# Promising Anticancer and Neuroprotective Compounds

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Flavonoids derived from citrus plants are favored by phytomedicinal researchers due to their wide range of biological activities, and relevant studies have been sustained (since the first paper published in 1955). The modern pharmacological effects of citrus flavonoids are primarily focused on their anticancer activities (such as breast cancer, gastric cancer, lung cancer, and liver cancer), neuroprotective effects (such as anti-Alzheimer's disease, Parkinson's disease), and metabolic diseases.

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## 1. Introduction

Citrus genome studies have shown that citrus plants originated in the Himalayas about 6 to 8 million years ago, and the majority of species are descendants of wild broad-hued oranges (*C. reticulata*), grapefruit (*C. maxima*), and citron (*C. medica*) [1]. As time went on, people found citrus fruits were not only beautiful and edible, but also fairly tasty. In a bid to improve the taste of citrus fruit, people have developed several citrus cultivation varieties, such as *C. hystrix*, *C. japonica*, C. *mitis*, *C. aurantifolia*, *C. paradisi*, *C. junos*, *C. limetta*, *C. maximas*, *C. aurantium*, *C. limon*, and *C. sinensis*. In recent years, citrus has become one of the most productive fruits in the world for economic cultivation [2]. Since ancient times in China, Egypt, and India, citrus fruit was not only used as a tasty fruit but also as a medicine. The dried peel of *Citrus reticulata Blanco* was used as an ingredient in tea and in Chinese patent medicines, which was beneficial to promote health by regulating "qi". Modern botanists are also interested in the medicinal value of citrus. Botanical medicine researchers have found that citrus fruits are rich in a variety of beneficial components, such as fibers [3], phenolic acids [4], and flavonoids [5]. Notably, citrus flavonoids, recognized as a class of substances with important nutritional value, are comprehensively investigated. Citrus flavonoids are usually classified according to their chemical structures, such as flavanone aglycones, flavone aglycones, flavanonols, flavanone-O-glucoside, polymethoxyflavonoids, other flavonoids, flavone-O-glucoside, and flavone-C-glucoside [6]. Studies have shown that citrus flavonoids possess a variety of pharmacological properties including antioxidant and and anti-inflammatory [7], among others. In view of the complex chemical composition and diverse pharmacological activities of citrus flavonoids,

The scientometric methods were first applied to obtain a holistic and comprehensive view based on the published studies on citrus flavonoids, which is an application of mathematical and statistical methods to perform retrospective reviews, calculate correlations in publication data, elucidate current research progress, and predict research directions [8]. Scientometric methods have played an important role in bone disease research [9], hotspots

of exercise for intervening diabetes [10], COVID-19 research [11], and exosome studies [12]. The numerous published articles were summarized through the scientometric methods for providing rich reference information for researchers in need based on keywords, highlights, and important research-related information.

## 2. Chemical Structures and Sources of Citrus Flavonoids

These compounds could be classified by structural type as flavanone aglycones, flavone aglycones, flavanonols, flavanone-O-glucoside, polymethoxyflavonoids, flavone-O-glucoside, flavone-C-glucoside, and other flavonoids. Flavanone aglycones constitute the parent nucleus of flavanone glycosides. They comprise a class of compounds derived from the parent nucleus of 2-phenyl dihydrochromone. 2-Phenyl dihydrochromone is a flavanone which is also known as dihydroflavone. The representative compounds of flavanone aglycones are hesperidin, naringin, dihydroquercetin, and isosakurin, respectively. Flavone aglycone refers to the parent nucleus of flavonoid aglycone, and its main components are acacia, 8-hydroxyapigenin, luteolin, kakaol, five-hydroxyl flavone, apigenin, and geraniol. Flavanonol compounds are the double bonds of flavonoids at the C2 and C3 positions hydrogenated to form flavanonols, and those with hydroxyl groups at the C3 position are generally called flavanonols, and there are three compounds in citrus flavonoids of this type. Flavanone-O-glucoside refers to the O-glycoside formed by the connection between the sugar substituents and flavanone carbon skeleton in the form of hydrogen oxidation. The typical compounds are hesperidin and naringin. Polymethoxyflavonoids are a kind of constituent exclusive to citrus plants. They contain multiple methoxyls which possess low polarities, flat structures, and strong biological activity. The representative components of polymethoxyflavonoids are tangeretin and nobiletin. Other flavonoids are *Myrica rubra* flavone and catechol. Flavone glycosides are the most abundant substances among Citrus flavonoids. According to the different linking modes between aglycones and sugar molecules, they could be divided into oxyside and carboside. The main components of the flavone glycoside type are vitzene-2, diosmin, and rutin.

*C. hystrix* only contains yukovanol; *C. japonica* only contains flavone-O-glucoside and flavone-C-glucoside; *C. medica* and *C. mitis* contain flavanone-O-glucoside and flavone glycosides; *C. aurantifolia* contains flavanone-O-glucoside, flavone glycosides, and polymethoxyflavonoids; *C. sinensis*, *C. limon*, *C. maximas*, and *C. paradisi* include all structure types; *C. junos* contains all structural types except flavanone aglycones; *C. reticulata* includes all structural types and contains the most flavone glycosides among this type of compound; *C. limetta* contains only flavanone aglycones and flavone glycosides. The abovementioned results indicate that citrus plants tend to enrich flavonoids in fruits rather than roots. Naringin, narirutin, hesperidin, and rutin are the most widely distributed compounds found in citrus plants.

## 3. Citrus Flavonoids and Cancers

According to the search results, citrus flavonoids have an obvious inhibitory effect against various cancers [13], the most studied of which is breast cancer; other cancers include rectal cancer, gastric cancer, liver cancer, lung cancer, prostate cancer, uterine cancer, ovarian cancer, epidermal cancer. Citrus flavonoids play a role in cancer therapy by inhibiting cancer cell proliferation [14], migration, angiogenesis, and inducing apoptosis [15].

It should be noted here that CYP3A4, as the most important oxidative enzyme, plays a metabolic role for most drugs [16], and the role of CYP3A4 on drug metabolism in cancer treatment has attracted more attention [17]. While grapefruit inhibits the expression of CYP3A4 [18], some studies have shown that *Fructus aurantia* and tangeretin induce CYP3A4 [19][20]. It is clear that some citrus flavonoids have a regulatory effect on CYP3A4.

## 3.1. Breast Cancer

Nobiletin, a natural flavonoid isolated from citrus peel, has anti-angiogenic effects [21]. Nobiletin was shown to inhibit MCF7 breast cancer cells by inducing its metabolism by up-regulating cytochrome P450 family 1 subfamily A member 1 (CYP1A1) and cytochrome P450 family 1 subfamily B member 1 (CYP1B1) [22]. Furthermore, nobiletin was shown to induce apoptotic cell death by reducing B-cell leukemia/lymphoma 2 xL (Bcl-xL) expression without affecting Bcl-2-associated x protein (Bax) levels and inhibit the activities of protein kinase B (AKT) and downstream mammalian target of rapamycin (mTOR) [23]. These targets are located in the apoptosis pathway, suggesting that the treatment of breast cancer by tangerine is mainly through inducing the apoptosis of cancer cells.

Naringenin was shown to inhibit the growth of metastases after surgery by modulating host immunity [24]. Naringin can inhibit cancer cell reproduction by inhibiting vascular endothelial factor release [25] and regulating the β-catenin pathway [26]. Hesperetin can induce apoptosis in breast cancer cells by triggering the accumulation of reactive oxygen species (ROS), activating the apoptosis signal-regulating kinase 1 (ASK1)/c-jun n-terminal kinase (JNK) pathway, and activating targets of caspase-9 and caspase-3. Hesperetin could increase the Bax: B-cell lymphoma-2 (Bcl-2) ratio in the intracellular environment [27]. The results indicate that hesperetin can inhibit cancer cells by inducing apoptosis. Polymethoxyflavonoids was shown to induce apoptosis in breast cancer cells [28] by activating a Ca ($2^+$)-dependent pro-apoptotic protease [29]. Retusin and Ayanin are potent inhibitors of breast cancer resistance protein (BCRP), showing only slightly lower potency than Ko143 [30].

According to the abovementioned results, it is known that the therapeutic mechanism of citrus flavonoids affecting breast cancer mainly depends on inducing apoptosis. In addition, citrus flavonoids inhibit cell proliferation pathways and slow breast cancer cell reproduction. Citrus flavonoids can also inhibit the metastasis of cancer cells. Overall, citrus flavonoids treat breast cancer in a variety of ways. In conclusion, the therapeutic effect of citrus flavonoids on breast cancer is clear. However, more comprehensive and in-depth studies are needed to make citrus flavonoids a suitable drug for the treatment of breast cancer.

## 3.2. Colorectal Cancer

Nobiletin showed a strong inhibitory effect on the growth of colon cancer cells [31] by inhibiting matrix metallopeptidase 7(MMP-7) gene expression [32]. Nobiletin inhibited cancer invasion and metastasis by increasing tissue the tissue inhibition of metalloproteinase-1 (TIMP-1) production [33]. In addition, it was found that nobiletin could down-regulate leptin levels [34]. High levels of leptin in mice are thought to be a key factor in promoting colorectal cancer. Tangerine was metabolized in the intestine to 3′-desmethylnorchol, 4′-desmethylnorchol and

3′,4′-didemethylnorchol. These metabolites were considered to be key compounds for the treatment of intestinal cancer [35].

Other citrus flavonoids such as tangeretin can induce cell cycle G1 arrest [36], and hesperidin can promote cancer cell apoptosis through Caspase-3 (CASP3) activation [37].

Naringenin and hesperetin play a critical role in inhibiting the formation of abnormal crypt foci [38] and reducing the activity of bacterial enzymes in colon cancer [39].

Nobiletin is an important component for the treatment of colon cancer. The mechanism of citrus flavonoids on colon cancer can induce apoptosis of cancer cells, inhibit the growth of cancer cells, and regulate intestinal enzymes. It is believed that the most important mechanism is still the induction of apoptosis. Additional research is needed to clarify the mechanism of citrus flavonoids in the treatment of colon cancer.

## 3.3. Gastric Cancer

Nobiletin could inhibit proliferation and induce apoptosis of gastric cancer cells [40]. Nobiletin could also slow the progression of cancer by extending the cell growth cycle [41]. The preliminary effect of naringenin in treating gastric cancer has been demonstrated [42] by inhibiting cell proliferation, migration, and invasion [43], and by causing ASK1-induced apoptosis mediated by ROS [44].

## 3.4. Lung Cancer

Citrus juice rich in beta-cryptoxanthin and hesperidin could inhibit lung tumor growth in mice [45]. Tangeretin suppresses interleukin-1 (IL-1) beta-induced cyclooxygenase (COX)-2 expression through inhibition of p38, mitogen-activated protein kinase (MAPK), JNK, and AKT activation in human lung carcinoma cells [46].

Nobiletin inhibited the epithelial–mesenchymal transition (EMT) of human non-small-cell lung cancer (NSCLC) cells by antagonizing the Transforming Growth Factor-β1 (TGF-β1)/SMAD Family Member 3 (Smad 3) signaling pathway, which could play a crucial role in inhibiting lung cancer metastasis [47].

5-Demethyltangeretin inhibited human non-small-cell lung cancer cell growth by inducing G2/M cell cycle arrest and apoptosis [48].

Flavanones and 2′-OH flavanones could inhibit the growth of A549 and Lewis lung cancer cells in vivo [49].

Hesperidin produced in vitro inhibitory effects NSCLC cells by modulating immune response-related pathways that affect apoptosis [50]. These results provide scientific support for the use of flavonoids extracted and isolated from citrus plants for the treatment of human lung cancer.

## 3.5. Liver Cancer

Naringenin induced cell cycle arrest and inhibited the growth of human hepatocellular carcinoma cells [51].

Hesperidin induced apoptosis of human hepatocellular carcinoma (HepG2) cells through mitochondrial and death receptor pathways [52].

### 3.6. Prostate Cancer

Naringenin induced apoptosis of prostate cancer cells by regulating Phosphatidylinositol 3-kinase (PI3K)/AKT and MAPK signaling pathways [53].

Naringenin could also promote deoxyribonucleic acid (DNA) repair and prevent carcinogenesis caused by oxidative damage [54].

### 3.7. Cervical Cancer

Hesperetin exhibited potential anticancer activity in vitro against human cervical cancer cell lines by reducing cell viability and inducing apoptosis [55].

Naringin also induced growth inhibition and apoptosis in human cervical cancer HeLa cell lines by activating the nuclear factor kappa-B (NF-κB)/Cyclooxygenase-2 (COX-2) -caspase-1 pathway [56].

### 3.8. Ovarian Cancer

Nobiletin inhibited ovarian cancer cells by secreting key angiogenic mediators such as AKT, HIF-1α, NF-κB, and vascular endothelial growth factor (VEGF) [57].

Tangeretin sensitized cisplatin-resistant human ovarian cancer cells by downregulating the PI3K/AKT signaling pathway [58].

### 3.9. Epidermal Carcinoma

Studies have shown that citrus flavonoids have anti-proliferative effects in inhibiting human squamous cell carcinoma in vitro [59], and the relevant studies proved that naringenin exerts anti-proliferative effects by inducing ROS generation and cell cycle arrest [60].

## 4. Neuroprotective Effects of Citrus Flavonoids

Studies have shown that fruits rich in flavonoids could protect the nervous system [61]. Citrus flavonoids inhibited Alzheimer's disease by reducing Presenilin 1 (PS1) phosphorylation-dependent amyloid production [62], and hesperidin, hesperetin, and neohesperidin exhibited neuroprotective effects [63]. Eriodictyol induced nuclear translocation of nuclear factor erythroid-2 related factor 2 (Nrf2), enhanced heme oxygenase 1 (HO-1) and

NAD(P)H quinone dehydrogenase 1 (NQO-1) expression, and increased intracellular glutathione levels against oxidative stress-induced cell death [64].

Nobiletin could stimulate protein kinase A (PKA)-mediated phosphorylation of glutamate receptor 1 (GluR1) receptors in the hippocampus to upregulate synaptic propagation through postsynaptic AMPA receptors [65]. It could also rescue cholinergic neurodegeneration and improve memory impairment in olfactory bulbectomy (OBX) mice by reducing the acetyl cholinesterase (AChE) staining and choline acetyltransferase (ChAT) expression density in the hippocampus [66]. Furthermore, nobiletin improved memory impairment and amyloid beta disease in a transgenic mouse model of Alzheimer's disease [67]. Additionally, triple transgenic (3xTg)-AD mice were orally administrated with 30 mg/kg nobiletin for 3 months, and the results showed that nobiletin reversed the impairment of short-term memory and recognition memory by reducing soluble amyloid beta 1–40 (Aβ1-40) and ROS levels in the mouse brains [68]. Oral administration of nobiletin reduced tau phosphorylation in the hippocampus of senescence-accelerated P8 (SAMP8) mice [69]. Nobiletin rescued 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's in a mouse model, reducing the dopamine level in the striatum and hippocampal CA1 region to prevent motor and cognitive dysfunction [70]. Nobiletin reversed learning disabilities associated with the n-methyl-d-aspartate receptor by enhancing cAMP/PKA/extracellular-regulated protein kinase (ERK) signaling in hippocampal neurons and PC12D cells [71]. These studies suggest that nobiletin has great potential in the study of neuropathic diseases.

Naringin protected nigrostriatal nigrothymic dopaminergic (DA) projections from 6-hydroxydopamine (6-OHDA)-induced neurotoxicity [72]. Naringin conferred an important capacity for DA neurons to produce the glial cell-derived neurotrophic factor (GDNF) [73]. In addition, naringin could improve cognitive performance and attenuate oxidative damage [74].

Naringenin exerted anti-inflammatory effects due to its interaction with the p38 signaling cascade and signal transducer and activator of the transcription 1 (STAT-1) transcription factor [75]. Naringenin can also inhibit the release of idiopathic oxide (NO) and pro-inflammatory cytokines in microglia [76].

Hesperidin protected against cognitive impairment by inhibiting the overexpression of inflammatory markers such as NF-κB, nitric oxide synthase (NOS), and cyclooxygenase-2 (COX-2) [77]. Furthermore, hesperidin significantly restored the deficits in non-cognitive nesting abilities and social interaction by attenuating amyloid beta deposition in the brain [78].

Hesperetin attenuated lipopolysaccharide (LPS)-induced neuroinflammation, apoptosis, and memory impairment by regulating the toll-like receptor 4 (TLR4)/NF-κB signaling pathway [79], also could reduce malondialdehyde (MDA) in the hippocampus and inhibit brain oxidative stress [80].

Tangeretin significantly protected striatum–substantia nigra integrity [81] by inhibiting LPS-induced phosphorylation of ERK, N-terminal kinase (JNK), and p38 [82]. Previous studies showed that tangeretin partially inhibited the growth of leukemic HL-60 cells by inducing apoptosis, and exhibited less cytotoxicity to normal lymphocytes [83].

Citrus flavonoids protect the nervous system by fighting against inflammation and protecting the function of nerve cells. It is promising to develop citrus flavonoids as an adjuvant treatment for neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, etc. It is believed that the protective effects of citrus flavonoids on the nervous system is worthy of further and in-depth research.

## 5. Citrus Flavonoid and Metabolic Disease

Oral administration of bergamot extract (150 mg containing 16% neohesperidin, 47% neohesperidin, and 37% naringin) for 6 months reduced moderate hypercholesterolemia, low-density lipoprotein, and blood lipids in patients with atherosclerosis [84]. Neohesperidin activated the AMPK pathway for hypoglycemic and exhibited lipid-lowering effects [85]. It was obvious that citrus flavonoids were beneficial in the treatment of metabolic diseases.

Nobiletin attenuated dyslipidemia by preventing hepatic triglyceride (TG) accumulation, reducing very low-density lipoprotein (VLDL) and TG secretion [86], while increasing hepatic and peripheral insulin sensitivity and glucose tolerance, and significantly attenuating atherosclerosis in the aortic sinus hardening [87]. In addition, nobiletin could enhance the circadian rhythm to combat metabolic diseases by intervening in the circadian rhythm network [88].

Naringenin reduced the progression of atherosclerosis by improving dyslipidemia [89], apolipoprotein B (apo B) overproduction, and hyperinsulinemia in high-fat-fed mice [90]. Additionally, naringenin maintained lipid homeostasis [91] by preventing cholesterol-induced systemic inflammation and metabolic dysregulation [92]. Naringenin and hesperetin could lower microsomal triglyceride transfer protein (MTP), acetyl-CoA acetyltransferase 1 (ACAT1), and acetyl-CoA acetyltransferase 2 (ACAT2) to reduce blood lipids [93]. Naringenin supplementation enhanced insulin sensitivity and helped to restore glucose homeostasis in diabetic rats [94]. Naringenin activated PI3K without inducing tyrosine phosphorylation of insulin receptor-substrate-1 (IRS-1) to produce insulin-like effects in vivo [95]. Furthermore, naringenin improved cholinergic function and alleviated oxidative stress against type 2 diabetes-induced memory dysfunction by inhibiting elevated cholinesterase (ChE) activity [96]. Naringenin exerted an anti-diabetic effect by upregulating AMPK. Besides, naringenin had a metformin-like effect that reduced inflammation and cell proliferation [97].

Naringin, the major grapefruit flavonoid, primarily affected the development of atherosclerosis in diet-induced hypercholesterolemia in mice [98] by modulating hepatic acetyl-CoA acetyltransferase (ACAT), aortic vascular cell adhesion molecule-1 (VCAM-1), and monocyte chemoattractant protein-1 (MCP-1) [99]. Other effects were reduced inflammatory cell infiltration, reduced oxidative stress, decreased plasma lipid concentrations, and improved hepatic mitochondrial function in rats [100]. Naringin improved bone properties in ovariectomized mice and exerted estrogen-like activity in rat osteoblast-like (UMR-106) cells [101].

Dietary hesperidin exerted hypoglycemic and hypolipidemic effects in streptozotocin-induced borderline type 1 diabetic rats [102].

Polymethoxyflavonoids are a novel flavonoid with cholesterol and triacylglycerol-lowering potential, and elevated levels of polymethoxyflavonoid metabolites in the liver may directly lead to its hypolipidemic effect in vivo [103]. Hesperidin stimulated nitric oxide production in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome [104].

Hesperetin alleviated hyperglycemia and dyslipidemia by improving the antioxidant capacity of streptozotocin (STZ)-induced experimental rats [105]. Hesperetin prevented diabetes-induced testicular damage by inhibiting oxidative stress, inflammation, and upregulation of enzymatic and non-enzymatic antioxidants [106].

After oral administration of bergamot extract (BPF) to rats and patients for 30 days, BPF significantly reduced triglyceride levels and blood glucose. Meanwhile, BPF inhibited 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and enhanced reactive vasodilation [87].

After diosmin was administered orally (100 mg/kg/day) for 45 days, both histological and biochemical parameters demonstrated antidiabetic effects in type 2 diabetic rats [107].

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