines and inhibiting key signaling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs)[11, 12]. Through these mechanisms, flavonoids can ameliorate the chronic inflammatory state associated with MetS. Beyond their antioxidant and anti-inflammatory properties, flavonoids have been shown to influence various aspects of metabolic regulation[13, 18]. For instance, several flavonoids enhance insulin sensitivity by modulating insulin signaling pathways, increasing glucose uptake in peripheral tissues, and preserving pancreatic β-cell function. Others improve lipid metabolism by reducing triglyceride synthesis, enhancing cholesterol efflux, and increasing the expression of peroxisome proliferator-activated receptors (PPARs), which are nuclear receptors involved in lipid and glucose homeostasis. Additionally, some flavonoids have been reported to lower blood pressure through vasodilatory effects mediated by the nitric oxide pathway and inhibition of angiotensin-converting enzyme (ACE) activity[11, 19]. The growing body of preclinical and clinical evidence underscores the potential of flavonoids as adjunctive therapies in the management of MetS[20]. Animal studies have demonstrated that flavonoid-rich diets can attenuate weight gain, improve insulin sensitivity, and reduce lipid levels in models of diet-induced obesity and insulin resistance. Human intervention trials, though varied in design and outcomes, have also reported favorable effects of flavonoid supplementation on biomarkers of MetS, including fasting glucose, lipid profile, blood pressure, and inflammatory markers[20]. For example, consumption of flavonoid-rich foods such as berries, dark chocolate, green tea, and citrus fruits has been associated with improvements in cardiovascular and metabolic parameters[21]. Despite these promising findings, several challenges remain in translating the benefits of flavonoids into clinical practice. One major limitation is the variability in bioavailability and metabolism of flavonoids, which can influence their efficacy. Factors such as gut microbiota composition, enzymatic activity, and food matrix can significantly affect the absorption and transformation of flavonoids in the body. Moreover, most clinical studies to date have been relatively short in duration and limited in sample size, underscoring the need for larger, long-term randomized controlled trials to establish the efficacy, safety, and optimal dosing of flavonoid interventions in diverse populations. Furthermore, the synergistic effects of flavonoids with other dietary components, as well as their interactions with pharmaceutical drugs, warrant further investigation[22]. A better understanding of the structure-activity relationships and molecular targets of individual flavonoids could facilitate the development of novel nutraceutical formulations and functional foods tailored for MetS management. Personalized nutrition approaches that consider genetic, epigenetic, and microbiome profiles may also enhance the therapeutic potential of flavonoid-based interventions[22]. In sum, Metabolic Syndrome represents a complex and multifaceted disorder that demands comprehensive and integrative management strategies. While current pharmacological treatments target individual components of the syndrome, they often fall short in addressing its root causes—namely, inflammation and oxidative stress. Flavonoids, owing to their pleiotropic biological effects, offer a promising natural alternative for the prevention and amelioration of MetS. As research in this field continues to evolve, it is imperative to deepen our understanding of the mechanisms by which flavonoids influence metabolic health and to translate these insights into practical dietary recommendations and therapeutic innovations. This review aims to explore the mechanistic underpinnings and clinical evidence supporting the role of flavonoids in the management of MetS, with an emphasis on their potential to serve as effective, safe, and accessible tools in the global fight against metabolic disorders.

Overview of Flavonoids

Classification and Sources

Flavonoids, a diverse group of naturally occurring polyphenolic compounds, are classified into six primary subgroups based on their unique chemical structures: flavones, flavonols, flavanones, flavanols, anthocyanins, and isoflavones[23]. These subgroups vary in the arrangement and number of hydroxyl groups and other structural elements, influencing their biochemical properties and physiological roles. Flavonols, such as quercetin and kaempferol, are widely distributed in onions, kale, and broccoli. These compounds are known for

their potent antioxidant and anti-inflammatory effects, contributing to cardiovascular health and immune support[24]. Flavanols, which include catechins, are abundant in green tea and cocoa. These are particularly valued for their role in enhancing vascular function, improving brain health, and reducing oxidative stress[17]. Flavanones, such as naringenin and hesperidin, are primarily found in citrus fruits like oranges and grapefruits. These compounds exhibit anti-inflammatory, lipid-lowering, and immune-modulating activities, making them crucial in metabolic and cardiovascular health[25]. Anthocyanins, responsible for the vibrant colors of berries and grapes, include cyanidin and delphinidin[26]. These flavonoids are recognized for their ability to protect against oxidative damage and inflammation, particularly in the context of neurodegenerative diseases and cancer. Isoflavones, mainly genistein and daidzein, are abundant in soybeans and have been studied extensively for their phytoestrogenic effects, especially in promoting bone health and mitigating menopausal symptoms in women[27]. Lastly, flavones such as apigenin and luteolin are predominantly found in parsley, celery, and other green herbs[28, 29]. These flavonoids are associated with anti-inflammatory, anticarcinogenic, and neuroprotective properties. Collectively, the broad spectrum of flavonoids found in everyday plant-based foods highlights their nutritional and therapeutic significance[24]. Regular consumption of flavonoid-rich foods contributes to the prevention of chronic diseases such as cancer, diabetes, cardiovascular disorders, and neurodegeneration[20]. Their multifaceted health benefits arise from their capacity to modulate signaling pathways, scavenge free radicals, and influence gene expression. As dietary components, flavonoids are indispensable in functional nutrition and represent promising leads for the development of novel nutraceuticals and therapeutic agents.

Bioavailability and Metabolism

Flavonoid bioavailability is a complex and multifaceted process influenced by several physiological and biochemical factors[30]. One of the primary determinants of flavonoid bioavailability is their chemical structure, particularly the presence of glycosylation. Glycosylated flavonoids, commonly found in plant-based foods, must undergo hydrolysis before absorption in the small intestine. This process can significantly delay or reduce their uptake into systemic circulation. Furthermore, conjugation reactions in the liver and intestinal mucosa—such as sulfation, glucuronidation, and methylation—further modify flavonoids post-absorption, impacting their stability, solubility, and ultimate bioavailability[31]. Another crucial factor influencing flavonoid bioavailability is the interaction with gut microbiota[32]. The colon houses a diverse community of microorganisms capable of metabolizing non-absorbed flavonoids into a variety of bioactive phenolic compounds. These microbial metabolites often possess enhanced biological activity compared to their parent compounds and may be more readily absorbed into the bloodstream[32]. This biotransformation by gut microbiota not only expands the spectrum of potential health effects but also contributes to the systemic and local actions of flavonoids. Although the parent compounds of many flavonoids exhibit poor systemic bioavailability, emerging evidence suggests that their metabolites and localized effects within the gastrointestinal tract play a substantial role in their overall biological efficacy[33]. These local effects include modulation of gut barrier function, anti-inflammatory activity, and interaction with immune cells residing in the gut-associated lymphoid tissue. Therefore, the health benefits associated with flavonoid consumption cannot be solely evaluated based on their plasma concentrations, but must also consider the contributions of their metabolites and local actions within the gut environment.

Inflammation and Oxidative Stress in Metabolic Syndrome

Inflammation and oxidative stress are central to the pathophysiology of MetS. Adipose tissue dysfunction in obesity leads to the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and reactive oxygen species (ROS), exacerbating insulin resistance and endothelial dysfunction[5].

Flavonoids as Anti-Inflammatory Agents

Flavonoids are natural polyphenolic compounds known for their potent anti-inflammatory properties[23]. They exert these effects by modulating critical cellular signaling pathways and transcription factors involved in the inflammatory response. For instance, flavonoids such as quercetin, luteolin, and apigenin suppress the activity of nuclear factor kappa B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory genes. Additionally, compounds like kaempferol and naringenin inhibit the mitogen-activated protein kinase (MAPK) pathway, which plays a vital role in transmitting inflammatory signals within cells[34].

Beyond signaling pathways, flavonoids also help attenuate inflammation by reducing the production of pro-inflammatory cytokines[34]. These include interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which are major mediators of inflammation and immune responses. By downregulating the expression of these cytokines, flavonoids contribute to the resolution of inflammation and the protection of tissues from chronic inflammatory damage. This multi-targeted approach highlights the therapeutic potential of flavonoids in managing inflammatory diseases[33].

Flavonoids and Obesity Management

Flavonoids have been shown to regulate adipogenesis by inhibiting the differentiation of preadipocytes into mature adipocytes[4]. Notable compounds such as genistein and epigallocatechin gallate (EGCG) exert these effects through the modulation of key transcription factors, particularly peroxisome proliferator-activated

receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα)[16, 35]. By downregulating these adipogenic factors, flavonoids can suppress fat cell formation and contribute to the management of obesity. In addition to regulating fat cell development, flavonoids also enhance energy expenditure. Compounds such as resveratrol and quercetin activate critical metabolic regulators like AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1)[36, 37]. Activation of these pathways promotes mitochondrial biogenesis and enhances fatty acid oxidation, leading to increased energy utilization. This metabolic shift supports weight management and improves overall metabolic health. Furthermore, flavonoids play a role in modulating the gut microbiota, which is increasingly recognized as an important factor in metabolic regulation. These bioactive compounds can alter the composition of gut microbiota by promoting the growth of beneficial bacteria that produce short-chain fatty acids (SCFAs). At the same time, they reduce the abundance of lipopolysaccharide (LPS)-producing bacteria, thereby lowering inflammation associated with metabolic disorders. This dual effect contributes to improved gut health and systemic metabolic function[38, 39].

Antidiabetic Properties of Flavonoids

Flavonoids have been shown to significantly improve insulin sensitivity through multiple molecular mechanisms. One key pathway involves the activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling cascade, which plays a crucial role in mediating insulin's metabolic actions[40]. Additionally, flavonoids upregulate the expression of glucose transporter type 4 (GLUT4), enhancing glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue. The activation of AMP-activated protein kinase (AMPK) by flavonoids further contributes to improved glucose utilization and overall insulin responsiveness[40]. In addition to enhancing insulin sensitivity, certain flavonoids contribute to glycemic control by inhibiting carbohydrate-digesting enzymes[41]. Specifically, they suppress the activity of α-glucosidase and α-amylase, enzymes responsible for the breakdown of complex carbohydrates into glucose. This inhibition slows down carbohydrate digestion and absorption, effectively reducing postprandial glucose spikes and helping maintain more stable blood glucose levels [41]. Furthermore, flavonoids protect pancreatic β-cells, which are vital for insulin production and secretion. These compounds exhibit potent antioxidant properties, countering oxidative stress that can damage β-cells. They also possess anti-apoptotic effects, thereby preventing β-cell death and preserving pancreatic function. Through these protective mechanisms, flavonoids help maintain endogenous insulin secretion, supporting long-term glucose homeostasis[42].

Challenges and Future Perspectives

Bioavailability Enhancement: Flavonoids are known for their health-promoting properties, including antioxidant, anti-inflammatory, and cardioprotective effects. However, one of the major limitations to their therapeutic application is poor bioavailability. This challenge arises due to low aqueous solubility, poor permeability across the intestinal epithelium, and rapid metabolism and excretion. To overcome this, innovative strategies are being explored to enhance the bioavailability of flavonoids. Nanoencapsulation involves incorporating flavonoids into nanoparticles, which protect them from degradation and enhance intestinal absorption. Liposomal delivery systems—comprising phospholipid bilayers—help improve the solubility, stability, and targeted delivery of flavonoids. Another promising strategy is glycoside modification, where attaching sugar moieties enhances water solubility and cellular uptake. These advanced delivery systems not only improve the pharmacokinetic profiles of flavonoids but also enhance their therapeutic efficacy. Continued research into these technologies holds promise for maximizing the clinical benefits of flavonoids in managing chronic diseases such as cancer, cardiovascular disorders, and metabolic syndromes.

Personalized Nutrition: The field of personalized nutrition is gaining attention as a promising approach for optimizing health outcomes through individualized dietary interventions [43]. In the context of flavonoid-based therapies, genetic and microbiome profiling offer valuable tools to tailor dietary recommendations based on an individual's unique biological characteristics. Variations in genes involved in flavonoid metabolism, absorption, and excretion—such as polymorphisms in cytochrome P450 enzymes—can significantly influence the effectiveness of flavonoid interventions. Similarly, the gut microbiota plays a critical role in modulating the biotransformation of flavonoids into bioactive compounds, and its composition can differ widely among individuals. By integrating genomic and microbiome data, it becomes possible to identify subgroups of individuals who may benefit most from specific flavonoid-rich foods or supplements. Personalized flavonoid nutrition could thus enhance therapeutic efficacy, reduce the risk of adverse effects, and contribute to the prevention and management of metabolic disorders, cardiovascular diseases, and other non-communicable conditions.

Drug-Flavonoid Interactions: As flavonoids gain attention for their therapeutic potential, it is critical to understand their interactions with pharmaceutical drugs, especially in patients undergoing polypharmacy. Flavonoids can modulate the activity of drug-metabolizing enzymes such as cytochrome P450 isoforms (e.g., CYP3A4, CYP2D6), and transporters like P-glycoprotein, which are responsible for drug absorption, distribution, metabolism, and excretion. Such interactions may lead to either enhanced toxicity or diminished efficacy of co-administered drugs. For instance, flavonoids like quercetin and naringenin have been shown to

inhibit CYP enzymes, potentially altering the plasma concentrations of drugs such as statins, anticoagulants, and chemotherapeutic agents. Moreover, flavonoids may affect drug transport across the blood-brain barrier or influence gut microbiota-mediated drug metabolism. Therefore, understanding the pharmacokinetics and pharmacodynamics of flavonoid-drug interactions is essential for ensuring safe and effective use. Incorporating this knowledge into clinical practice and drug development can help avoid adverse outcomes and support the integration of flavonoids into evidence-based therapeutic regimens.

CONCLUSION

Flavonoids present a compelling natural alternative for the management of metabolic syndrome through their multifaceted effects on inflammation, obesity, and insulin resistance. Despite promising preclinical and clinical evidence, challenges related to bioavailability and standardization remain. Future research should focus on developing optimized flavonoid formulations and personalized dietary strategies to maximize their therapeutic potential in metabolic health.

REFERENCES

1. Islam, Md.S., Wei, P., Suzauddula, M., Nime, I., Feroz, F., Acharjee, M., Pan, F.: The interplay of factors in metabolic syndrome: understanding its roots and complexity. Mol Med. 30, 279 (2024). https://doi.org/10.1186/s10020-024-01019-y
2. Swarup, S., Ahmed, I., Grigorova, Y., Zeltser, R.: Metabolic Syndrome. In: StatPearls. StatPearls Publishing, Treasure Island (FL) (2025)
3. Amor, A.J., Gómez-Guerrero, C., Ortega, E., Sala-Vila, A., Lázaro, I.: Ellagic Acid as a Tool to Limit the Diabetes Burden: Updated Evidence. Antioxidants (Basel). 9, 1226 (2020). https://doi.org/10.3390/antiox9121226
4. Uti, D.E., Atangwho, I.J., Alum, E.U., Egba, S.I., Ugwu, O.P.-C., Ikechukwu, G.C.: Natural Antidiabetic Agents: Current Evidence and Development Pathways from Medicinal Plants to Clinical use. Natural Product Communications. 20, 1934578X251323393 (2025). https://doi.org/10.1177/1934578X251323393
5. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
6. Ashour, M.M., Mabrouk, M., Aboelnasr, M.A., Beherei, H.H., Tohamy, K.M., Das, D.B.: Anti-Obesity Drug Delivery Systems: Recent Progress and Challenges. Pharmaceutics. 15, 2635 (2023). https://doi.org/10.3390/pharmaceutics15112635
7. Annett, S., Moore, G., Robson, T.: Obesity and Cancer Metastasis: Molecular and Translational Perspectives. Cancers. 12, 3798 (2020). https://doi.org/10.3390/cancers12123798
8. Udeozor, P.A., Ibiam, U.A., Uti, D.E., Umoru, G.U., Onwe, E.N., Mbonu, F.O., Omang, W.A., Ijoganu, S.I., Anaga, C.O., Mbah, J.O., Nwadum, S.K.: Antioxidant and Anti-Anemic Effects of Ethanol Leaf Extracts of Mucuna poggei and Telfairia occidentalis in Phenyl-Hydrazine-Induced Anemia in Wistar Albino Rats. Ibnosina Journal of Medicine and Biomedical Sciences. 14, 116–126 (2022). https://doi.org/10.1055/s-0042-1756684
9. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Nna, V.U., Udeozor, P.A.: African walnuts attenuate ectopic fat accumulation and associated peroxidation and oxidative stress in monosodium glutamate-obese Wistar rats. Biomed Pharmacother. 124, 109879 (2020). https://doi.org/10.1016/j.biopha.2020.109879
10. Obeidat, A.A., Ahmad, M.N., Ghabashi, M.A., Alazzeh, A.Y., Habib, S.M., Abu Al-Haijaa, D., Azzeh, F.S.: Developmental Trends of Metabolic Syndrome in the Past Two Decades: A Narrative Review. Journal of Clinical Medicine. 14, 2402 (2025). https://doi.org/10.3390/jcm14072402
11. Wenzel, U.: Flavonoids as drugs at the small intestinal level. Current Opinion in Pharmacology. 13, 864–868 (2013). https://doi.org/10.1016/j.coph.2013.08.015
12. AL-Ishaq, R.K., Abotaleb, M., Kubatka, P., Kajo, K., Büsselberg, D.: Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and Effects to Improve Blood Sugar Levels. Biomolecules. 9, 430 (2019). https://doi.org/10.3390/biom9090430
13. Bouyahya, A., Balahbib, A., Khalid, A., Makeen, H.A., Alhazmi, H.A., Albratty, M., Hermansyah, A., Ming, L.C., Goh, K.W., El Omari, N.: Clinical applications and mechanism insights of natural flavonoids against type 2 diabetes mellitus. Heliyon. 10, e29718 (2024). https://doi.org/10.1016/j.heliyon.2024.e29718
14. Sandoval, V., Sanz-Lamora, H., Arias, G., Marrero, P.F., Haro, D., Relat, J.: Metabolic Impact of Flavonoids Consumption in Obesity: From Central to Peripheral. Nutrients. 12, 2393 (2020). https://doi.org/10.3390/nu12082393
15. Alum, E.U, Nwuruku, A. O, Edwin, N.: Targeting oxidative stress in cancer management: The role of antioxidant phytochemicals. KJHS. 4, 1–10 (2024). https://doi.org/10.59568/KJHS-2024-4-2-01
16. Andreu Fernández, V., Almeida Toledano, L., Pizarro Lozano, N., Navarro Tapia, E., Gómez Roig, M.D., De la Torre Fornell, R., García Algar, Ó.: Bioavailability of Epigallocatechin Gallate Administered with

Different Nutritional Strategies in Healthy Volunteers. Antioxidants (Basel). 9, 440 (2020). https://doi.org/10.3390/antiox9050440
17. Basu, T., Selman, A., Reddy, A.P., Reddy, P.H.: Current Status of Obesity: Protective Role of Catechins. Antioxidants (Basel). 12, 474 (2023). https://doi.org/10.3390/antiox12020474
18. Alum, E.U., Ugwu, O.P.C.: Beyond Nutrients: Exploring the Potential of Phytochemicals for Human Health. IAA JAS. 10, 1–7 (2023). https://doi.org/10.59298/IAAJAS/2023/4.1.3211
19. Wen, D., Li, M.: The Emerging Role of Flavonoids in the Treatment of Type 2 Diabetes Mellitus: Regulating the Enteroendocrine System. Exploratory Research and Hypothesis in Medicine. 10, 56–68 (2025). https://doi.org/10.14218/ERHM.2024.00055
20. Gouveia, H.J.C.B., Urquiza-Martínez, M.V., Manhães-de-Castro, R., Costa-de-Santana, B.J.R., Villarreal, J.P., Mercado-Camargo, R., Torner, L., de Souza Aquino, J., Toscano, A.E., Guzmán-Quevedo, O.: Effects of the Treatment with Flavonoids on Metabolic Syndrome Components in Humans: A Systematic Review Focusing on Mechanisms of Action. Int J Mol Sci. 23, 8344 (2022). https://doi.org/10.3390/ijms23158344
21. Thompson, A.S., Jennings, A., Bondonno, N.P., Tresserra-Rimbau, A., Parmenter, B.H., Hill, C., Perez-Cornago, A., Kühn, T., Cassidy, A.: Higher habitual intakes of flavonoids and flavonoid-rich foods are associated with a lower incidence of type 2 diabetes in the UK Biobank cohort. Nutr Diabetes. 14, 32 (2024). https://doi.org/10.1038/s41387-024-00288-0
22. Wang, X., Ma, Y., Xu, Q., Shikov, A.N., Pozharitskaya, O.N., Flisyuk, E.V., Liu, M., Li, H., Vargas-Murga, L., Duez, P.: Flavonoids and saponins: What have we got or missed? Phytomedicine. 109, 154580 (2023). https://doi.org/10.1016/j.phymed.2022.154580
23. Yang, C., Gundala, S.R., Mukkavilli, R., Vangala, S., Reid, M.D., Aneja, R.: Synergistic interactions among flavonoids and acetogenins in Graviola (Annona muricata) leaves confer protection against prostate cancer. Carcinogenesis. 36, 656–665 (2015). https://doi.org/10.1093/carcin/bgv046
24. Ahn-Jarvis, J.H., Parihar, A., Doseff, A.I.: Dietary Flavonoids for Immunoregulation and Cancer: Food Design for Targeting Disease. Antioxidants. 8, 202 (2019). https://doi.org/10.3390/antiox8070202
25. Nouri, Z., Fakhri, S., El-Senduny, F.F., Sanadgol, N., Abd-ElGhani, G.E., Farzaei, M.H., Chen, J.-T.: On the Neuroprotective Effects of Naringenin: Pharmacological Targets, Signaling Pathways, Molecular Mechanisms, and Clinical Perspective. Biomolecules. 9, 690 (2019). https://doi.org/10.3390/biom9110690
26. Solverson, P.: Anthocyanin Bioactivity in Obesity and Diabetes: The Essential Role of Glucose Transporters in the Gut and Periphery. Cells. 9, 2515 (2020). https://doi.org/10.3390/cells9112515
27. Alshehri, M.M., Sharifi-Rad, J., Herrera-Bravo, J., Jara, E.L., Salazar, L.A., Kregiel, D., Uprety, Y., Akram, M., Iqbal, M., Martorell, M., Torrens-Mas, M., Pons, D.G., Daşstan, S.D., Cruz-Martins, N., Ozdemir, F.A., Kumar, M., Cho, W.C.: Therapeutic Potential of Isoflavones with an Emphasis on Daidzein. Oxidative Medicine and Cellular Longevity. 2021, 6331630 (2021). https://doi.org/10.1155/2021/6331630
28. Allemailem, K.S., Almatroudi, A., Alharbi, H.O.A., AlSuhaymi, N., Alsugoor, M.H., Aldakheel, F.M., Khan, A.A., Rahmani, A.H.: Apigenin: A Bioflavonoid with a Promising Role in Disease Prevention and Treatment. Biomedicines. 12, 1353 (2024). https://doi.org/10.3390/biomedicines12061353
29. Guedj, F., Siegel, A.E., Pennings, J.L.A., Alsebaa, F., Massingham, L.J., Tantravahi, U., Bianchi, D.W.: Apigenin as a Candidate Prenatal Treatment for Trisomy 21: Effects in Human Amniocytes and the Ts1Cje Mouse Model. The American Journal of Human Genetics. 107, 911–931 (2020). https://doi.org/10.1016/j.ajhg.2020.10.001
30. Thilakarathna, S.H., Rupasinghe, H.P.V.: Flavonoid Bioavailability and Attempts for Bioavailability Enhancement. Nutrients. 5, 3367–3387 (2013). https://doi.org/10.3390/nu5093367
31. Department of Research and Publications, Kampala International University, P. O. Box 20000, Main Campus, Uganda., E.U, A.: Phytochemicals in malaria treatment: Mechanisms of action and clinical efficacy. KJHS. 4, 71–84 (2024). https://doi.org/10.59568/KJHS-2024-4-2-06
32. Cronin, P., Joyce, S.A., O'Toole, P.W., O'Connor, E.M.: Dietary Fibre Modulates the Gut Microbiota. Nutrients. 13, 1655 (2021). https://doi.org/10.3390/nu13051655
33. Hu, L., Luo, Y., Yang, J., Cheng, C.: Botanical Flavonoids: Efficacy, Absorption, Metabolism and Advanced Pharmaceutical Technology for Improving Bioavailability. Molecules. 30, 1184 (2025). https://doi.org/10.3390/molecules30051184
34. Chen, A.Y., Chen, Y.C.: A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food Chem. 138, 2099–2107 (2013). https://doi.org/10.1016/j.foodchem.2012.11.139
35. James, A., Wang, K., Wang, Y.: Therapeutic Activity of Green Tea Epigallocatechin-3-Gallate on Metabolic Diseases and Non-Alcoholic Fatty Liver Diseases: The Current Updates. Nutrients. 15, 3022 (2023). https://doi.org/10.3390/nu15133022

36. Aghababaei, F., Hadidi, M.: Recent Advances in Potential Health Benefits of Quercetin. Pharmaceuticals (Basel). 16, 1020 (2023). https://doi.org/10.3390/ph16071020
37. Dong, J., Zhang, X., Zhang, L., Bian, H.-X., Xu, N., Bao, B., Liu, J.: Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: a mechanism including AMPKα1/SIRT1. Journal of Lipid Research. 55, 363 (2014). https://doi.org/10.1194/jlr.M038786
38. Chen, J., Chen, B., Lin, B., Huang, Y., Li, J., Li, J., Chen, Z., Wang, P., Ran, B., Yang, J., Huang, H., Liu, L., Wei, Q., Ai, J., Cao, D.: The role of gut microbiota in prostate inflammation and benign prostatic hyperplasia and its therapeutic implications. Heliyon. 10, e38302 (2024). https://doi.org/10.1016/j.heliyon.2024.e38302
39. Cunningham, A.L., Stephens, J.W., Harris, D.A.: Gut microbiota influence in type 2 diabetes mellitus (T2DM). Gut Pathogens. 13, 50 (2021). https://doi.org/10.1186/s13099-021-00446-0
40. Zhou, M., Konigsberg, W.H., Hao, C., Pan, Y., Sun, J., Wang, X.: Bioactivity and mechanisms of flavonoids in decreasing insulin resistance. J Enzyme Inhib Med Chem. 38, 2199168. https://doi.org/10.1080/14756366.2023.2199168
41. Martín, M.Á., Ramos, S.: Dietary Flavonoids and Insulin Signaling in Diabetes and Obesity. Cells. 10, 1474 (2021). https://doi.org/10.3390/cells10061474
42. Taheri, R., Mokhtari, Y., Yousefi, A.-M., Bashash, D.: The PI3K/Akt signaling axis and type 2 diabetes mellitus (T2DM): From mechanistic insights into possible therapeutic targets. Cell Biology International. 48, 1049–1068 (2024). https://doi.org/10.1002/cbin.12189
43. Alum, E.U., Ugwu, O.P.-C.: Artificial intelligence in personalized medicine: transforming diagnosis and treatment. Discov Appl Sci. 7, 193 (2025). https://doi.org/10.1007/s42452-025-06625-x

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