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Pharmacological, medicinal and biological properties of flavonoids: A comprehensive review

Oruç YUNUSOĞLU[1]*, İlknur AYAZ[1], Ebru Havva DOVANKAYA[1]

[1] Department of Pharmacology, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye.
*Corresponding Author. E-mail: orucfarm@gmail.com (O.Y.); Tel. + 90-374-254 10 00.

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ABSTRACT: Plant-based phytochemicals are currently being used to prevent and treat several diseases. Flavonoids are plant-based compounds that are widely found in the plant kingdom, which contain the benzopyrone ring, and possess various biological activities. To date, approximately more than 6000 different flavonoids have been identified and classified as flavones, flavanones, flavanols, isoflavones, anthocyanidins, and catechins. Many *in vitro* and *in vivo* experimental studies were published on the use of flavonoids in different conditions. Antioxidant, antiinflammatory, antibacterial, antifungal, antiviral, antihypertensive, antihyperlipidemic, antithrombotic, antiasthma, antiallergic, antidiabetic, antiobesity, antiarthritis, antiulcer, hepatoprotective, osteoprotective, immunomodulation, anticancer, antiaging, neuroprotective, antiaddictive, antiparkinsonian, antiepileptic, anxiolytics and antidepressant are among the primary pharmacological properties of these compounds. Despite a wide range of the ongoing research on the potential health benefits of flavonoids, the U.S. FDA (and similar organizations) has not approved any flavonoid compounds for therapeutic use. However, these compounds are available as nutritional supplements in various dosage forms. In this review, we used the databases like PubMed, Web of Science, ScienceDirect, Scopus, ResearchGate and Google Scholar to find the best-matched information about flavonoids' pharmacological, medicinal and biological properties to elucidate the therapeutic potential as well as their side effects. A comprehensive systematic literature review was carried out to achieve the main goal of this study.

KEYWORDS: Flavonoids; polyphenols; pharmacological activity; therapeutic potential; systematic review.

1. INTRODUCTION

Flavonoids are substances widely found in nature and constitute an important class of secondary plant metabolites [1, 2]. These compounds provide protection in plants against ultraviolet pathogens, herbivores and radiation. There are currently about 6000 distinct flavonoid compounds that have been identified [3]. All portions of plants include flavonoids, which make about 60% of all naturally occurring polyphenols. However, flavonoids are most abundant in flowers and leaves. The discovery of flavonoids can be attributed to a novel chemical isolated from oranges in an experiment conducted by Hungarian scientist Albert Szent-Gyorgyino in 1930. Initially categorized as vitamin P, subsequent investigations led to the conclusion that it did not qualify as a vitamin [4-6]. Numerous distinct flavonoids have been recognized up to the present. Flavonoids constitute a group of phenolic compounds characterized by low molecular weight polyphenolic structures. Among flavanols, there are various classes, including flavones, anthocyanins, flavanones, isoflavones, and flavanols [5]. Vegetables, fruits, and certain beverages are common sources of flavonoids [7, 8]. These compounds are absorbed into the plasma and undergo metabolism through reactions like glycosylation, glucuronidation, sulfation, and methylation. Enzymes in the small intestine, liver, and colon play a role in these processes, leading to the excretion of flavonoids in bile and urine [9]. Flavonoids can modulate the activity of enzymes and exert beneficial effects on the organism by influencing the behaviour of many cellular systems. The wealth of evidence supporting the health benefits of flavonoids has sparked increased interest in these compounds. Numerous scientific studies have been undertaken to comprehensively grasp the potential advantages and activities of flavonoids, yet there remains a need for further extensive research in this domain. In our study, research was conducted on the various effects of flavonoids through PubMed, Web of Science, ScienceDirect, Scopus, ResearchGate and Google Scholar

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databases and therapeutic effects were observed in many flavonoids. Obtaining this information is very important for chronic diseases (e.g. cancer), which will shed light on future research in the scientific literature and is one of the most important health problems of today. The observed therapeutic effects of flavonoids are thought to be influenced by their antioxidant and anti-inflammatory properties, given the importance of oxidative damage and chronic inflammation in the etiology of many diseases.

Numerous investigations, both in vitro and in vivo, have been carried out on medicinal plants to investigate their potential therapeutic uses in treating a range of illnesses [10-12]. Due to its lower adverse effect profile when compared to regular pharmaceuticals, herbal treatment is thought to be safer. Though herbal medicine or isolated substances obtained from plants are widely used to treat various diseases, there is a lack of robust evidence for the efficacy and toxicity of most herbs [13-21]. Medicinal plants show promise in the prevention and treatment of numerous ailments that are thought to be challenging to manage. Worldwide, there is a "renaissance" of herbs and a resurgence of herbs [22]. 75% of people worldwide use herbs for basic medical requirements, according to the World Health Organization (WHO). Herbal products such as plant extracts, herbal supplements, and active substances isolated from plants are now the mainstay of approximately 75% close of the world population for primary health care. In actuality, using plants and herbs as medicine has been a practice from the beginning of humankind [22]. More than a tenth of plant species (more than 50,000 species) are used in pharmaceutical and cosmetic products. However, the distribution of medicinal plants around the world is uneven and medicinal plants are mainly collected from wildlife populations [10, 23]. About 100,000 of the 500,000–600,000 plant-derived chemicals that have been reported have shown interesting biological activity and may be useful in the treatment of human ailments [24].

The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are globally significant organizations. In general, the FDA oversees and regulates pharmaceuticals, biological products, medical devices, foods, cosmetics, herbal products (herbal supplements, herbal isolated active ingredients, etc.), tobacco products, and radiation-emitting goods in order to safeguard and improve public health. According to literature sources, although many patent applications have been filed for pharmaceutical compositions containing flavonoids and the use of flavonoids, the FDA has not yet approved any flavonoids as pharmaceutical drugs [25]. The broad consensus among authorities and healthcare professionals is that food-based medicines are "safer" than treatments produced from chemicals. Customers all throughout the world have embraced natural healthcare products to enhance health and well-being, despite the scant data supporting this differentiation. Consequently, research on therapeutic activities, both present and prospective, may be useful in the treatment of illnesses. Throughout history, traditional societies have utilized herbs and plant-based medicine extensively. In contemporary society, these natural substitutes for synthetic medicines are gaining popularity [26]. A reference guide on plants and their products that is both user-friendly and scientifically correct is needed, especially as more and more natural medicines are being sold commercially. Scientific studies have determined the biological activity of many medicinal plants, and a simple check of the literature will demonstrate that fresh research findings are being contributed daily [26]. Over half of all pharmaceuticals used in clinical settings worldwide are made up of natural compounds or their derivatives. Herbal medications are well-known and include atropine, quinine, morphine, codeine, reserpine, colchicine, and digoxin [10, 27-30]. Clinical evidence has demonstrated that a number of naturally occurring compounds that have been extracted from herbs, including vincristine, paclitaxel, cantharidin sodium injection, and magnolol, have strong anti-cancer activity [10, 31]. Natural treatments and self-medication are becoming increasingly popular, according to health stores and pharmacies worldwide. Based on research, it is seen that flavonoids are one of the most important groups of substances with high pharmacological, medicinal, biological, and treatment potential among the phytochemicals contained in medicinal plants.

2. Pharmacological, Medicinal And Biological Properties Of Flavonoids

2.1. Quercetin

Quercetin (3,3',4',5,7-Pentahydroxyflavone) a secondary metabolite, is a natural flavonoid found abundantly in vegetables and fruits [32]. It can be found in a wide range of foods, including tomatoes, tea pepper, coriander, brassica onions, berries, and citrus fruits. It can also be found in many different seeds, flowers, nuts, leaves, and bark [32, 33]. Additionally, medicinal plants such as *Hypericum perforatum*, *Sambucus nigra* and *Ginkgo biloba* also contain quercetin [32]. Due to its poor water-solubility, chemical

stability, and absorption profile, quercetin's bioavailability is frequently relatively low (<10%). The effects of quercetin's dietary matrix, physicochemical characteristics, and chemical structure all affect its bioavailability [34].

Antiasthmatic Activity

Quercetin is natural flavonoid which showing to have anti-asthma effect. It has strong anti-inflammatory and antioxidant properties and suppress the producing of inflammatory cytokines, which play significant role in the pathogenesis of asthma [35]. Examinations have displayed that quercetin can decrease airway increased responsiveness, mucus hypersecretion and eosinophilic inflammation, which are key features of asthma [33]. Research indicates that *Elaeagnus pungens* leaves may have therapeutic benefits for asthma and chronic bronchitis, primarily attributed to the presence of quercetin. Studies suggest that quercetin, a key component in these leaves, could play a role in treating asthma and chronic bronchitis. However, it's crucial to seek advice from a healthcare professional for personalized guidance [36]. In a mouse experiment focusing on allergic airway inflammation, the impact of quercetin was investigated concerning histological features and airway epithelium in respiratory tissues. The findings suggest that quercetin mitigated chronic histopathological changes in lung tissue, excluding basement membrane thickness.

The observed anti-inflammatory effects may be linked to mediators such as cytokines released from the epithelium and epithelial apoptosis [37]. A study on neonatal asthmatic rats explored the impact of quercetin glycosides. Notably, quercetin effectively suppressed the expression of inducible nitric oxide synthase (iNOS) protein. The asthmatic rats exhibited lung eosinophil accumulation, along with vascular and airway constriction. Yet, the application of quercetin notably alleviated eosinophil-induced inflammation and infiltration. In summary, the substantial reduction in inflammatory markers demonstrated the protective efficacy of quercetin glycosides against neonatal asthma in rats [38]. Another study indicates that quercetin can serve as a valuable tool for understanding the synthesis of novel bronchodilator compounds. These compounds have potential applications in the treatment of chronic obstructive pulmonary disease and obstructive lung conditions like asthma [39].

Antibacterial Activity

Quercetin demonstrated potent bacteriostatic effects against diverse bacterial species, including *Salmonella enterica* serotype and *Helicobacter pylori*. Its efficacy was observed to be higher against Gram-positive bacteria in comparison to Gram-negative bacteria [40]. Quercetin's antibacterial mechanism, as indicated by recent research, primarily involves enhancing cell permeability by disrupting bacterial cell walls. Additionally, it influences protein synthesis and expression, diminishes enzyme activities, and inhibits nucleic acid synthesis in bacteria [41].

Anticancer and Anti-apoptosis Activity

Quercetin exhibits potent anticarcinogenic properties, functioning as an inducer of apoptosis. This action contributes to the suppression of tumour growth and hinders the dissemination of malignant cells in various tissues, including the brain, liver, and colon [42, 43]. The study investigated a combination therapy involving curcumin and quercetin in patients with familial adenomatous polyposis (FAP). Results indicated that the combination of curcumin and quercetin effectively decreased both the number and size of ileal and rectal adenomas, demonstrating minimal potential for side effects [44]. Quercetin inhibits hexavalent chromium ion a chemical carcinogen-induced cell transformation such as loss of cell viability, reactive oxygen species (ROS) production, and elevation of MicroRNA-21 in human colon cancer Caco-2 cells [45, 46]. Quercetin has been reported to exhibit a beneficial impact on prostate in experimental studies [47].

Antidiabetic Activity

Quercetin's positive effects on glycemia are known. Different experimental studies have highlighted the hypoglycemic properties of quercetin in different diabetic animal models [48]. In various studies, quercetin has exhibited significant inhibition of both alpha-amylase and alpha-glucosidase activities, the extent of which is concentration-dependent. Additionally, it has demonstrated the capacity to prevent lipid oxidation in pancreatic tissue homogenates [49]. Slowing down the increase in blood sugar levels may result from the inhibition of the two enzymes responsible for carbohydrate breakdown. Furthermore, preventing pancreatic lipid peroxidation may serve to shield the pancreas from cellular damage, consequently averting

conditions that could exacerbate insulin production and secretion [50]. In a study investigating the expression of glucokinase and glucose-6-phosphatase-two enzymes crucial in glucose metabolism adult rodents were categorized into three groups: diabetic rats treated with streptozotocin, a control group, and a group administered quercetin. The findings from this experiment, as interpreted by medical experts, indicate that quercetin has the potential to be utilized as a nutritional supplement, affirming its positive impact on diabetes [51].

Antifungal Activity

By altering oxidative stress kinetics and modifying the cell membrane composition of fungi, quercetin hinders cell growth and, at elevated doses, induces cell death. Notably, there is emphasis on quercetin's synergistic effects with other antifungal agents, highlighting its potential as a promising alternative or complementary therapy in the management of fungal infections [52]. When tested on *Candida albicans* cultures, quercetin had antifungal action [53]. In a different investigation, quercetin decreased the biomass and metabolic activity of the *Candida parapsilosis* complex's developing biofilms [54].

Antihypertensive Activity

Quercetin's anti-hypertensive impact involves inhibiting nitric oxide (NO) production and countering endothelial dysfunction, marked by heightened oxidative stress, a characteristic feature of hypertension. It has demonstrated the ability to enhance NO bioavailability by elevating the expression of endothelial NO synthase (eNOS) and impeding the activity of NO-degrading enzymes, including reduced nicotinamide adenine dinucleotide phosphate oxidase and arginase [55]. Furthermore, quercetin displays antioxidant attributes by effectively neutralizing ROS and mitigating oxidative stress. This has the potential to safeguard endothelial cells from harm and preserve their optimal functioning. Quercetin's enhancement of endothelial function might contribute to its anti-hypertensive effects, inducing vasodilation and the resulting decrease in vascular resistance cause a decrease in blood pressure [56]. Besides its impact on endothelial function, quercetin has demonstrated the ability to influence additional pathways relevant to blood pressure regulation. Specifically, it has been observed to inhibit angiotensin-converting enzyme (ACE). Through the inhibition of ACE activity, quercetin decreases the production of angiotensin II, resulting in vasodilation and a consequent reduction in blood pressure [57].

Quercetin has been identified as a substance capable of reducing blood pressure in hypertensive rats by enhancing the antioxidant defence system. Hypertension and oxidative stress were induced in rat models using deoxycorticosterone acetate-salt. Treatment with quercetin in these rats resulted in the reinforcement of the antioxidant defence system, a decrease in cardiac hypertrophy and diastolic blood pressure, along with the restoration of glutathione levels in the liver and heart [58, 59]. Research has explored the impact of quercetin on hypertension in human subjects. Over a period of 28 days, 19 individuals with prehypertension and 22 with stage 1 hypertension were administered quercetin or a placebo. While quercetin treatment did not influence the blood pressure of prehypertensive patients, it did influence those with stage 1 hypertension. The capacity of quercetin to reduce blood pressure has also received affirmation from various studies [60].

Antiinflammatory Activity

One of quercetin's most powerful activities is its ability to regulate inflammation. It exerts potent anti-inflammatory effects by inhibiting the inflammatory enzymes cyclooxygenase (COX) and lipoxygenase, leading to a reduction in key mediators like prostaglandins and leukotrienes [58, 61]. Researchers specializing in nutrition explored the impact of dietary flavonoids, including quercetin, to identify compounds with systemic anti-inflammatory properties [62]. Elevated C-reactive protein (CRP) levels are linked to various health conditions, including obesity, heart disease, and systemic lupus erythematosus. This investigation revealed that the consumption of specific foods can lead to a reduction in CRP levels. Experimental research, quercetin demonstrated a noteworthy decrease in the levels of inflammatory mediators such as CRP, NO synthase and cyclooxygenase 2 (COX-2) in a human hepatocyte-derived cell line [63]. In rats, quercetin reduced the levels of these inflammatory parameters. It showed significant antiarthritic activity against acute and chronic inflammation as well as adjuvant-induced arthritis [64].

Antithrombotic Activity

Quercetin inhibited platelets' concentration-dependent release of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) in response to thrombin [64]. Additionally, quercetin inhibited neutrophil migration toward thrombin-induced platelet supernatants, so averting the neutrophils' enhanced respiratory burst in response to platelets that had been thrombin-activated. Quercetin normalized adenosine monophosphate and adenosine levels measured in in vitro research and restored reduced CD39/ATPdase activity. Quercetin inhibited the activities of c-Jun NH2-terminal kinase (JNK), mitogen-activated protein kinase (MAP), and focal adhesion kinase in endothelial cells triggered by thrombin [64].

Antiobesity Activity

Quercetin has demonstrated the ability to hinder adipocyte differentiation and adipogenesis, pivotal processes in the onset of obesity [65]. It has been observed to enhance lipolysis, promoting the breakdown of stored fat, and elevate thermogenesis, the heat-generating activity of adipose tissue. Additionally, it has been identified to augment energy expenditure [66]. Moreover, through the inhibition of pro-inflammatory cytokine formation, quercetin demonstrates anti-inflammatory effects by targeting mechanisms implicated in inflammation associated with obesity [67]. In the study involving curcumin and quercetin, it was noted that the nanoparticle forms of quercetin outperformed their free counterparts in terms of potency. This heightened efficacy can be attributed to the improved solubility and bioavailability associated with the nanoformulations. The potential therapeutic advantages of incorporating quercetin into nanoencapsulation suggest the feasibility of developing clinically applicable approaches for treating individuals with obesity [68].

Antioxidant Activity

Quercetin has been shown to have a strong antioxidant effect potential in numerous in vivo and in vitro studies. In other words, many therapeutic effects of quercetin are thought to be due to its antioxidant effect. Examples of these therapeutic effects include anticancer, anti-allergic, anti-ulcer, anti-viral, anti-inflammatory activities, gastroprotective, anti-diabetic, antihypertensive and immunomodulatory [69]. Quercetin is suggested to provide protection against the impact of free radicals generated by smoking. The damage to erythrocyte membranes induced by cigarette tar is linked to the presence of free radicals. Additionally, studies have revealed that quercetin and its conjugated metabolites offer safeguarding effects on erythrocytes, shielding them from membranous damage caused by smoking [70].

Antiviral Activity

Quercetin has demonstrated efficacy against human T-lymphotropic virus 1 and Japanese encephalitis virus, the causative agent of Japanese encephalitis mosquito-borne disease [70]. A study indicates that quercetin exhibits antiviral effects against hepatitis C (HCV) [71]. Because quercetin has demonstrated promise antiviral effects by inhibiting reverse transcriptase, proteases, polymerases, decreasing DNA gyrase, and binding viral capsid proteins, it has been examined in a variety of viral infection types and models. Furthermore, patients with corona virus disease 19 pandemic (COVID-19) symptoms who received quercetin as adjuvant medication saw improvements in their clinical symptoms and shorter hospital stays [72].

Cardioprotective Activity

Quercetin protects against chronic heart disease by inhibiting platelet aggregation, improves endothelial function, and reduces the risk of death caused by low-density lipoprotein (LDL). By showing vasodilator activity, it reduces the blood pressure of isolated arteries and protects from cardiac hypertrophy [73]. Quercetin prevents the activation of the last step of LDL cholesterol synthesis. As a result of the research, it was revealed that consuming high amounts of foods containing flavonoids reduces cholesterol levels. One study found that people consuming quercetin and non-alcoholic red wine extract inhibited LDL oxidation [74]. In 6-week clinical tests conducted in patients at high risk of heart disease, it was observed that quercetin consumed reduced systolic blood pressure by reducing oxidized LDL levels in plasma [75]. Quercetin has properties that prevent fat accumulation in human fat cells and direct them to apoptosis in existing adipocytes [76, 77]. Additionally, in another study, quercetin indirectly inhibits adipocyte development by blocking glucose uptake from the blood and increases fat cell necrosis [78]. The independent consumption of dietary fiber from either grains or fruits is linked to a lower risk of mortality from coronary heart disease (CHD). In a separate study, it was found that dietary fiber from grains was associated with a

reduction in the risk of CHD death, while a similar increase in dietary fiber from fruits was associated with more reduction in the risk of CHD death [79, 80].

Antiaddictive Activity

Quercetin has been found to have positive effects on addiction caused by substances with addictive potential from various groups [32, 81, 82]. In a study conducted with animals examined with the conditioned place preference model, quercetin ethanol caused an increase in the time spent in the paired part, however, there was no significant change in locomotor activity and motor coordination [32]. Quercetin boosted gamma-aminobutyric acid type A (GABAA) and gamma-aminobutyric acid type B (GABAB) mediated inhibitory postsynaptic currents in ventral tegmental area (VTA) dopamine neurons. Protein kinase A-dependent increases in presynaptic GABA release made this action possible [83]. Quercetin raised striatal interferon 6 (IL-6) levels and prevented naloxone-precipitated heroin withdrawal. Quercetin treatment simultaneously prevented heroin-conditioned location preference from forming, while quercetin promoted heroin-induced reinstatement [83].

2.2. Kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one), a secondary metabolite found in plants, is a naturally occurring flavonoid demonstrating important potential in different biological activities [84, 85]. It represents one of the numerous encountered aglycone flavonoids in the form of glycoside. Kaempferol is most found in numerous plants and plant-derived foods including grapes spinach, kale, broccoli, bean, tomatoes, and tea leaves [85]. The plasma concentration-time profiles showed a reasonably quick absorption following oral dosing. Following intravenous and oral doses, the area under the curve values grew roughly proportionate to the dose. At about 2%, the bioavailability was low [86].

Anticancer Activity

Kaempferol has been discovered to exhibit significant anti-tumor effects by causing cell cycle arrest and inducing regulated cell death in HeLa cells. These findings suggest that kaempferol could hold therapeutic promise for treating cervical carcinoma. In the study, the observed G2/M phase cell cycle arrest induced by kaempferol was associated with a decrease in cyclin B1 and cyclin dependent kinases1 levels, and this effect occurred independently of p53 [87]. Compared to the current standard chemotherapeutic medications used in cancer treatment, kaempferol shown low adverse effects in the various studies and demonstrated an effective synergistic potential when combined with different synthetic cytotoxic agents [88].

Antidiabetic Activity

Kaempferol has been demonstrated to effectively normalize both elevated serum glucose and diminished serum insulin levels in diabetic rat models induced by streptozotocin-nicotinamide. These findings indicate that the therapeutic impact of kaempferol on diabetes manifests through the modulation of serum glucose and insulin levels [89]. Furthermore, kaempferol was observed to alleviate neuropathy and nephropathy in streptozotocin (STZ)-induced diabetic rat models, suggesting a potential preventive role against diabetes-related complications. Additionally, this flavanol has been shown to reduce both the occurrence and severity of collagen-induced arthritis in experimental animals [89].

Antiepileptic Activity

Among the 11 studied flavonoids, the authors observed that five kaempferol derivatives (KPFs) effectively inhibited the activity of P-glycoprotein (gp-P) derived from Madin-Darby canine kidney cells. The KPFs also exhibited inhibitory effects on P-glycoprotein associated with specific anti-epileptic drugs, including carbamazepine, oxcarbazepine, phenytoin, lamotrigine, and and its active metabolites carbamazepine-10,11-epoxide and licarbazepine [90]. This suggests that KPFs may facilitate the intracellular accumulation of anti-epileptic medications. However, the precise mechanism by which KPF enhances gp-P inhibition remains incompletely understood, and further investigations are required to elucidate the impact of kaempferol in epilepsy [90].

Antiparkinson Activity

Growing research in contemporary pharmacology indicates that kaempferol and its derivatives have neuroprotective properties, particularly when treating neurodegeneration. Cellular studies have proven that kaempferol has anti-inflammatory properties. Kaempferol dramatically reduces the expression levels of COX-2, (iNOS), and nuclear factor kappa-B (NF-κB) in the PC12 cell model treated with 6-hydroxydopamine (6-OHDA), while increasing cell viability [90, 91]. Additionally, by decreasing the activity of β-secretase, kaempferol can prevent the production of beta-amyloid (Aβ), encourage the formation of non-toxic oligomers by binding to Aβ42 oligomers, prevent the conformational shift of Aβ plaques, and finally enhance the death of nerve cells caused by Aβ [90, 92]. In a study, a Parkinson's model was conceived with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a substance used as a neurotoxin, and kaempferol was administered to the subjects in this group at different doses, and kaempferol was observed. It has been observed that it improves motor coordination, increases striatal dopamine and metabolite levels, increases levels of endogenous antioxidant systems; glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD), and reduces malondialdehyde (MDA) levels [90, 93].

Anti-Glioblastoma Activity

In a specific investigation, researchers noted that treating the human glioblastoma multiforme (GBM8401) cell line with 12-otetradecanoylfoly-13-acetate at different concentrations, and resulted in elevated association of matrix metalloprotease 9 (MMP9) activity [94]. The study also investigated the impact of kaempferol in vitro by assessing cell migration and invasion through the activation of the extracellular-receptor kinases (ERK) and NF-kB pathways. Upon exposure to kaempferol, a notable reduction in protein kinase α (PKCα) protein levels were observed, along with the inhibition of the ERK and NF-kB pathways. This resulted in decreased MMP9 expression, leading to a subsequent reduction in both cell invasion and migration [94].

Osteoprotective Activity

While it is well known that calcium, vitamin D, and micronutrients are necessary for healthy bones, other substances, such the copious polyphenols found in fruits and vegetables, may also have a protective effect on bones [95]. In a study conducted with kaempferol supplementation in neonatal rats, it showed protective effects on bone in bone fracture models created in addition to glucocorticoid-induced and ovariectomy-induced osteoporotic models and it showed an osteoprotective effect [96].

2.3. Hesperidin

Hesperidin (3,5,7-trihydroxyflavanone 7-rhamnoglucoside, hesperetin-7-*O*-rutino- side) a secondary metabolite found in plants. It is a natural occurring flavanone glycoside present in citrus fruits such as, orange (*Citrus sinensis*), lemon (*Citrus limon*), grapefruit (*Citrus paradise*), lime (*Citrus aurantifolia*) and tangerine (*Citrus reticulata*). Hesperidin, unlike many other flavonoids, has high lipophilicity and is therefore easily absorbed in the small intestine by passive and facilitated diffusion or active transport. Hesperidin was once referred to as "vitamin P" along with other bioflavonoids that were comparable [98]. Hesperetin was quickly absorbed, according to pharmacokinetic studies, and its plasma concentrations were seen 20 minutes after dosage and peaked in 4.0. A mean maximum drug concentration (Cmax) of 825.78±410.63 ng/ml (2731.8±1358.4 nmol/l) was observed for hesperetin. Hesperetin was discovered to have an elimination half-life of 3.05 ± 0.91 hours. The relative cumulative urine excretion mean values for hesperetin were determined to be 3.26±0.44, expressed as a percentage of the administered dose [97, 98].

Antiallergic Activity

In one study, although hesperidin didn't inhibit histamine release from reactive cells induced by IgE, although its metabolite hesperidin potently inhibited histamine release from reactive cells induced by IgE and passive cutaneous anaphylaxis reaction [99]. It has been demonstrated that hesperetin has an inhibitory action similar to that of the antiallergic medication azelastine, and that it can effectively suppress the formation of prostaglandin E2 in lipopolysaccharide-stimulated RAW 264.7 cells [100]. According to a different study, hesperidin efficiently cures asthma by inhibiting the GATA-3 transcription factor, which in turn reduces the synthesis of ovalbumin-specific IgE, eotaxin, Th2 cytokines and eosinophil infiltration [100].

Anticancer Activity

According to reports, hesperidin inhibits the growth of a number of cancer cells in vitro, including those from gliomas, prostate, pancreas, ovarian, skin, liver, colon, lung, cervical, and breast cancers [102]. By causing apoptosis and cell cycle arrest, hesperidin suppresses the proliferation of cancer cells by interacting with a wide range of known cellular targets. It has a variety of roles in the ability to prevent cancer, including apoptosis and autophagic induction as well as prevention of cancer cell invasion, proliferation, metastasis, migration, and angiogenesis [101]. It against human malignant pleural mesothelioma cell caused a time and dose dependent high inhibitory effect on cell proliferation, nuclear condensation, as well as amplification of the Sub-G1 population. Additionally, hesperidin at different doses reduced Sp1 proteins (poly(ADP-ribose)) polymerase activator protein, which process of differentiation, apoptosis and cell growth effects mRNA expression [102].

Antithrombotic Activity

Arachidonic acid and collagen induced platelet aggregation, phospholipase C (PLC)-γ2 phosphorylation and cyclooxygenase 1 (COX-1) inhibition mechanisms, hesperidin metabolite, hesperidin, strongly inhibited platelet aggregation [103]. When compared to control mice, g-hesperidin dramatically decreased atherogenesis and greatly inhibited thrombogenesis in vivo [104]. It has been highlighted that by raising the bioavailability of NO, hesperidin may help have positive impacts on thrombosis processes and hypertension [105].

Neuroprotective Activity

It has been demonstrated that hesperidin is even more effective than L-DOPA (L-3,4-dihydroxyphenylalanine), the current medication [106]. Hesperidin and L-DOPA coadministration improved the drug's bioavailability in the rat model and prevented the striatal and midbrain's 6-hydroxydopamine (6-OHDA)-mediated cytoplasmic vacuolation from degenerating [106]. A study showed that hesperidin activates mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. The results confirm other findings showing that a similar flavonoid, hesperidin, affects the phosphorylation of extracellular signal-related kinases ½ (ERK 1/2), a member of the MAPK pathway. On the other hand, while these experimental studies show differences between the antioxidant and neuroprotection properties of hesperidin, the data suggest that ERK1/2 activation may be closely related to the antioxidant properties of hesperidin [107].

Osteoprotective Activity

Hesperidin has been shown in numerous studies to have the capacity to reduce bone loss and encourage the repair of bone defects. Remarkably, researchers discovered proof of the significant preventive effect of hesperidin against bone loss in ovariectomy-prone rodents [108]. It has been emphasized that hesperidin has an anti-osteoporosis effect by regulating estrogen signaling pathways [108]. Hesperetin-7-glucoside was discovered to be highly concentrated in plasma during an in vivo investigation aimed at examining the association between the ability of hesperidin and its aglycone to protect bone tissue and plasma bioavailability. Because hesperetin-7-glucoside reached plasma levels twice as high as hesperidin, it may have a higher plasma availability than hesperidin, which may explain why it shown a better osteoprotective effect [95].

2.4. Apigenin

Apigenin chemically known as 4′, 5, 7,-trihydroxyflavone, a naturally occurring plant flavone, is abundantly present in common fruits such as oranges and vegetables such as parsley, celery, onions, plant-based beverages such as tea, wine and beer [3]. It has been found that apigenin oral bioavailability is quite low in both humans and rats. When rats were given a single dose of apigenin, its oral bioavailability was found to be extremely low, at 7.06% [109, 110].

Anticancer Activity

The method applied in a study investigating the chemoprevent potential of apigenin in 7,12-dimethylbenzanthracene induced hamster buccal sac carcinogenesis was as follows [111]. Apigenin was administered meanwhile about a dose of 2.5 mg/kg body weight in a day, starting one week before exposure to the carcinogen until the end of the study. The results acquired that apigenin prevented tumor formation compared to the control sample [111].

Antihyperlipidemic Activity

In an experimental in vivo investigation, apigenin drastically improved blood fat levels in mice fed a high-fat diet. It lowered the weight of the test tubes while also lowering total cholesterol, triglycerides, and low-density lipoprotein cholesterol [112]. Data suggest that apigenin may help prevent and treat atherosclerosis and reduce the incidence of cardiovascular and cerebrovascular diseases [112].

Cognitive Activity

In the study investigating the effects of apigenin on double transgenic structures in the amyloid precursor protein in Alzheimer's disease, the neuroprotective effects were tested with 40 mg/kg apigenin in mice for three months. Improvements in memory and learning deficiencies have been noted [113]. Apigenin has been shown to cause restoration of the signal-regulated kinase/cAMP response element binding protein /brain-derived neurotrophic factor (ERK/CREB/BDNF) pathway, which is involved in memory and is usually affected in Alzheimer's disease [113].

2.5. Naringin

Naringin (4,5,7-trihydroxy flavonone-7-rhamnoglucoside) a secondary metabolite found in plants, is a flavanone found primarily in citrus species such as, (*Rutaceae family*) such as tangerine (*Citrus reticulata*), lemon (*Citrus limon*), grapefruit (*Citrus paradise*), lime (*Citrus aurantifolia*) and orange (*Citrus sinensis*). Pharmaceutical and nutraceutical research is interested in naringin because has strong biological effects [114]. Naringin as a compound absorbs very little. Nonetheless, naringin taken orally is consistently accessible as its aglycone, naringenin. At a dose of 50 mg, which is equivalent to aglycone, the oral bioavailability of naringin is approximately 5-9%, while its Cmax value is approximately 5.5 hours. Naringenin has a 15% oral bioavailability and a poor solubility, meaning that very small amounts are absorbed in the human gastrointestinal tract [115].

Anticancer Activity

Naringin can depress focal adhesion kinase enzyme in glioblastomas. Moreover, experiments have evidenced several important effects of naringin in glioblastoma cells through down-regulation of the activity of matrix metalloproteinase enzymes [116]. At least 20% of instances of cancer have a history of chronic inflammation. Tumor growth blood supply is improved by a process stimulated by transforming growth factors, such as mitogen activated protein kinase (VEGF) and cytokines, or inflammatory mediators, such as tumor necrosis factor-α (TNF), interferon 1α/ β (IL-1α/β) interferon gamma (IFN-γ), and IL-6 [115, 117]. It has been demonstrated that naringin and naringenin inhibit the growth, spread, and metastasis of cancer by influencing a number of dysregulated signaling pathways linked to inflammation, proliferation, apoptosis, autophagy, angiogenesis, invasion, and metastasis [115, 117].

Antihyperlipidemic Activity

Naringin shows anti-adipogenic and anti-atherogenic effects, which reduce the ester reactions of cholesterol and the bioavailability of lipids-incorporated protein through inhibition of hepatic the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase [118, 119]. Additionally, some studies have proven the potential of naringin to have antiatherogenic effects in hypercholesterolemic rabbits [120].

Antidiabetic Activity

Some studies have shown that naringin or its aglycone naringenin has antidiabetic effects. The effects of naringin in type 2 diabetes mellitus is corporate with the blockade of hepatically gluconeogenesis. Additionally, naringenin has been experimentally shown to increase glucose uptake in skeletal muscles [121]. The in vivo hepatoprotective effects of naringin are explained by the regulation of lipid metabolism in liver [122]. Furthermore, naringenin dramatically boosted the phosphorylation and activation of 5′ AMP-activated protein kinase (AMPK), and the stimulation of glucose absorption by AMPK was eliminated by AMPK silencing with small interfering RNA [123].

Antiasthma Activity

By balancing mucosal production and reducing bronchial inflammation, naringin indirectly reduces reactive oxygen species production, minimizes nuclear factor-kappa B activity, inflammatory mediator secretions, and shows antiasthmatic activity [124]. When compared to the control group, naringin

administration progressively dramatically decreased ovalbumin-induced cough and airway hyper-responsiveness [125]. Leukocytes prevented interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) from increasing in bronchoalveolar lavage fluid. Furthermore, it was noted that naringin administration markedly improved the degenerative alterations in the lung tissues [126].

2.6. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxy flavone) a secondary metabolite, is a flavone naturally occurring as a glycosylated form, and is present in different wide range of dietary sources, including green pepper, broccoli, dandelion, artichoke, perilla, chamomile tea, carrots, olive oil, oregano and rosemary [126, 127]. At a dose of 50 mg/kg, luteolin's low bioavailability of 4.10% is most likely caused by the large first pass effect. The maximal luteolin concentration for intravenous injection was 23.4 µg/mL at 0 hours [127].

Antidiabetic Activity

Potentially beneficial in several ways, luteolin has been shown to mediate a number of actions that together support its exceptional antidiabetic properties. In a study luteolin inhibited alpha-glucoside and was stronger in inhibitory potency than acarbose [128]. Luteolin also has strong inhibitor effects alpha amylase, although less potently than acarbose [128]. An enzyme called K+ transport in the phloem tissues (AKT2), or RAC-beta serine/threonine-protein kinase, is encoded by the AKT2 gene in humans. It has been observed that luteolin increases insulin sensitivity by affecting AKT2 kinase. Additionally, the translocation of the glucose transporter 4 (GLUT4) glucose transporter to the cell surface mediates the influence of AKT2 on the control of glucose absorption [129].

Neuroprotective Activity

It has been demonstrated that luteolin both in vitro and in vivo attenuates microglial activation and mediates brain-derived neurotrophic factor (BDNF)-like behaviour. Luteolin treatment in a triple transgenic mouse model was found to improve learning, reduce memory deficits, and reduce the level of astrocyte hyperactivation and neuronal inflammation [130]. Furthermore, luteolin only partially exhibited affinity for the GABAA receptor's benzodiazepine binding site, indicating that luteolin's anxiolytic effects are mediated by an as-yet-undiscovered mechanism [131]. According to a recent study, luteolin administration can reduce the oxidative stress, cytotoxicity, and caspase-3 activation caused by 6-OHDA in PC12 cells [131].

Antiatherosclerosis activity

Luteolin-7-glucoside tended to reduce hepatic expression of sterol regulatory element binding protein-1 (SREBP-1) without affecting fatty acid synthase protein levels [132]. Although SREBP-2 and LDL receptor mRNA levels were unchanged, expression of HMG CoA reductase was significantly suppressed by Luteolin-7-glucoside [132]. Luteolin-7-glucoside also inhibited the in vitro activity of this enzyme in a dose-dependent manner, but only at high and physiologically non-significant concentrations. One study discovered that luteolin remarkably reduced AS in ApoE−/− mice fed a spheric fat diet by reducing inflammation. Luteolin also reduced oxidized LDL induced inflammation [133].

Osteo-Chondroprotective Activity

One study found that luteolin effectively reduced the statement of Jun N-terminal kinase, as well as the levels of NO, TNF-α, and IL-6 in osteoarticular cartilage cells. Luteolin also successfully suppressed the growth of osteoarticular cartilage cells. The medicinal effect of luteolin on osteoarthritis has been demonstrated experiments [134].

2.7. Genistein

Genistein (7-(β-D-Glucopyranosyloxy)-4′,5-dihydroxyisoflavone), an isoflavone, occurs in several medicinal plants including *Erythrina indica* (Fabaceae), *Ficus chlamydocarpa* (Moraceae) and, *Cajanus cajan* (Fabaceae), *Genista tinctoria* L. (Fabaceae) and *Pongamia pinnata* (Fabaceae) [135-138]. Following both intravenous and oral administration of 20 mg/kg genistein to mice, it has been shown that more than 80% of genistein is converted to sulfates and glucuronides and, the absolute bioavailability of the genistein aglycone is 23.4% [139].

Adipocyte Differentiation and Apoptosis

It has been emphasized in different studies that genistein has antiobesity properties. Genistein has been demonstrated to activate ROS generation as well as induction of adipocyte apoptosis by activation of 5′-adenosine monophosphate activated protein kinase (AMPK) and inhibition of adipocyte differentiation, as an energy sensor. AMPK is activated by various stimuli such as ROS. Moreover, when AMPK is activated, it inhibits the anabolic pathways and activates the catabolic pathway, and therefore activated AMPK affects cell proliferation and inhibition of apoptosis [140].

Apolipoprotein Metabolism

Phytoestrogens from soy have been shown to be antiatherogenic by multiple mechanisms [141]. Animal and human studies examining their effects on plasma lipid and lipoprotein levels have been conducted to illustrate the useful effects of soy isoflavones. Soy isoflavones have been shown to have an effect on apoB metabolism due to decreased hepatic apoB production. ApoB production decreases significantly in a genistein dose-dependent manner, while apoAI release remains unchanged [141].

Humoral Immunity

It has been emphasized that genistein has positive effects on the immune system. Experimental research with genistein has been shown to reduce the delayed-type hypersensitivity response by reducing cellular immunity. This is similar to the reported decrease in humoral immunity; This suggests that genistein has suppressive effects on the cell-mediated and humoral components of the adaptive immune system. Genistein has also been shown to reduce thymus weight, but its effects on immune function have not been studied [142].

Cardioprotective Activity

Some studies have observed that genistein has a cardioprotective effect. Genistein binds to estrogen receptors and may exert estrogenic effects in some tissues, such as heart tissue, because its structure is similar to estradiol and diethylbestrol [143]. According to one study's findings, genistein may protect against cardiovascular dysfunction by enhancing glucose homeostasis, lowering oxidative stress, and lessening the endothelial dysfunction brought on by diabetes in rats [144].

2.8. Myricetin

Myricetin (3, 5, 7, 3′, 4′, 5′-hexahydroxyflavonol) is a flavonoid consisting of yellow crystals isolated from the bark of the *Myrica rubra* (Lour.) tree and is a polyhydroxyflavonol compound that is soluble in polar solvents such as ethanol [145]. The results demonstrated that the bioavailability of myricetin by oral route was small due to the low absorption (9.62 and 9.74% at oral doses of 50 and 100 mg/kg, respectively) [136]. Modern pharmacological studies have shown that myricetin has various biological activities, such as anti-inflammatory [146], antitumor [147], antibacterial [148], antiviral [149] and anti-obesity [150] effects and provides cardiovascular protection [151]. It has also been shown to protect against neurological damage and possible injury to the liver [152]. Thanks to its antioxidant and cholesterol-lowering effects, myricetin-containing food supplements are developed and marketed in European countries, but no new myricetin-containing drug has been approved on the market yet [145].

Antidiabetic Activity

In experimental research, it was emphasized that the expression of insulin, hemoglobin and some signaling molecules was significantly reduced in diabetic nephrotoxic rats induced by STZ. In the same study, myricetin showed positive effects such as decreasing the expression of these signaling molecules and improving carbohydrate metabolism after treatment [153].

Antimicrobial Activity

One study showed that myricetin has potential as an antivirulence candidate to control the *S. aureus* pathogen [154]. Hemolysin has been shown to be an important viral factor of *Streptococcus suis* type 2 infection [155]. Myricetin has been shown to alleviate inflammatory infection caused by *Streptococcus suis* virulence factor by inhibiting hemolysin and p38 fragments [156].

Immunomodulatory

Myricetin has been suggested to have an immunomodulatory effect in some studies. Myricetin inhibits the activity of some immune cells such as T lymphocytes and dendritic cells. Myricetin has been shown to inhibit mouse T lymphocyte activation and inhibit IL-2, IL-4, and interleukin-17 (IL-17) synthesis [157]. However, the fact that dendritic cells or bone marrow-derived macrophages in the same environment attenuated the positive effect of myricetin on inhibited T cell activation demonstrates the importance of the interaction between immune cells [157].

Antiinflammation Activity

Receptor activator of NF-κB ligand [158] and receptor activator of the NF-κB, which play a role in the bone loss mechanism caused by inflammation, are important transcription factors in the formation of osteoclasts involved in bone resorption. Myricetin has been shown to significantly inhibit receptor activator of NF-κB ligand/ receptor activator of NF-κB (RANKL/RANK) expression in bone marrow macrophages. This revealed that myricetin may have a potential therapeutic effect against inflammatory osteolysis [159].

Antiaddictive Activity

It has been emphasized that myricetin reduces the addiction potential of addictive substances through various mechanisms [160]. Results of a study examining the effects of myricetin on ethanol addiction showed that myricetin reduces the rewarding effect of ethanol [160].

2.9. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is the parent molecule of the viniferins, a family of phytoalexin polymers whose trans form is more active, and is a polyphenol compound produced by plants in response to fungal infection [161]. Resveratrol, a member of the stilbene family, is a compound consisting of 2 aromatic rings joined by a methylene bridge. *Polygonum cuspidatum* is frequently used in Chinese and Japanese medicine and is one of the richest sources of resveratrol. Resveratrol has also been detected in the content of trees such as Eucalyptus and spruce. It is also found in peanuts, peanut butter, grapes and wine and is generally obtained through these foods in the human diet [161]. About 75% of resveratrol taken orally by humans is absorbed through transepithelial diffusion, according to current theories. Oral bioavailability is much less than 1% due to extensive processing in the liver and intestine [162].

Anticancer Activity

In a study using female rats, resveratrol was shown to reduce the number of tumors induced and the incidence of mammary tumors by suppressing NF-κB expression [163]. It has been observed that piceatannol the natural resveratrol analogue prevents cancer cells from proliferating by stopping the cell cycle and apoptosis [164]. NF-κB suppression is among the possible molecular mechanisms associated with anti-proliferative effects in cancer cells [165]. NF-κB is a transcription factor and regulates genes involved in tumor and inflammation formation. It is thought that resveratrol may show antitumoral activity through NF-κB inhibition. Resveratrol has been observed to inhibit NF-κB activation in some cell lines [166].

Antihypertensive Activity

According to the findings of one trial, blood pressure may be brought down to normal levels with just resveratrol added to regular hypertension therapy, negating the need for additional antihypertensive drugs [167]. Resveratrol relaxed potassium chloride (KCl)-vasoconstricted endothelial intact rat aortic rings through the release of NO; however, it has no vasorelaxing effect on endothelium-independent loops [168]. Resveratrol enhances the function of perivascular adipose tissue, regulates immune cell activity, and prevents immune cell penetration into the arterial wall. The preventive effects of resveratrol on blood pressure and vascular function in vivo are facilitated by each of these pathways. The primary molecules mediating the vascular effects of resveratrol are sirtuin 1, AMP-activated protein kinase, and estrogen receptors [169].

Antiinflammatory Activity

Resveratrol inhibited the expression of COX-2, an enzyme involved in the inflammation mechanism, in an in vitro and in vivo model [170]. Furthermore, by reducing inflammatory cytokines such TNF-α, interleukin-1β (IL-1β), and IL-6, resveratrol can alleviate STZ-mediated diabetic neuropathy symptoms in mice [171]. Furthermore, resveratrol preconditioning has been demonstrated to modify the hippocampal

inflammatory response following global cerebral ischemia in rats. Furthermore, resveratrol has been shown to be able to prevent neurons from being damaged by inflammation, decrease airway inflammation brought on by asthma and airway remodeling, and decrease neuro-inflammation mediated by microglia [171].

Antithrombotic Activity

Resveratrol has been shown to inhibit human platelet aggregation in vitro and in vivo models. Additionally, rabbits fed a high-cholesterol diet and treated with resveratrol were shown to have reduced platelet aggregation rates [172]. The concentration-dependent release of ADP and ATP from platelets was reduced by resveratrol in response to thrombin. Resveratrol also prevented neutrophil migration toward thrombin-induced platelet supernatants, which in turn prevented the increased respiratory burst of neutrophils in response to thrombin-activated platelets [173]. Resveratrol restored the reduced CD39/ATPdase activity in human umbilical vein endothelial cells in response to thrombin, as demonstrated by adenosine monophosphate and adenosine measured in endothelial culture supernatants. Resveratrol inhibited the thrombin-induced MAP, JNK, and focal adhesion kinase activities in endothelial cells [173].

Antiaddictive Activity

In some studies, resveratrol alleviated addiction to some addictive substances [8, 83, 174]. Resveratrol boosted GABAA and GABAB-mediated inhibitory postsynaptic currents in VTA dopamine neurons. Protein kinase A-dependent increases in presynaptic GABA release made this action possible [174]. Resveratrol treatment simultaneously prevented heroin-conditioned location preference from forming, while resveratrol promoted heroin-induced reinstatement [83]. The animals' withdrawal ratings were significantly greater than the control group's after receiving resveratrol. Resveratrol was shown in another study to lessen nicotine addiction in mice [8]. In another in vivo study, resveratrol reduced the place preference of ethanol [175].

Effect of Resveratrol on Psychostimulant Exposure

Dopamine overflow and hyperactivity brought on by methamphetamine are reduced by repeated resveratrol therapy. All things considered, these findings imply that resveratrol may have metaplastic and preventive properties that lessen the effects of methamphetamine on the release of dopamine and an increase in locomotor activity [176]. In every region of the brain (hippocampus, frontal cortex and striatum) examined, resveratrol stopped and reversed the oxidative and nitrosative damage caused by m-amphetamine (m-AMPH) to proteins and lipids [177]. The depressive-like behaviour of rats treated with 3,4-methylenedioxymethamphetamine (MDMA, designated as "Ecstasy" if illicitly marketed in tablet form) was sufficiently ameliorated by resveratrol [178]. Resveratrol did not affect cocaine-induced conditioning behaviours but did reduce anxiety-like behaviours [179].

2.10. Oleuropein

Oleuropein belongs to a specific group of coumarin-like compounds, is the main bioactive compound of *Olea europaea*, widely known as the olive tree, and is present in high amounts in unprocessed olive leaves and fruit [180]. Olive oil, olives, and olive leaves contain many polyphenols, including oleuropein [180]. According to a recent human trial, oral oleuropein ingestion is resistant to the stomach's acidic conditions and is rapidly absorbed (55-60%) in the intestinal tract [181, 182]. It reaches a maximum plasma concentration (23-30 min, depending on the pharmaceutical form) earlier than conjugated hydroxytyrosol metabolites, glucuronidated and sulfated, which comprised 64-93 min and 96-99% of the oleuropein phenolic metabolites found in plasma and urine after intake [181, 182].

Anticancer Activity

There are various mechanisms of oleuropein's anticancer activities. downregulate NF-kB and cyclin D1; In addition to activating p21, it inhibits breast cancer cell proliferation by delaying the cell cycle in S phase. Oleuropein also has cytotoxic effects on breast cancer cells [183]. Oleuropein, decreases the viability of MCF-7 cells and reduces the number of breast cancer cells by inhibiting the rate of cell proliferation and inducing cell apoptosis [183]. Consumption of olive oil was found to be negatively correlated with cancer prevalence in a meta-analysis of 23,340 controls and 13,800 cancer patients. Those who consumed the most olive oil were also less likely to get any type of cancer than those who consumed the least [184].

Antidiabetic Activity

Preclinical research suggests that oleuropein enhances insulin sensitivity, promotes glucose transport, and aids in pancreatic β-cell insulin secretion, all of which lend credence to the idea that managing hyperglycaemia may have advantages [185]. Oleuropein regulates the modulation of insulin secretion, maintains islet morphology at normal standards, regulates hepatic AMP-activated protein kinase activation and inhibits glucose tolerance. It shows antidiabetic activity with all these mechanisms. At the same time, oleuropein prevents diabetes-related complications such as neuropathy, nephropathy, retinopathy, and delayed wound healing [186].

Antioxidant Activity

Oleuropein, like other flavonoids, has been shown to have a strong antioxidant effect in many in vitro and in vivo studies. The positive results of studies on oleuropein in the literature have been interpreted in terms of the antioxidant effect of oleuropein [187]. Olive-derived phenolic compounds, including oleuropein, can reduce the production of monocytic inflammatory mediators and reduce IL-1β production in human whole blood cultures stimulated with lipopolysaccharide (LPS)-induced monocytes [188].

Neuroprotective Activity

In a study conducted on rats, it was found that intraperitoneal oleuropein administration once a day for 6 months increased the neuron density in the substantia nigra region of the rats' brain, thus preventing dopaminergic neuron loss. These findings provide evidence for an antiparkinson effect [189]. The results of a study investigating its effect on Alzheimer's disease showed that oleuropein prevented the formation and accumulation of amyloid plaques. Additionally, oleuropein may be effective in protecting the rat spinal cord from secondary injuries [190].

3. CONCLUSION

There are various subtypes of flavonoids, which are secondary metabolites with a phenolic molecular structure that are mainly synthesized and stored in plants. Nowadays, a lot of scientific research and animal experiments are being carried out on natural compounds for the treatment and prevention of diseases, and in addition to the presence of flavonoids in different types and rates in almost every plant in nature, flavonoids are in the first place among the natural compounds where research is carried out because the risk of possible side effects of these flavonoids is predicted to be minimal. It was observed in the studies we reviewed while creating this review that each flavonoid type showed various activities by affecting different mechanisms at different doses. Even though they have different activities, the fact that most of the flavonoids have anti-inflammatory and anti-cancer effects is an issue that should be taken into consideration, especially in health problems such as inflammation, which forms the basis of many chronic diseases and cancer, which is diagnosed in millions of people every year and has a high mortality rate. The findings of the research, including the summarized effects of flavonoids discussed in the review, are presented in Figure 1.

As a result, we require regulations about herbal products overseeing every stage of the medicine development process. Ensuring the effectiveness and safety of these goods will boost their acceptance globally and enable them to serve a larger number of people responsibly on a global scale. In this regard, nearly every nation has created a plan of action for regulating herbal products, which are also known as complementary, alternative, traditional, natural health products, and health supplements. Although the effects we have mentioned in our review excite the scientific community, it is another issue that should be taken into consideration that any of the flavonoid types sold in the forms used as nutritional supplements have not yet been authorized by the EMA and FDA for use as a medicine, and undoubtedly, it is important to closely follow the developments in this field, as well as mechanisms and indirect effects. Based on a review of the preclinical and clinical study results published in the literature, it seems that further thorough investigation of flavonoids is required.

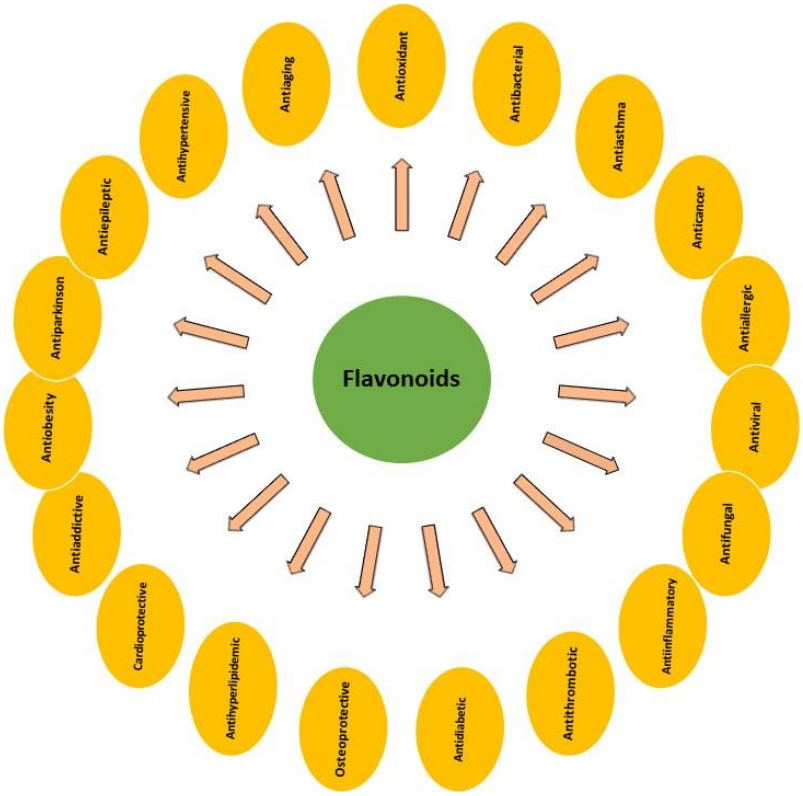

Figure 1. Summary of a variety of therapeutic effects of flavonoids.

4. MATERIALS AND METHODS

The search for articles involved querying pertinent databases like PubMed, Web of Science, ScienceDirect, Scopus, ResearchGate and Google Scholar using terms such as flavonoids, pharmacological properties, medicinal properties, biological properties, and therapeutic potential. Subsequently, abstracts were scrutinized, and articles were pre-selected. A compilation was then created by extracting relevant data from the chosen articles and organizing bibliographies.

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