REVIEW
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Traditional Chinese Medicine

Plant distribution and pharmacological activity of flavonoids

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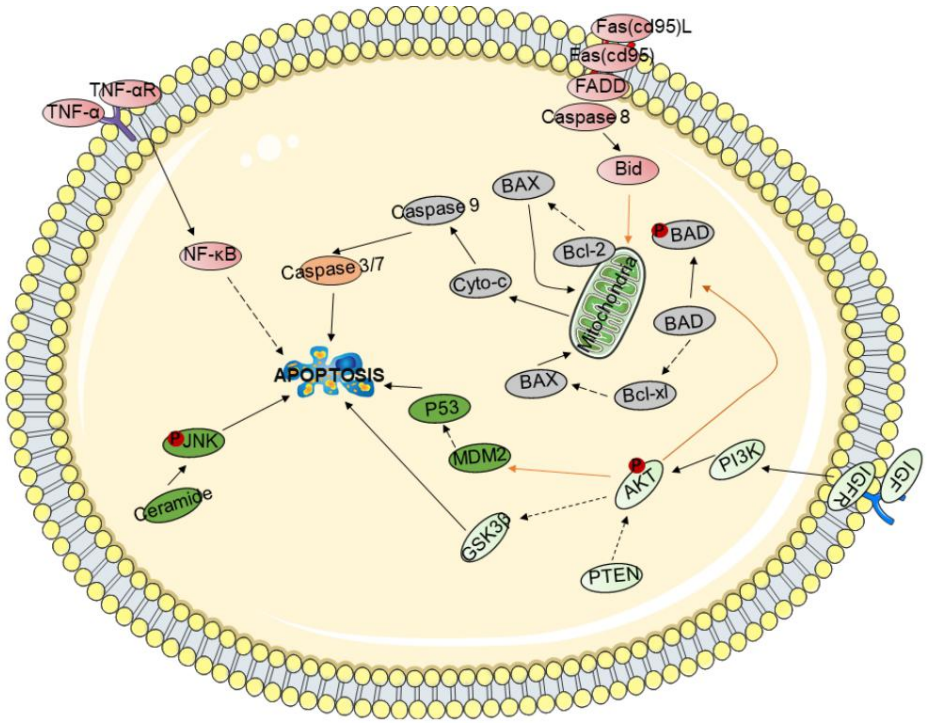
Highlights

This review covers the plant distribution and pharmacological activities of flavonoids, stressing the importance of identifying such valuable flavonoids in another genus or family while providing a basis for fully exploiting the therapeutic potential of flavonoids.

Traditionality

Flavonoids are found in some traditional Chinese medicines that function to clear heat and dampness, some pathological products resulted from diseases. The most representative drugs among them are Huangqin (*Scutellaria baicalensis*), Chuanhuangbai (*Phellodendri Chinensis Cortex*), and Kushen (*Sophora flavescens*). As early as the Donghan dynasty of China, these three herbs were recorded in an ancient book of Chinese medicine called *Shennong Bencao Jing*.



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Abstract

Flavonoids are natural organic compounds that are widely found in nature, their structural types are complex, and they mainly include flavonoids, flavonols, dihydroflavonols, isoflavones, dihydroisoflavones, chalcones, orange ketones, flavanoids, anthocyanidins, and biflavonoids. This review covers the plant distribution and pharmacological activities of flavonoids. Flavonoids are mainly distributed in *angiosperms* and *gymnosperms*, and they are abundant in plants such as *Rutaceae*, *Labiatae*, *Zingiberaceae*, *Scrophulariaceae*, and *Leguminosae*. Because of their wide distribution and variety, researchers have found that flavonoids have diverse biological activities, mainly focusing on anti-inflammatory, antibacterial and antitumor activities. Mechanistically, the anti-inflammatory effects are mainly related to the NF-κB and MAPK (mitogen-activated protein kinase) signaling pathway and then the inhibition of the production of inflammatory cytokines and mediators. The antibacterial activity is mainly manifested as inhibitory effects on many strains, including *Escherichia coli*, *Cryptococcus neoformans*, and *Pseudomonas aeruginosa*, via destroying the stability of the microbial membrane, inhibiting the invasion of virulent bacteria into host cells, promoting the apoptosis of bacteria, inhibiting bacterial fatty acid synthesis, etc. The antitumor activity of flavonoids is related to their inhibition of cell proliferation and induction of apoptosis via the mitochondria-mediated, endoplasmic reticulum-mediated, and death factor and its receptor-mediated signal transduction pathways. Understanding the plant distribution and pharmacological activity of flavonoids not only reveals the importance of identifying such valuable flavonoids in another genus or family but also provides a basis for fully exploiting the therapeutic potential of flavonoids.
Keywords: Flavonoids, Plant distribution, Pharmacological activity, Antitumor, Anti-inflammatory, Antibacterial.

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***Abbreviations*:**

ROS, Reactive oxygen species; Bcl-2, B-cell lymphoma 2; BAX, Bcl-2 associated X protein; PERK, Protein kinase R-like ER kinase; ATF, Activated transcription factor; IRE1, Inositol-requiring enzyme-1; XBP1, X-box binding protein 1; MMP-2: Matrix metalloproteinase-2, MMP-9: Matrix metalloproteinase-2; PARP: Poly (ADP-ribose) polymerase; Akt: Protein kinase B; DPPH, 1,1-Diphenyl-2-picrylhydrazyl; TLR: Toll-like receptor; RIG, Retinoic acid-inducible gene; AQP, Aquaporin; iNOS, Inducible nitric oxide synthase; COX, Cyclooxygenase; IL, Interleukin; AFC, Alveolar fluid clearance; Nrf2: Nuclear factor erythroid-2-related factor 2.

***Competing interests*:**

The authors declare that they have no conflict of interest.

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Background

Flavonoids are an important class of natural organic compounds that includes more than 4,000 polyphenolic compounds that are widely found in various natural plants [1]. Flavonoids are also present in some traditional Chinese medicines. The most representative drugs among them are Huangqin (*Scutellaria baicalensis*), Chuanhuangbai (*Phellodendron chinense Schneid*), and Kushen (*Sophora flavescens*). As early as the Donghan dynasty of China, these three herbs were recorded in an ancient book of Chinese medicine called *Shennong Bencao Jing*.

The C_6-C_3-C_6 skeleton is formed in plants by the condensation of three malonyl residues with hydroxy cinnamic acid [2], labeled as rings A, B, and C. Currently, flavonoids are roughly classified into 10 categories based on their structure, including flavonoids, flavonols, dihydroflavonols, isoflavones, dihydroisoflavones, chalcones, orange ketones, flavanoids, anthocyanidins, and biflavonoids. In addition, the 5 and 7 positions of ring A; 3', 4', and 5' positions of ring B; 3 and 2 positions of ring C of flavonoids are often replaced by hydroxyl groups, these readily form glycosides with a variety of five- or six-carbon sugars through a β glycoside bond, most of which are oxyglycosides, such as 7-o-glycosides in flavones, flavanones, and isoflavones. Compared with oxygen glycosides, which have been widely studied, there are relatively few studies on carbon glycosides in the literature [3]. Carbon glycosides can be directly connected to the skeleton through acid-resistant C-C bonds, and they mainly occur at the C_6 and C_8 positions. The basic structures and glycosylation sites of common flavonoids are summarized in Figure 1.

Because of their wide distribution and variety, flavonoids have been found to possess diverse biological activities, such as antioxidation, antibacterial, antihypertensive, liver protection, antitumor, and neuroprotection effects. In this review, the plant distribution and pharmacological activities of flavonoids are systematically summarized, and the results not only reveal the importance of identifying such valuable flavonoids in another genus or family but also provide a basis for fully exploiting the therapeutic potential of flavonoids.

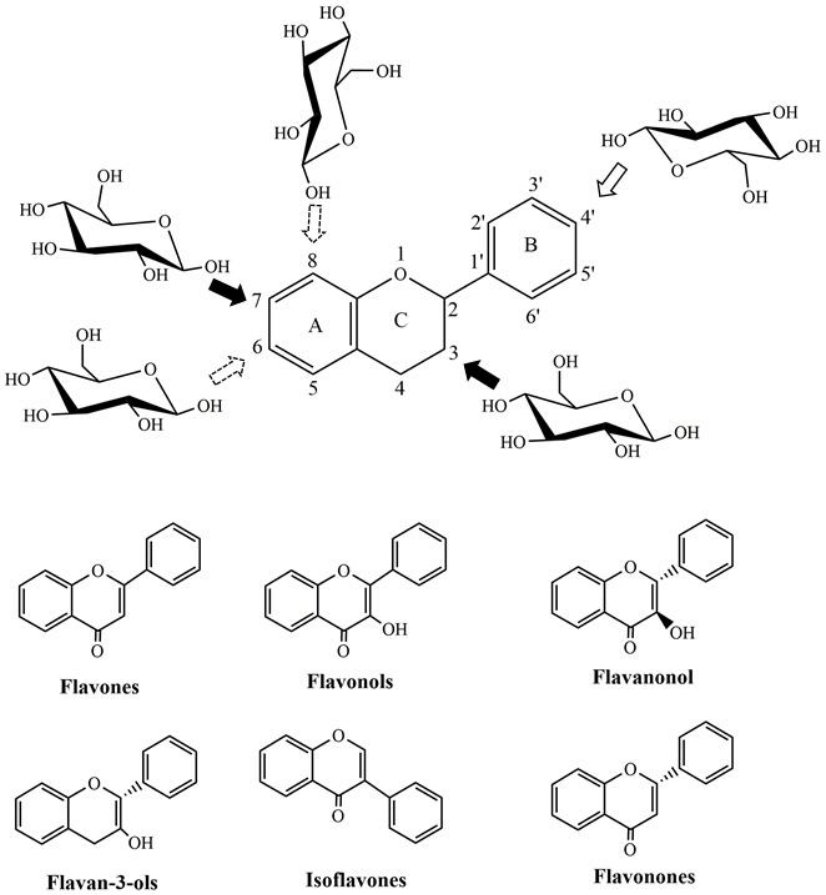

Figure 1 Basic structure of the common classes of flavonoids and the common points of glycosylation
Common glycosylation points are C_3 and C_7 (black arrows); B ring glycosylation is also observed in some plants (hollow arrow); C-glycosides are the rarest in plants (arrow with dotted lines); C-glycosylation mostly occurs at the C_6 and C_8 positions.

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Plant distribution of flavonoids

A search in *Phenol-Explorer* (http://phenol-explorer.eu/) produced 492 different flavonoids and isoflavone components in 400 types of food; thus, there are even more flavonoids distributed in plants. By sorting through the plant sources of flavonoids, we found that the distribution of flavonoids was the highest in the families of *Rutaceae*, *Zingiberaceae*, *Scrophulariaceae*, *Leguminosae*, *Ranunculaceae*, *Labiatae*, and *Myrtaceae* (Table 1). Kaempferol, quercetin, apigenin, luteolin, isorhamnetin, and quercetin are the most common chemical constituents. In addition, many new compounds that have been isolated, purified, and identified were all modified from the existing flavonoids such as kaempferol and luteolin.

Table 1 Plant sources of flavonoids

Families	Plants/Sources	Components	References
Selaginellaceae	Juanbai (*Selaginella tamariscina*), Cuiyuncao (*Selaginella uncinate*)	Apigenin, Amentoflavone, Hinokiflavone, Isocrytomerin, Arnentoflavone, Unciflavones A-F	[4, 5]
Cupressaceae	Cebaiye (*Platycladus orientalis*)	Acacetin	[6]
Gramineae	*Oryza sativa*	Apigenin, Luteolin, Isovitexin-2'-O-(6'-(E)-ferric-glucopyranoside, Quercetin, Kaempferol	[7]
Sinopteridaceae	Libingjinfenjue (*Onychium lucidum*)	Luteolin-7-glucoside, 2,7-Dimethoxyquercetin, Quercetin-3-glucoside, Onychin	[4]
Acrostichaceae	*Acrostichum aureum*	Quercetin-3-O-β-D-glucoside, Quercetin-3-O-β-D-glucosyl-(6→1)-α-L-rhamnoside, Quercetin-3-O-α-L-rhamnoside, Quercetin-3-O-α-L-rhamnosyl-7-O-β-D-glucoside, Kaempferol	[8]
Polypodiaceae	Youbingshiwei (*Pyrrosia petiolosa*)	Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-arabinofuranoside	[9, 10]
Cycadaceae	*Cycas revoluta*	Ginkgetin, Bilobetin, Isoginkgetin	[4]
Ginkgoaceae	Yinxing (*Ginkgo biloba*)	Quercetin, Kaempferol, Isorhamnetin, Genkwanin, Sciadopitysin, Ginkgetin, Isoginkgetin, Apigenin, Luteolin, Naringenin, Diosmetin	[4, 11, 12]
Typhaceae	*Typha orientalis*	Catechin, Isorhamnetin-3-O-neohesperidoside, Isorhamnetin-3-O-β-D-glucoside, Naringenin, Kaempferol, Isorhamnetin	[13]
Ephedraceae	Mahuang (*Ephedra*)	Luteolin-7-O-glucuronide flavone, Myricetin 3-rhamnoside	[14]
Salicaceae	*Populus X canadensis*, *Populus tomentosa*	Pinostrobin, Pinocembrin, Chrysin, Galangal-3-methoxy, Quercetin-3,7-dimethoxy, Rhamnetin, Kaempferol-3-methoxy, Apigenin	[4, 15]
Moraceae	*Morus alba*, Pijiuhua (*Humulus lupulus*), *Artocarpus lingnanensis*	Mul-berin, Morin Hydrate, Cyclomorusin, Cyclomorin, Procyanidin dimer, Quercetin，Kaempferol glycoside, Rhamnoside, 2-Hydroxynaringin 4'-O-β-D-glucopyranoside, 2-Hydroxynaringenin, Anthocyanin-3-O-glucoside, Rutin, Isoquercetin, Anthocyanin-3-O-rutinoside, Pelargonin-3-O-glucoside, Kaempferol	[3, 4, 16-18]
Polygonaceae	Batiansuanmo (*Rumex patientia*), Juanjingliao (*Fallopia convolvulus*), Bianxu (*Polygonum aviculare*)	Kaempferol, Quercetin-3-O-β-D-glucoside, Isorhamnetin, Kaempferol-3-O-β-D-glucoside	[4, 19]

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Caryophyllaceae	Maicailan (*Vaccaria segetalis*), *Paronychia argentea*	Apigenin-6-C-arabinose-glucoside, Apigenin-6-C-diglucoside, Vaccarin	[4, 20]
Ranunculaceae	Jian'eloudoucai (*Aquilegia oxysepala*), Tiankui (*Semiaquilegia adoxoides*), Mudanhua (*Paeonia suffruticosa*), Wutou (*Aconitum carmichaelii*)	Genkwanin, Luteolin, Apigenin, Sweroside, Tiliroside, Semiaquilinoside, Apigenin-7-O-D-glucoside, Apigenin-7-O-D-neohesperidin, Kaempferol-7-O-D-glucopyranoside, Kaempferol-3-O-D-glucopyranosyl-7-O-D-Pyranoglucoside, Dihydrokaempferol	[4, 21-24]
Berberidaceae	Yinyanghuo (*Epimedium*)	Baohuoside I/II, Icariin A/B/C/D/E/F/G/H, Icariin, Quercetin, Sagittatoside A/B/C, New icariin, Chuanhuoside, Dehydrated icariin, Epimedium B/C/I, Korean icariin I/II	[4, 25-30]
Geraniaceae	Tianzhukui (*Pelargonium hortorum*)	Kaempferol, Quercetin	[31]
Crassulaceae	Chuipencao (*Sedum sarmentosum Bunge*), Hongjingtian (*Rhodiola rosea*), Fojiacao (*Sedum lineare*), Aoyejingtian (*Sedum emarginatum*), Gaoshanhongjingtian (*Rhodiola cretinii*)	Tricin, Luteolin, Glycyrrhizin, Citrin, Quercetin, Kaempferol, Rutin, Rhodiola rutin, Kaempferol-7-rhamnoside	[4, 32, 33]
Lauraceae	*Cryptocar-ya chinensis*	Cryochinones A/B/C/D/E/F	[34]
Gentianaceae	Longdancao (*Gentiana scabra*), Qinjiao (*Gentiana macrophylla*)	Isophorin-4'-O-glucoside, Isophorin, Isovacilin	[35, 36]
Rosaceae	*Rosa davurica*, *Rosa sericea*, Shanzha (*Crataegus pinnatifida*), Pipa (*Eriobotrya japonica*)	Quercetin, Kaempferol, Hypericin, Rutin，Hesperidin, Cephalosporin, Cephalosporin, Tiliarin, Vitexin	[4, 37]
Leguminosae	Zhilihuangqi (*Astragalus Pall.*), *Kummerowia striata*, *Sophora davidii*, Huluba (*Trigonella foenum-graecum*), *Oxytropis deflexa*, Houguojixueteng (*Millettia pachycarpa*), Huzhizi (*Lespedeza bicolor*), Caohongteng (*Sargentodoxa cuneata*), Gancao (*Glycyrrhiza uralensis*), *Eriosema chinense*, Luohuasheng (*Arachis Linn.*), *Oxytropis psamocharis*, Kushen (*Sophora flavescens*), Mihuadou (*Spatholobus suberectus*), Maoguoyuteng (*Derris eriocarpa*), Dahongpao (*Vigna (Willd.) Ohwi et Ohashi*), Buguzhi (*Psoralea corylifolia*), Ge (*Pueraria lobata*), *Oxytropis falcata*, Jixueteng (*Millettia reticulata*)	3'7-Dihydroxy-2'4'-dimethoxyisoxane, Zapotinin, Astragalin, Isoquercitrin, Rutin, Apigenin, Apigenin-7-O-β-D-glucoside, Kaempferol-3-O-β-D-glucoside, Apigenin-7-O-neohesperidin, Diosmetin, Naringenin, Quercetin, Tricin, Kaempferol, Pachycarin, Orientin, Isoorientin, Isovitexin, Myricetin, Dihydromyricetin, Liquiritin, Isoliquiritin, Liquritigenin, Isoliquiritigenin, Formononetin, Licoricone, Rhamnose isoliquiritin，Rhamnosin-3-O-[(S)-3-hydroxy-3-methyl-glutaryl (1→6)]-β-D-glucopyranoside, Rhamnoside-3-O-[(S)-3-hydroxy-3-methyl glutaryl (1→6)]-β-D-glucopyranoside, Isorhamnetin-3-O-[(S)-3-hydroxy-3-Methylglutaryl (1→6), Kurarinol, Kurarinol K/H, Trifolirhizin, Kuraridine, Isobavachalcone, Rhamnetin, 2',4'-Dihydroxychalcone, 2',4',β-Trihydroxydihydrochalcone, Bavachinin, (-)- Epicatechin, 5,7,3',5'-Tetrahydroxyflavanone, Genistein	[4, 38-48]
Zygophyllaceae	Duolieluotoupeng (*Peganum multisectum*)	Acacetin, Deacetyl peganetin, Peganetin, 7,4'-Dihydroxy-3'-methoxyflavone-5-O-rutinoside	[4]
Saururaceae	Yuxingcao (*Houttuynia cordata*)	Quercetin, Rutin, Hyperoside, Isoquercitrin, Houttuynoid G/H/I/J	[49, 50]
Verbenaceae	*Vitex negundo*)	Isophorin, Luteolin-7-O-β-D-glucopyranoside, Luteolin-3'-O-β-D-glucopyranoside,	[51]

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		Apigenin-7-O-β-D-glucoside	
Rutaceae	Chuanhuangbai (*Phellodendri Chinensis Cortex*), *Citrus aurantium*, *Citrus maxima*, *Citrus sinensis*, Huangpi (*Clausena lansium*), Wuzhuyu (*Evodia rutaecarpa*), Qianlixiang (*Murraya paniculata*), Huajiao (*Zanthoxylum bungeanum*)	Phellamurin, Amuresin, Hyperoside, Phellochinin A, Nobiletin, Xanthoxylin, Vitexin	[4, 52]
Meliaceae	Xiangchun (*Toona sinensis*)	5,7-Dihydroxy-8-methoxyflavone, Kaempferol	[4]
Rhamnaceae	*Poncirus trifoliata*, Xizangmaoru (*Rhamnella gilgitica*), Shuli (*Rhamnus davurica*)	Dihydrokaempferol, Quercetin, (+)-3,3',5',5,7'-Pentahydroxydihydroflavone, (+)-Dihydromyricetin, Methadone, Aromadendrin, Naringenin, Kaempferol, Quercetin, Taxifoliol	[2, 4]
Lamiaceae	Huaqizhu (*Mosla grosseserrata*), Huoxiang (*Agastache*), Huangqin (*Scutellaria baicalensis*), Xunyicao (*Lavandula angustifolia*), Jingjie (*Nepeta cataria*), Shixiangru (*Mosla chinensis*), Zisu (*Perilla frutescens*), Xiakucao (*Prunella vulgaris*), Baihuazhizihua (*Dracocephalum heterophyllum*)	5-Hydroxy-6,7-dimethylflavone, 5,7-Dihydroxy-4'-methoxyflavone, Carotene, Rhamnolidin, Morin-7-O-β-D-glucoside, Kaempferol-3-O-β-D-glucoside, Acacetin, Baicalein, Baicalin, Apigenin, Luteolin, Quercetin, Naringenin, Myricetin, Wogonoside, Wogonin, Luteolin-7-O-Glucoside, Apigenin-7-O-Glucoside, Chrysoeriol, Orohylin-A, Rutin, Kaempferol, Kaempferol-3-O-glucoside, Anthocyanins, Delphinidin, Trimethyl-delphin-3,5-diglucoside, Acacetin-7-O-β-D-glucopyranoside, Isoorientin, Quercetin-3-O-β-D-rhamnoside, Hesperidin, Norwogonin, Diosmetin	[4, 53-65]
Scrophulariaceae	Liuchuanyu (*Linaria vulgaris*), Paotongguo (*Paulownia fortune*), Maxianhao (*Pedicularis resupinata*)	Pectolinarin, Acacetin, Pectolinarigenin, Hispiduline acetyllinarin, Taxifolin-7-O-α-rhamnoside, Baicalein, 3'-O-methyl-5'-hydroxydiacetone, 3'-O-methyl-5'-O-methyldipyrone, 3'-O-methyldipropanediol, 3'-O-methyl dipyridone, Quercetin, Quercetin-4'-O-D-galactoside, Quercetin-7-O-D-galactoside, Luteolin-5-O-β-D-glucoside, Luteolin-7-O-glucoside, Luteolin, 4'-O-β-D-glucoside, Apigenin, Apigenin-7-O-glucoside, Apigenin-7-O-β-glucopyranoside	[4, 66, 67]
Asteraceae	Duoshefeipeng (*Erigeron multiradiatus*), Beiyeju (*Dendranthema indicum*), Duantingfeipeng (*Erigeron breviscapus*), Tianshanxuelian (*Saussurea involucrata*), Shuifeiji (*Silybum marianum*), Xuetuzi (*Saussurea gossypiphora*), Huanghuahao (*Artemisia annua*), Caiji (*Cynara scolymus*), Hanliancao (*Eclipta prostrata*), Liulengju (*Laggera alata*), Guizhencao (*Bidens*	Apigenin, Quercetin, Luteolin, Apigenin-7-O-glucuronide, Isoquercetin, Scutellarin, Baicalein-7-β-D-glucoside, Apigenin, Acacetin-7-O-α-L-rhamnosin (1→6)-β-D-glucoside, Silymarin, Silymarin II, Luteolin-7-glucoside, Myricetin, Apigenin-7-O-glucuronide	[4, 68-73]

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Aquifoliaceae	*Ilex centrochinensis*, Maodongqing (*Ilex pubescens*)	Huazhong Holly Flavonoids, Hesperidin, Isosakuranetin	[4, 74]
Myrtaceae	*Eucalyptus camaldulensis*, *Cleistocalyx operculatus*, Taojinniang (*Rhodomyrtus tomentosa*)	Quercetin, Rutin, Myricetin, Dihydromyricetin, Kaempferol, Quercetin-7,4'-diglucoside, Vitexin	[4, 75, 76]
Liliaceae	*Allium fistulosum*, *Allium cepa*, *Aletris spicata*, Tufuling (*Smilax glabra*), Xuejie (*Daemonorops draco*)	Alliumoside A, Kaempferol, Quercetin 4'-O-β-D-glucopyranoside, Quercetin-4'-glucoside, Quercetin-3,4'-diglucoside, 5-Hydroxy-7,8,4'-trimethoxyflavone, Amentoflavone, Apigenin, Isoengelitin, Isoastilbin, Taxifolin, Astilbin, Engeletin, Neoastilbin, 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(3,4,5-trihydroxy-6-methyl-oxa n-2-yl)oxy-chroman-4-one, (-)-Epicatechin, Naringenin, Dihydrokaempferol, Kukulkanin B, Myricetin,	[4, 77-80]
Campanulaceae	Dangshen (*Codonopsis pilosula*), Banbianlian (*Lobelia chinensis*)	Luteolin, Apigenin, Kaempferol, Wogonin, Quercetin, 5-Hydroxy-4',6,7-trimethoxyflavone, 5-Hydroxy-4',7-dimethoxyflavone, Apigenin-7-O-β-D-glucopyranoside, Codonopilodiynoside C/D/E/F/G, Cordifolioidyne B, Tangshenyne A/B, Buddleoside, Luteolin-3',4'-dimethyl ether-7-O-β-D-glucoside	[81]
Zingiberaceae	Shanjiang (*Alpinia japonica*), Caodoukou (*Katsumada galangal*), Gaoliangjiang (*Alpinia officinarum*), Jianghuang (*Curcuma longa*)	Izalpinin, Alpinone, Rhamnocitrin, Kumatahenin, Alpinetin, Cardamonin, Quercetin, Kaempferol, Quercetin-3-methyl ether, Isorhamnetin, 4'-Methyl kaempferin, Galangin, Galangin-3-methyl ether, Turmerone	[4]
Capparaceae	*Malvastrum coromandelianum*	Methoxy-trihydroxyflavone	[4]
Passifloraceae	Xifanlian (*Passiflora coerulea*)	Isophorin, 7-O-β-glucosyl-6-C-β-glucosyl luteolin, orientin, 7-O-α-rhamnosyl 6-C-β-glucosyl luteolin	[82]
Ebenaceae	Shiye (*Diospyros kaki*)	Quercetin, Kaempferol	[83, 84]
Flacourtiaceae	*Oncoba spinosa*	Kaempferol, Quercetin, Apigenin-7-O-β-D-glucuronic acid pyranoside, Quercetin-3-O-β-D-galactopyranoside	[85]
Solanaceae	Suanjiang (*Physalis alkekengi*), Jindenglong (*Calyx seu Fructus Physalis*)	Luteolin, Luteolin-7-O-glucopyranoside, Quercetin, Kaempferol, Apigenin-O-β-D-glucopyranoside, Diphosphate-O-β-D-diglucopyranoside, 3',4'-Dimethoxyartem, 5,4',5'-Trihydroxy-7,3'-dimethoxyflavonol, Luteolin-7-O-β-D-glucopyranoside, Luteolin-4'-O-β -D-glucopyranoside, Luteolin-7,4'-dioxy-β-D-glucopyranoside, Luteolin-7,3'-dioxy-β-D-glucopyranoside, 3',7-Dimethylquercetin, 3',4',7-Trimethylquercetin, 3', 4'-Dimethylquercetin, Quercetin-3-O-β-D-glucopyranoside, Quercetin-3,7-dioxo-β-D-glucopyranoside,	[86-88]

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		Kaempferol-3-O-β-D-glucose, 3,7-Dioxo-α-L-rhamylacetyl, Kaempferol, Diosmetin-O-β-D-glucopyranoside, 5,4',5'-Trihydroxy-7,3'-dimethoxyflavonol, Chrysoeriol	
Brassicaceae	*Arabidopsis thaliana*	Kaempferol, Quercetin	[89]
Cynomoriaceae	Shuoyang (*Cynomorium songaricum*)	Epicatechin, Cis-5-deoxypentanoic acid-γ-lactone, (+)-Catechin, Rutin, Naringenin, Isoquercitrin, (-)-Epicatechin-3-O-gallate, Isoquercetin, Luteolin-7-O-glucoside, Naringenin-4'-O-β-glucopyranose, Phloridzin, (-)- Epicatechin, Procyanidin B3/B1/B6, Epicatechin-(4β-8)-epicatechin-(4β-8)-catechin, Catechin-(6'-6)-catechin, Catechin-(6'-8)-catechin, Epicatechin-(4β-6)-epicatechin-(4β-8)-catechin, Cyanidin 3-O-glucoside, Cyanidin 3-O-(6-O-rhamnosylglucoside)	[90, 91]
Loganiaceae	Zuiyucao (*Buddleja lindleyana*)	Acacetin, Apigenin, Luteolin, Luteolin-7-O-rutinoside, Luteolin-7-O-glucoside	[92, 93]
Oleaceae	Nvzhen (*Ligustrum lucidum*), Lianqiao (*Forsythia suspensa*)	Apigenin, Apigenin-7-O-acetyl-β-D-glucoside, Apigenin-7-O-β-D-rutin, Luteolin, Luteolin-7-O-β-D-glucopyranoside, Quercetin, Rutin, Baicalin	[94-96]
Convolvulaceae	Tusizi (*Cuscuta chinensis*)	Quercetin 3-O-β-D-galactoside-7-O-β-D-glucoside, Quercetin 3-O-β-D-ribofuranosyl-(1→2)-β-D -galactoside, Hyperoside, Quercetin, Kaempferol	[97]
Thymelaeaceae	*Daphne giraldii*, Legewang (*Wikstroemia indica*), Langdu (*Stellera chamaejasme*)	Luteolin-7-methylether-5-β-D-glucoside, 4',5-Dihydroxy-3',7-dimethoxyflavone, Luteolin-3',7-dimethyl Ether-5-β-D-glucoside, 5-Methoxy-7-β-D-glucopyranosyl-(-)-afzelechin, Rutin	[98-100]
Caprifoliaceae	Badongrendong (*Lonicera henryi*), Jinyinhua (*Lonicera japonica*).	Luteolin, Apigenin, Luteolin-O-hexosides, Luteolin-7-O-β-glucoside, Luteolin-O-rhamnosyl-hexoside, Kaempferol-O-rhamnosyl-hexoside	[101, 102]
Orchidaceae	Jinxianlian (*Anoectochilus roxburghii*)	Isorhamnetin-3-O-β-D-rutinoside, Isorhamnetin-3-O-β-D-glucopyranoside	[103]
Violaceae	Zihuadiding (*Viola philippica*), *Viola prionantha*, Sansejin (*Viola tricolor*)	Delphinidin-3-O-rutinoside, Cyanidin-3-O-rutinoside, Delphinidin-3-O-rhamnosylglucoside-5-O-Glucoside	[104]
Saxifragaceae	Ganhuangcao (*Penthorum chinense*), Luojingjinyao (*Chrysosplenium nudicaule*)	Pinusin-7-O-β-D-glucopyranoside, Pinocin, 5-Methoxyxypin-7-O-β-D-glucoside, Kaempferol, Quercetin, Quercetin-3-O-β-D-xyloside, Apigenin, Luteolin, Catechin, 6,7,3'-Trimethoxy-3,5,4'-trihydroxyflavone, 5,4'-Dihydroxy-3,6,3'-trimethoxyflavone-7-O-β-D-glucoside	[105, 106]

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Malvaceae	Qingma (*Abutilon theophrasti*)	Quercetin-7-O-β-glucoside, Rutin, Kaempferol-3-O-α-rhamnosyl (1→6)-β-D-glucopyranoside, Luteolin, Apigenin -7-O-β-diglucoside	[107]
Anacardiaceae	Renmianzi (*Dracontomelon duperreanum*)	Luteolin, L-Epicatechin, Quercetin, Catechin	[108]
Celastraceae	Leigongteng (*Tripterygium wilfordii*)	(±)-5, 4'-Dihydroxy-2'-methoxy-6', 6'-dimethyl-(2', 3', 7, 8)-6-methyl flavanone	[109]

Pharmacological Activity of Flavonoids

Anti-inflammatory activity

Inflammation is not only a defensive protective response but also a stimulus to various injury factors. It is dedicated to the defense and elimination of pathogenic factors *in vivo* and *in vitro*. However, persistent and intense inflammation can cause damage to human tissues and cells. Macrophages are important immunoregulatory cells that secrete different inflammatory factors, stimulate inflammatory responses, clear pathogens, and maintain the balance of the internal environment. LPS stimulates the RAW 264.7 monocyte/macrophage-like cell line, a commonly used inflammatory model, and many flavonoids provide good resistance to this stimulation. It was reported that luteolin blocked the activation of NF-κB and inhibited the expression of NO, PGE2 (prostaglandin E2), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)2 , TNF-α, and interleukin (IL)-6 in a dose-dependent manner under LPS stimulation in a RAW264.7 cell inflammation model [87]. Alpinetin can block the phosphorylation of IκBα protein, p65, p38, and ERK (extracellular signal-regulated kinase) and significantly inhibit the production of TNF-α, IL-6, and IL-1β [96]. Baicalein was shown to upregulate the expression of estrogen receptor ERα/ERβ in an LPS-induced RAW264.7 cell inflammation model, downregulate *TNF-α*, *iNOS*, and *COX2* mRNA, inhibit NO and cytokine production in cells, and ultimately regulate the NF-κB pathway and estrogen-like activity to inhibit LPS-induced inflammatory cytokine production, thereby preventing inflammation-related diseases [110]. It can also play an anticomplement role through classical and alternative approaches [64]. Total flavonoids of Sangshen (*Fructus Mori*) can inhibit the expression of IL-6, induce iNOS, phosphorylate p65 and IκB, increase the expression of IL-10, and exert anti-inflammatory and analgesic effects by inhibiting the pro-inflammatory cytokines iNOS and NF-κB [18]. Also acting on the classical NF-κB inflammatory signaling pathway, the total flavonoids of Qingma (*Abutilon theophrasti*) can reduce the content of COX2, NO, IL-1β, IL-6, and TNF-α, increase the concentration of IL-10, inhibit the mRNA expression and phosphorylation of p65, and regulate the expression of inflammation-related factors through the NF-κB and MAPK (mitogen-activated protein kinase) signaling pathways, in turn affecting the process of inflammation [107].

Acacetin inhibits 5-lipoxygenase activity in a concentration-dependent manner, which exerts an anti-inflammatory effect through inhibiting the activity of 5-lipoxygenase and preventing the production of leukotrienes, and it also inhibits the biosynthesis of TNF-α and NO [6]. In addition, some scholars have found *in vivo* anti-inflammatory experiments that luteolin and the ethyl acetate fraction of Suanjiang (*Physalis alkekengi*) can significantly alleviate edema in a carrageenan-induced acute rat inflammation model [87]. In the chronic rat inflammatory model, luteolin was also found to inhibit cotton ball-induced granuloma formation at 110 mg/kg and 50 mg/kg, and its anti-inflammatory effect was comparable to that of 50 mg/kg indomethacin [87]. Compared with 2 mg/kg aspirin, 5 mg/kg and 10 mg/kg of the ethanol extract of Youbingshiwei (*Pyrrosia petiolosa*) were shown to exert significant anti-inflammatory activity against xylene-induced ear swelling in mice, and the maximum inhibition rate was as high as 67% [10]. Apigenin, quercetin, kaempferol, and their analogues have similar anti-inflammatory activities [87].

Antibacterial activity

Since Fleming discovered penicillin, antibiotics have been used extensively in the clinic to reduce the prevalence and spread of a large number of diseases, but the struggle between humans and infectious diseases is endless. Despite the tremendous progress we have made, the emergence of various drug-resistant germs due to the abuse of antibiotics has made it difficult to treat certain infectious diseases. Faced with such a dilemma, researchers have turned their attention to the natural chemical ingredient flavonoids. Studies have found that the flavonoids from *Oncoba spinosa* can bind to soluble proteins outside the bacteria, destroying the stability of the microbial membrane [85]. Baicalin increases alkaline phosphatase activity and attaches to and penetrates the cell membrane of bacteria, causing the surface of the membrane to sag, changing the permeability, and increasing the susceptibility to various antibiotics [111]. Another study reported that baicalein could penetrate bacterial biofilm, promote the hydrolysis of the quorum sensing regulatory protein TraR protein, interfere with cell signaling, and inhibit bacterial quorum sensing [112].

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In addition, baicalein can inhibit bacterial virulence by inhibiting *Salmonella typhimurium* invasion into host cells by covalently binding to the protein substrates SipA/B/C/D and SopB of *Salmonella typhimurium* SPI-1 T3SS [60]. It has been shown that the flavonoids from Paotongguo (*Paulownia fortune*) can activate the apoptotic pathway of Leishmania and methicillin-resistant *Staphylococcus aureus* and have synergistic effects with oxacillin and tetracycline [66]. Some scholars have reported that luteolin can inhibit the activity of enoyl-ACP reductase and inhibit bacterial fatty acid synthesis in a non-competitive manner and then exert its antibacterial effect [108, 113]. Interestingly, 1 mg/mL quercetin reduced the F-ATPase activity of *Streptococcus mutans* by 47.37% and 0.5 mg/mL kaempferol reduced it by 49.66%; they significantly inhibited the production of acid by *Streptococcus mutans*, suggesting that quercetin and kaempferol may have potential for the prevention and treatment of dental caries [114]. Apigenin alone or in combination with LysGH15, a lysin from phage GH15, which exhibits a highly efficient and extensive cleavage profile for MRSA (methicillin-resistant Staphylococcus aureus), was found to reduce rabbit erythrocyte lysis, protect lung tissue from mice with *S. aureus* pneumonia, and reduce the number of the bacteria in the lungs and blood, and TNF-α, IL-1β, and IL-6 levels were very similar to those in healthy mice [115]. Other studies have found that flavonoids have antimicrobial activity, but the mechanisms of their antimicrobial activity have not been thoroughly studied. For example, the total flavonoids of Sangshen (*Fructus Mori*) [18], the total flavonoids of Qingma (*Abutilon theophrasti*) [107], catechin [108], quercetin [108, 114], L-epicatechin [108], the ethyl acetate fraction of the ethanol extract of Leigongteng (*Tripterygium wilfordii*) [109], and kaempferol [114] were all found to have inhibitory effects on many strains of *Escherichia coli*, *Cryptococcus neoformans*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Streptococcus sanguis*, *Actinomyces naeslundii* and *Lactobacillus rhamnosus* (Table 2).

Antiviral effects

In one study, 120-360 mg/kg of the total flavonoids from Shiqizhu (*Mosla scabra*) was used to treat influenza A virus-infected mice for 5 days, and the results indicated that the total flavonoids from Shiqizhu (*Mosla scabra*) upregulated the expression of *Toll-like receptor* (*TLR*)*-7*, *retinoic acid-inducible gene (RIG)-1*, *TRAF6* (*TNF receptor associated factor 6*), *BCL-2*, *BAX*, *VIPR1 (Vasoactive intestinal polypeptide receptor 1*), *PKCα (Protein kinase C alpha*), and *Aquaporin* (*AQP*)*-5* mRNAs and downregulated the expression of Caspase-3, NF-κB, and p65 proteins. In addition, the total flavonoids from Shiqizhu (*Mosla scabra*) reduced the levels of IL-6, TNF-α, and IL-1β in serum and increased the expression of IFN-α. These results clearly demonstrate that the total flavonoids from Dendrobium can significantly alleviate lung inflammation, apoptosis, and water transport abnormalities induced by influenza A virus, which may be achieved by regulating the TLR7, RIG-1, and AQP5 signaling pathways [116].

Immunomodulatory effects

The total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) were found to downregulate the expression of *FASL* and *TNFR1* mRNAs, upregulate the level of BCL-2 mRNA, and decrease the apoptosis rate of T cells; moreover, the activities of caspase-8 and caspase-3 in T cells of corticosterone rats were significantly inhibited, and the number of T cells was maintained [117]. Another study found that the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) significantly enhanced phagocytosis by the monocyte-macrophage system in normal mice, increased the level of serum hemolysin antibody formation, and antagonized the inhibition of monocyte-macrophage phagocytosis by cyclophosphamide, reducing serum hemolysin antibody levels and delayed-type hypersensitivity [30].

Antioxidant activity

There is a complete oxidation system in cells, including ROS/RNS (reactive nitrogen species), O_2, HO, HO_2, H_2, NO, NO+, and N_2O_3. Endogenous products mainly originate from mitochondria, peroxisomes, NADPH oxidase, cytochrome P450, and the xanthine redox enzyme system, and exogenous products are mainly related to ultraviolet and ionizing radiation. Low levels of ROS provide a stable microenvironment for maintaining the normal function of various intracellular biological macromolecules. On the contrary, high levels of free radicals can destroy the redox environment in cells and cause cell damage and death, and a persistent imbalance will eventually lead to aging and related diseases. Many flavonoids are excellent free radical scavengers because they can be used as hydrogen or electron donors. HORAC (Hydroxyl radical antioxidant capacity), TEAC [6-hydroxy-2, 5,7,8-tetramethylchroman-2-carboxylic acid (Trolox)-equivalent antioxidant capacity], ABTS [2, 2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt], FCR (Folin-Ciocalteu), ORAC (oxygen radical absorbance capacity), 1,1-diphenyl-2-picrylhydrazyl (DPPH), FRAP (ferric reducing antioxidant power), POV (peroxide value), and others are commonly used indicators to detect antioxidant activity, especially DPPH (Table 3). Compared with the commonly used antioxidants such as vitamin C and ascorbic acid, quercetin [85] in *Oncoba spinosa* and flavonoids [21] in the methanol extract of peony have the same antioxidant activity as

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vitamin C. At the same concentration, the total flavonoids of Taojinniang (*Rhodomyrtus tomentosa*) [76] and Maobaiyang (*Populus tomentosa*) stamen [15] were shown to be better than ascorbic acid at scavenging DPPH. The levels of SOD and GSH-Px (glutathione peroxidase) increased and that of MDA (malonic dialdehyde) were found to decrease in the plasma of Kunming mice after administration, which indicated that flavonoids could promote the expression of antioxidant enzymes and protect the body from peroxidation [76].

Antitumor effect

Inhibit the proliferation of tumor cells. The first step in cancer research is to study antiproliferation, which forms the basis for subsequent research. Both plant total flavonoid extracts, such as total flavonoids from Shuli (*Rhamnus davurica*), total flavonoids extracted from Shiye (*Diospyros kaki*), and the N-butanol extract of Shiwei (*Pyrrosia petiolosa*), and monomeric compounds, such as 6,7,3'-trimethoxy-3,5,4'-trihydroxyflavone, genistein, and rutin, all have good inhibitory effects on the growth of various tumor cell lines. Their sources and corresponding IC_{50} values are shown in Table 4.

Table 2 The MICs values of flavonoids

Compounds	Plants/Sources	MICs
Derrubon-5-methyl ether	Maoguoyuteng (*Derris eriocarpa*)	25-100 μg/mL [118]
MeOH extract [a]	The leaves of *Oncoba spinosa*	256-204 8 μg/mL [85]
Quercetin	The leaves of *Oncoba spinosa*, Fengfang (*Nidus vespae*)	64-128 μg/ml [85], 1-4 mg/mL [114]
Kaempferol	Fengfang (*Nidus vespae*)	1-2 mg/mL [114]
Apigenin-7-O-β-D-glucuronopyranoside	The leaves of *Oncoba spinosa*	64-256 μg/mL [85]
Quercetin 3-O-β-D-galactopyranoside	The leaves of *Oncoba spinosa*	32-256 μg/mL [85]
2′-Hydroxyerythrin A	Soya beans	10.6-16.5 μg/mL [119]
Isoerythrinin A	Soya beans	15.2-22.6 μg/mL [119]
3′-O-methyldiplacol	Paotongguo (*Paulownia fortune*)	2-8 μg/mL [66]
Mimulone	Paotongguo (*Paulownia fortune*)	2-8 μg/mL [66]
Icariin	Yinyanghuo (*Epimedium*)	0.05%-0.23% [30]
Ethanol extract [a]	Youbingshiwei (*Pyrrosia petiolosa*)	1.25-10 mg/mL [10]
Ethyl acetate fraction [a]	Youbingshiwei (*Pyrrosia petiolosa*)	2.5 mg/mL [10]
Hydromethanolic extract of rhizome [a]	Ximalayadahuang (*Rehum emodi*)	25-125 μg/mL [120]
Petroleum ether fraction [a]	Youbingshiwei (*Pyrrosia petiolosa*)	2.5 mg/mL [10]
N-butanol fraction [a]	Youbingshiwei (*Pyrrosia petiolosa*)	1.25-5 mg/mL [10]
Ethyl acetate fraction [a]	Suanjiang (*Physalis alkekengi*)	500 μg/ml [88]
Aqueous fraction [a]	Youbingshiwei (*Pyrrosia petiolosa*)	2.5-5 mg/mL [10]
Ethanol extract [a]	Dingxiangye (*Folium syringae*)	0.65 mg/mL [121]
Hexane extracts [a]	Guizhencao (*Bidens pilosa*)	1.25-20 mg/mL [122]
Methanol extracts [a]	Guizhencao (*Bidens pilosa*)	2.5-20 mg/mL [122]
Ethanol extract [a]	Tufuling (*Smilax glabra*)	50-200 μg/ml [79]
Total flavonoids [a]	Qingma (*Abutilon theophrasti*)	0.06-1.02 g/mL [107]
Methanol extract [a]	Qinjiao (*Gentiana macrophylla*)	60-240 μg/mL [36]
Baicalin	Huangqin (*Scutellaria baicalensis*)	4 mg/ml [111], 1-2 mg/mL [64]
Baicalein	Huangqin (*Scutellaria baicalensis*)	0.125-0.5 mg/mL [64]
Wogonin	Huangqin (*Scutellaria baicalensis*)	0.5-2 mg/mL [64]
Oroxylin A	Huangqin (*Scutellaria baicalensis*)	0.125 mg/mL [64]
Norwogonin	Huangqin (*Scutellaria baicalensis*)	0.0625-0.25 mg/mL [64]
Nanoparticle-encapsulated [a]	Huangqin (*Scutellaria baicalensis*)	12.5 μg/mL [61]
Genistein	Unspecified	378 μg/mL [113]
Gentamicin [b]		0.5-2 μg/mL [107]
Metronidazole [b]		8 μg/mL [88]
Levofloxacin [b]		1.25-2.5 μg/mL [119]
Streptomycin [b]		15 ± 0.8 μg/mL [120]

Minimum inhibitory concentration (MICs); [a] mixture; [b] positive control.

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Table 3 Determination of the antioxidant capacity of flavonoids

Compounds	Plants/Sources	DPPH
		IC_{50} Value(μg/mL)
Quercetin	Xifanlian (*Passiflora loefgrenii*)	2.56 [82]
Total flavonoids [a]	Qingma (*Abutilon theophrasti*)	8.96 [107]，8.41 [107]，14.41 [107]
Ethanol extract [a]	Xifanlian (*Passiflora loefgrenii*)	350 [82]
Ethanol extract [a]	Mudanhua (*Paeonia suffruticosa*)	32.6 [21]
Dihydrokaempferol	Mudanhua (*Paeonia suffruticosa*)	24.6 [21]
Apigenin-7-O-β-D-glucoside	Mudanhua (*Paeonia suffruticosa*)	34.2 [21]
2′-Hydroxyerythrin A	Soya beans	28.5 ± 2.2 [119]
Daidzein-7-O-β-D-glycoside	Soya beans	> 50.0 [119]
7,4′-Dihydroxy-6-methoxyisoflavone	Soya beans	24.2 ± 1.5 [119]
Daidzein	Soya beans	31.3 ± 2.0 [119]
Genistein	Soya beans	13.6 ± 0.8 [119]
Apigenin-7-O-β-D-neohesperidoside	Mudanhua (*Paeonia suffruticosa*)	40.1 [21]
Kaempferol-7-O-β-D-glucopyranoside	Mudanhua (*Paeonia suffruticosa*)	35.3 [21]
Kaempferol-3-O-β-D-glucopyranosyl-7-O-β-D-glucopyranoside	Mudanhua (*Paeonia suffruticosa*)	20.9 [21]
Total flavonoids [a]	Yinyanghuo (*Epimedium*)	4.67 [30]
Trolox [b]		1.2 ± 0.1 [119]
2,6-Di-Tert-Butyl hydroxytoluene[b]		8.11 [107]

DPPH: 1,1-Diphenyl-2-picrylhydrazyl. [a] mixture; [b] positive control.

Table 4 IC_{50} values of flavonoids that inhibit the proliferation of tumor cell lines

Cell lines	Compounds	Plants/Sources	IC_{50}
SGC-7901	Total flavonoids [a]	Shuli (*Rhamnus davurica*)	89.53 ± 4.11 μg/mL [2]
	Cambodianal	Xuejie (*Daemonorops draco*)	5.0 μg/mL [80]
	Paclitaxel [b]		8.7 μg/mL [80]
	6,7,3’-Trimethoxy-3,5,4’-trihydroxy flavone	Luojingjinyao (*Chrysosplenium nudicaule*)	8.33 μg/mL [106]
HT-29	Total flavonoids [a]	Shuli (*Rhamnus davurica*)	24.96 ± 0.74 μg/mL [2]
PC-3	Total flavonoids extracted	Shiye (*Diospyros kaki*[a])	42.7 ± 6.1 μg/mL [83]
	Quercetin [b]		48.0 ± 5.4 μg/mL [83]
	Rutin [b]		49.2 ± 8.2 μg/mL [83]
	Docetaxel [b]		0.041 ± 0.005 μg/mL [83]
K562	Cambodianal	Xuejie (*Daemonorops draco*)	1.5 μg/mL [80]
	Paclitaxel [b]		7.3 μg/mL [80]
SMMC-7721	Cambodianal	Xuejie (*Daemonorops draco*)	2.8 μg/mL [80]
	Paclitaxel [b]		2.1 μg/mL [80]
A549	N-Butanol extract [a]	Shiwei (*Pyrrosia petiolosa*)	0.33 mg/mL [10]
SK-Hep-1	Genistein	Jixueteng (*Millettia reticulata*)	16.23 μmol/L [48]
HepG2	Bavachin	Buguzhi (*Psoralea corylifolia*)	24.4 μmol/L [46]
L-O2	Total flavonoids [a]	Shuli (*Rhamnus davurica*)	229.19 ± 8.52 μg/mL [2]

Promote apoptosis of tumor cells. Apoptosis, known as programmed cell death, is an autonomous and orderly procedure for death controlled by genes. Apoptosis not only participates in the regulation of the number of cells in the body but also can remove cells in the body that are not functional, cells that are harmful to the body, mutated cells, and cells that cannot survive after being damaged. Moreover, apoptosis plays an important role in the development and homeostasis of the body. Therefore, promoting the apoptosis of tumor cells can effectively inhibit the occurrence and development of tumors. There are three main apoptosis-related signal transduction pathways (Figure 2).

Mitochondria-mediated signal transduction pathway. Some scholars have found that the total flavonoids extracted from Shiye (*Diospyros kaki*) [83], 7-hydroxy-2',2'-dimethyl-2'H,4H-3,6'-bichromen-4-one [46], Baicalein [123], quercetin, and resveratrol [124] can reduce mitochondrial membrane potential, change the mitochondrial morphology, induce the production of large amounts of reactive oxygen species (ROS), reduce the ratio of B-cell lymphoma-2 (Bcl-2)/ Bcl-2 associated X protein (BAX), promote the release of cytochrome C from mitochondria, and then induce the activation of caspase-9 and caspase-3, followed by

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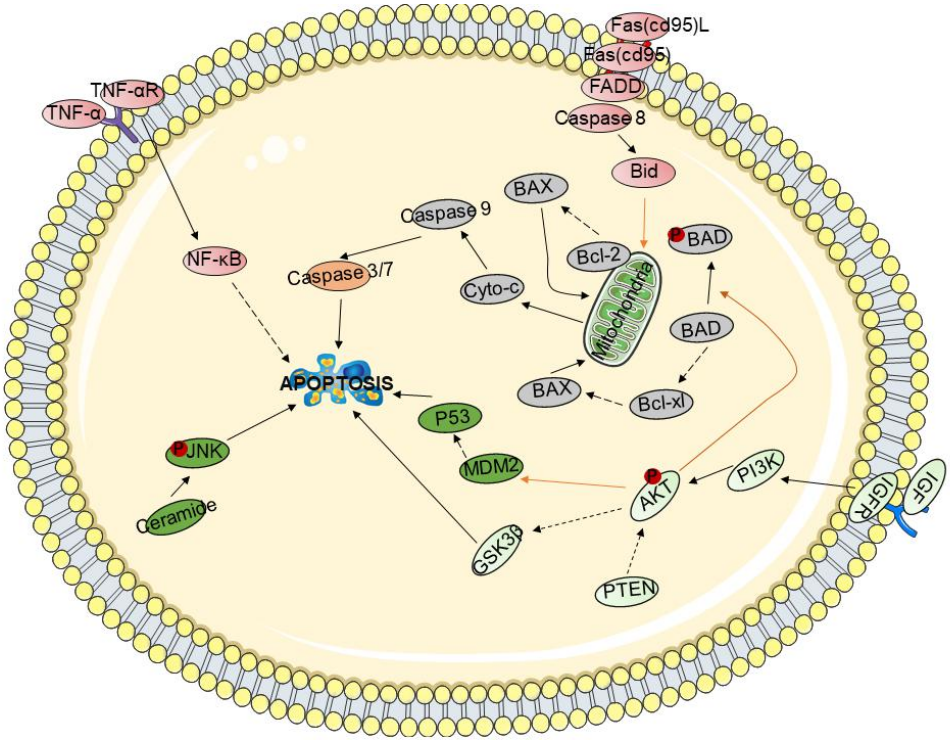

Figure 2 Schematic representation of the cell apoptosis signaling pathway

Shown are the extrinsic (receptor-mediated, red) and intrinsic (mitochondria-driven, gray) apoptosis pathways, which act in opposition to the survival proteins such as the PI3K/Akt signaling circuitry (light green). Other signaling loops (dark green) and executioner caspases (orange) are activated in both the extrinsic and intrinsic pathways; inter-talk between pathways (arrows) and the activation and suppression effects are indicated by solid arrows and dashed arrows, respectively.

cleavage of poly (ADP-ribose) polymerase (PARP), leads to DNA fragmentation and ultimately to tumor cell apoptosis. In addition, studies have reported that the combination of quercetin and resveratrol can affect the expression of mammalian target of rapamycin (mTOR), p-protein kinase B (Akt), p-mTOR, NF-κB, matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-2 (MMP-9), and TIMP-2 (tissue inhibitor of metalloproteinases-2) proteins, which may further enhance the antitumor activity of the drug by targeting mitochondria, Akt/mTOR, and NF-κB signaling pathways [124].

Endoplasmic reticulum-mediated signal transduction pathway. It has been shown in the literature that the treatment of HepG2 cells with 20 μmol/L Bavachin can activate activating transcription factor (ATF)4, the transcription factors CHOP(C/EBP-homologous protein) and X-box binding protein1 (XBP1), and protein kinase R-like ER kinase (PERK)-ATF4, inositol-requiring enzyme1(IRE1)-XBP1s, and ATF6. Three pathways induce endoplasmic reticulum stress. Bavachin induces endoplasmic reticulum stress by inducing PERK-ATF4, IRE1-XBP1s, and ATF6; moreover, the depletion of Mfn2 (mitochondrial fusion 2) aggravates ER stress by phosphorylating Akt, activating apoptosis-responsive proteins such as death receptors, and inducing tumor cell apoptosis [46].

Death factor and its receptor-mediated signal transduction pathway. Studies in the literature have shown that genistein can upregulate the expression of Fas, FasL, and p53 proteins in SK-Hep-1 cells, subsequently induced the activation of caspase-9 and caspase-3, which was followed by cleavage of PARP, leading to DNA fragmentation and ultimately to apoptosis [48]. Baicalin can block cells in G0/G1 phase; decrease mitochondrial membrane potential; activate caspase-3, caspase-8, and caspase-9; initiate FasL/Fas expression; and induce apoptosis significantly through internal and external sources. Moreover, the proto-oncogene *C-MYC* and its target gene, *hTERT* (human telomerase reverse transcriptase) are downregulated to inhibit telomerase activity, ultimately inhibiting the proliferation of tumor HL-60 cells [125]. Some scholars have found through miRNA microarray analysis that baicalin downregulates many oncomiRs such as miR-10a, miR-23a, miR-30c, miR-31, miR-151a, and miR-205 *in vitro* and *in vivo*, inhibiting *C-MYC* expression. It effectively promotes apoptosis in the HT-29 colon cancer cell line in dose- and time-dependent manners and inhibits tumor growth in corresponding transplanted nude mice [126].

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Antihypertensive effect

In one study, 26 mg/kg Epimedium flavonoids was injected into the lateral ventricle of mice, and epimedium flavonoids were found to increase the secretion of the amino acid neurotransmitter r-aminobutyric acid in the periventricular system and increase its affinity for receptors; strengthen the inhibition of the central sympathetic nervous system; expand coronary blood vessels, the femoral artery, and the cerebrovascular system; and reduce peripheral resistance, thus lowering blood pressure [30].

Reduce obesity

The occurrence and development of various diseases are related to obesity, and in recent years, the incidence of diabetes, hyperlipidemia, hypertension, and endocrine disorders in obese patients has increased significantly. Obesity has become an important cause of cardiovascular and cerebrovascular diseases, hypertension, and diabetes. Some scholars found that the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) increased the appetite and exercise volume of rats, but the weight of the rats was lower than that of untreated rats after 24 months. Moreover, the concentration of age-related metabolites returned to a level seen in younger animals; the amount of unsaturated fatty acids decreased; saturated fatty acids, deoxycholic acid, triglycerides, and total cholesterol increased; and their fur was smoother and more lustrous. These results suggest that the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) may have potential body weight controlling and anti-aging effects [117].

Role in liver protection

Dihydromyricetin can significantly improve the abnormal expression of cytochrome P450 2E1, Kelch-like ECH-binding protein 1, and heme oxygenase-1 in the liver of mice with alcoholic liver disease, improve the disordered nuclear localization of NF-κB and nuclear factor erythroid-2-related factor 2 (Nrf2), and play a role in liver protection. Further exploration of the mechanism revealed that dihydromyricetin may mediate the activation of Nrf2 via the autophagy pathway, upregulate p62 positive feedback Nrf2 activation, reduce inflammation in liver steatosis and the pathological progression of alcoholic liver disease, and partially restore liver pathological changes [127].

Neuroprotection

Some researchers have found that in mice, isobavachalcone can inhibit the excessive activation of microglia, reduce the expression of IL-6 and IL-1β in the brain of Parkinson's disease mice, prolong the residence time of mice on a Rota-rod, reduce neuronal necrosis, and effectively alleviate Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *In vitro* experiments showed that isobavachalcone inhibited NF-κB by blocking LPS-induced NF-κB subunit transfer from mouse microglia BV-2 cytoplasm to the nucleus, reduced the LPS-induced oxidative stress response to inflammatory cytokine expression, and protected nerves through antagonism [44].

Other effects

In one study, the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) (150 mg/kg) were administered to young rats by intraperitoneal injection for 7 days. It was found that the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) significantly increased the weight of the anterior pituitary, epididymis, and seminal vesicles in young rats; increased testosterone, estradiol, and luteinizing hormone levels; and promoted the secretion of testosterone by rat stromal cells [30]. In addition to promoting the male reproductive system and reproductive endocrine activity, the total flavonoids extracted from Yinyanghuo (*Epimedium brevicornu* Maxim) were shown to promote the proliferation of primary osteoblasts and osteoblast-like MAGR106 cells, enhance the extent of mineralized tuberculosis in vitro, and enhance the mRNA expression of *BMP-2*(human Bone morphogenetic protein 2), *BMP-4* (human Bone morphogenetic protein 4), *RUNX2* (runt-related transcription factor 2), *β-catenin*, and *cyclin D1*, as well as promote the osteogenic differentiation of human bone marrow mesenchymal stem cells [30]. Icariin can significantly increase the expression of eNOS (endothelial nitric oxide synthase) and cGMP in corpus cavernosum smooth muscle, inducing the relaxation of corpus cavernosum smooth muscle and penile erection [28]. Another study reported that baicalin increased the concentration of cAMP and AFC (alveolar fluid clearance) in a dose-dependent manner in rats with acute lung injury, and baicalin prevented the reduction of AFC by upregulating α-ENaC (α-epithelial Na+ channel) protein expression, which was activated by stimulating the cAMP/PKA (cyclic adenosine monophosphate/protein kinase A) signaling pathway [128].

Prospective

The structure of flavonoids in plants is diverse, and many plant families contain them. The research topics mentioned in this review include flavonoid monomer components, different polar extraction sites, and total flavonoids. Flavonoids have a variety of pharmacological effects, including anti-oxidation, antitumor, weight loss, antibacterial, antihypertensive, liver protective, anti-inflammatory, and

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neuroprotective activities. In short, plant-derived flavonoids are widely used as a bulk component, and whether the monomer is administered alone, monomers are administered in combination, or the total extract is administered directly, good effects have been obtained. However, the research on the mechanisms of the various activities of flavonoids is still in its infancy. Therefore, further studies are needed on the mechanisms by which flavonoids affect diseases and their long-term effects. Such studies will provide a sound scientific basis for the development and application of natural medicines, bringing relief to patients with various diseases.

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