REVIEW

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THERAPEUTIC AND PHYTOCHEMICAL POTENTIAL OF BIFLAVONOIDS- A COMPREHENSIVE REVIEW

K.P Jithamol*, Neethu Joseph, Bhagyalakshmi A.S

Dept. of Pharmaceutical Analysis, Chemists College of Pharmaceutical Science and Research, Varikoli,

\Puthencruz, Kochi-682308

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ABSTRACT:

Biflavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom. They represent a biosynthetically important group of natural products with significant biological activities. Although a wealth of biflavonoids have been discovered from various plant species, their biological and pharmacological data are limited. In this review we have attempted to describe the present status of their classification, pharmacological effects and their therapeutic potential.

KEY-WORDS: Biflavonoids, Chemistry, Pharmacology, Therapeutic potential

Corresponding author: **K. P. Jithamol**
Mob no: 994761446
Email id: kpjithamol@gmail.com

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INTRODUCTION:

Biflavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom. To date More than 100 biflavonoids have been identified from plants since the isolation of gingetin in 1929 [1, 2]. Biflavonoids comprise a group of the flavonoid family, that possess a variety of structures and biological activities of high relevance, such as anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antinociceptive, antioxidant, vasodilator and anticlotting. The chemistry of biflavonoids is very important in many fields of research, especially because these compounds are structurally different bioactive molecules with potential for biomedical applications. It has been reported that the class of biflavonoids represents a library of structurally diverse molecules, which remains to be fully exploited, since most of them have not yet been found in nature or else have not been synthesized or else its biological properties have not been described [3]. In this review we have attempted to describe the present status of their classification, pharmacological effects and their therapeutic potential.

STRUCTURE OF BIFLAVONOIDS:

Structurally biflavonoids are formed by the linkage of two flavonoids units. The biflavonoids vary considerably depending on the flavonoid units, point of linkage between the units and degree of methylation. The majority of the naturally occurring biflavonoids contain carbon-carbon linked monomers with any of the ring involved in the inter flavonoid linkage. The inter flavonoid linkage may exist between the two flavanone or flavones units, one flavanone and flavone or flavanonol, flavonols and flavanonol, isoflavones and flavones and two isoflavone units [4]. They are dimmers of C4-carbonyl flavonoids (i.e., chalcones, flavanones, flavones, flavanols, flavonols, aurones, and isoflavones) which vary at the oxygenation pattern of their monomers, oxidation level of the C_3 moiety, and interflavonyl linkage. The inter flavonyl linkage may involve the A ring (at positions 5, 6, 7, or 8), the B ring (at positions 2', 3', 4', 5', or 6') or the C ring (at positions 2 or 3), through C–C or C–O–C bonds [5, 6].

CLASSIFICATION OF BIFLAVONOIDS

Biflavonoids can be classified indicating the rings involved in the interflavonyl linkage (AA, BB, AB, CC, etc.). Most natural biflavonoids contain an interflavonyl linkage between the B-ring of one and the A-ring of the other flavonoid moiety (AB type) or between two A rings (AA type) and are widely distributed in Spermatophyta. The first isolated biflavonoid was ginkgetin, 1, by Furukawa in 1929 from Ginkgo biloba L. (a gymnosperm), (Fig. 1). [7–11] Also, cupressuflavone ([I-8, II-8]-biapigenin), 3, and robustaflavone, ([I-6, II-3']-biapigenin), 5, were isolated from different species of Gymnosperms. In Angiosperms, the following biflavonoids were isolated from Rhus succedanea (Anacardiaceae) and Garcinia multiflora (Guttiferae): robustaflavone, amentoflavone ([I-8, II-3']-biapigenin), 2 and agathisflavone ([I-6, II-8]-biapigenin), 4. Biflavonoids of the BC type are found in Angiosperms. Biflavonoids with a 3, 8'' interflavonyl linkage, 6, are often found in different species of Garcinia. Ochnaflavone, 7, and hinokiflavone, ([I-6-O-II-4']-biapigenin), 8, are examples **of** biflavonoids that contains C–O–C bonds. The interflavonyl linkage between the two B-rings (BB type) is less

common. In Gymnosperms, biflavonoids of this type are very rare. That is the case of 5', 5'''-bisdihydroquercetin, 9, which has been found only in the Douglas-fir (Pseudotsuga menziesii; Pinaceae) [12]. This type of biflavonoids can be found in mosses and ferns. For example, 3', 3'''-binaringenin, 10, was isolated from Homalothecium lutescens, [13] Selaginella chrysocaulos, [14] some species of Pilotrichella [15, 16] and Thuidium kanedae [17]. Examples of biflavonoids of the 3, 3'''-CC type are chamaejasmine, 11, and its derivatives[18–20].

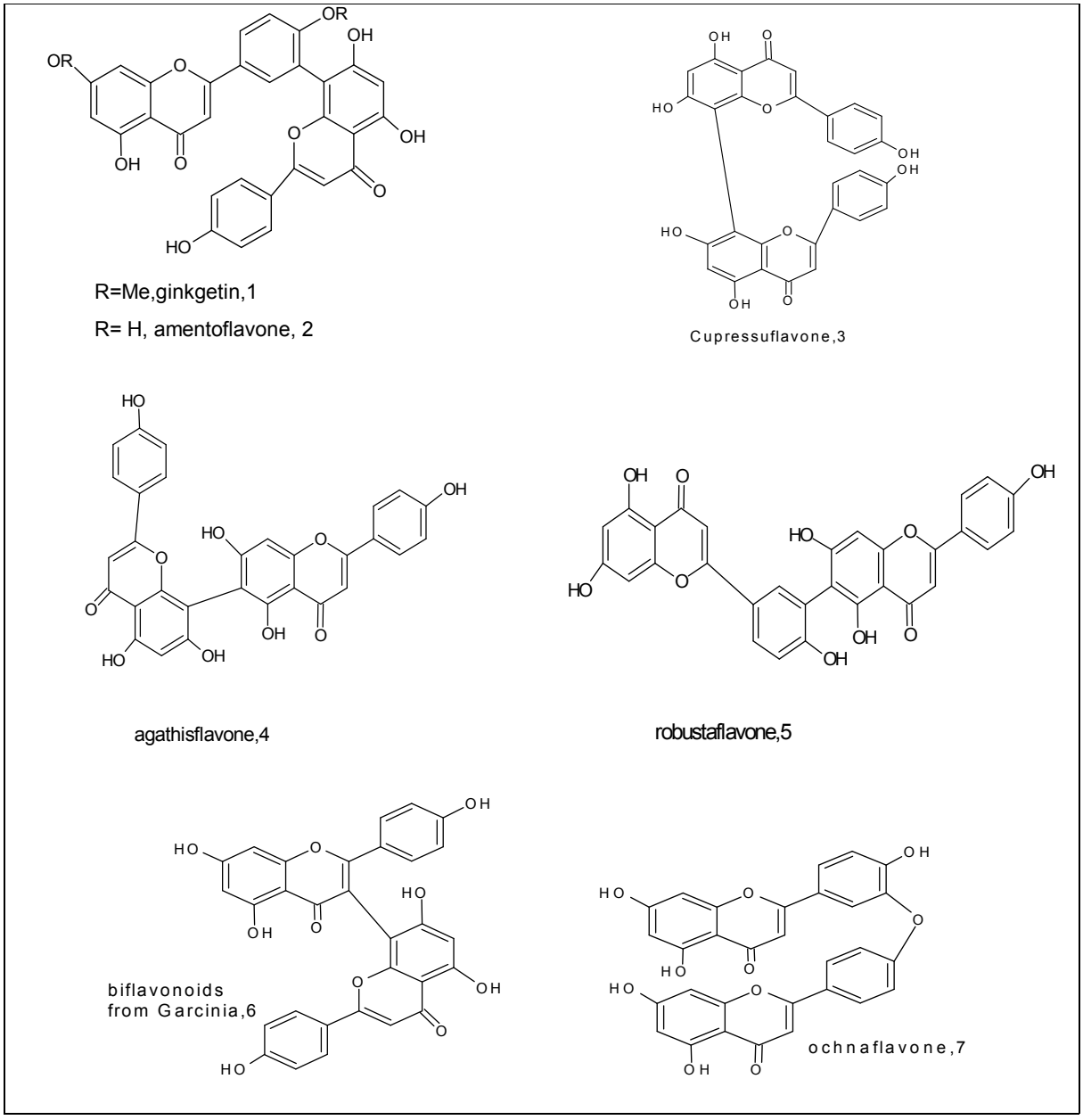

Figure 1: Some representative biflavonoids

PHARMACOLOGICAL EFFECTS OF BIFLAVONOIDS:

Biflavonoids display several biological activities, namely antifungal [21–23] antiviral, [24–26] antibacterial, [27,28] antioxidant, [29,30] antitumor, [24,31–35] antiplasmodial, [36] antiallergenic, anti inflammatory, [37,38] hepatoprotective, [39–41] vasodilating, [29,42,43] and hypotensive [26,43–46] activity, sometimes better than that of the corresponding monomers [22,37]. There is a renewed interest in the biological activities of biflavonoids, since, as stated by Rahman et al. in a recent review,6 'the theoretical library of biflavanoids spans a wide range of configurational and conformational space suggesting that possibilities of interesting biological activity are strong, each of which is capable of multiple H-bonding and hydrophobic interactions'. In a recent paper, Kim et al. reported [37] that not only naturally-occurring biflavonoids but also synthetic biflavonoids show antibacterial, antifungal and antiviral activity and there have only been a few trials to synthesize a biflavonoid library. In that sense, Chen et al., prepared a C–C biflavonoid library and showed that the anti-inflammatory activity depends on the position of the C–C linkage. Also, it was reported that some synthetic biflavonoids have anti-inflammatory activity [48, 49].

A variety of biological activities, such as peripheral vasodilation, stimulating RNA synthesis in rat hepatocyte suspensions, hypoglycemic effect, cytotoxicity against tissue cultured cells of human mouth epidermis carcinoma, inhibition of the expression of the Epstein- Barr virus (EBV) gene, inhibition of the interleukin-1β- induced expression of tissue factor on human monocytes, inhibitory effects on lipid peroxidation, anti-spasmodogenic, hepatoprotective, antimicrobial and antiviral activities have been reported for the different biflavonoids [50,51]. Biflavonoids were reported as antioxidants [52], antibacterial [53], anti-inflammatory [54], and anti –HIV [55].

CNS Activity:

Amentoflavone were shown to displace [3H] flumazenil binding to membranes from rat cerebellum. The binding of amentoflavone to the flumazenil site has previously been reported [56]. Another group reported amentoflavone to be a relatively weak negative allosteric modulator of GABA action acting independently the flumazenil binding site [57]. Thus the report shows that biflavonoids possess anxiolytic like properties. The biflavone rich fraction from A. bidwillii was found to protect rat brain against I/R induced oxidative stress, and attributable to its antioxidant properties. Amentoflavone, ginkgetin, and isoginkgetin exhibited strong neuroprotection against cytotoxic insults induced by oxidative stress and amyloid b, suggesting their therapeutic potential against neurodegenerative diseases, including ischemic stroke and Alzheimers disease.

Anti Oxidant And Lipid Lowering Activity:

Biflavonoids are powerful antioxidants against free radicals and are described as free-radical scavengers. This activity is attributed to their hydrogen-donating ability. Indeed, the phenolic groups of Biflavonoids serve as a source of a readily available ''H" atoms such that the subsequent radicals produced can be delocalized over the flavonoid structure [58].

Free radical scavenging capacity is primarily attributed to high reactivity of hydroxyl substituents that participate in the reaction [59] as shown in fig 2:

"Figure 2: Scavenging capacity of free radical (R.)"

Biflavonoids inhibit lipid peroxidation in vitro at an early stage by acting as scavengers of superoxide anion and hydroxyl radicals. They terminate chain radical reaction by donating hydrogen atom to a peroxy radical as in fig 3, thus, forming flavonoids radical, which, further reacts with free radicals thus terminating propagating chain [60, 61].

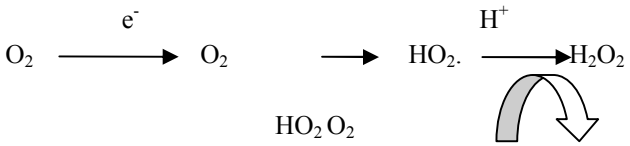

Figure 3: Formation of peroxy radical

Naturally, the organism has developed a defence against toxic substances such as peroxynitrite and nitrous acid. An important mechanism is catalyzed by the enzyme superoxide dismutase (SOD), which converts two superoxide anions to H2O2 and O2 [60] as shown in fig 4.

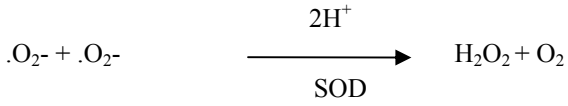

Figure 4: Mechanism catalysed by SOD

According to kinetic studies of aroxyl radical formation and decomposition reactions, the antioxidant capacity of a biflavonoid is linked to its three structural groups [58] as shown in fig 15.

1. The ortho-dihydroxy (catechol) structure in the B-ring, which confers greater stability to aroxyl radicals, possibly through hydrogen bonding, and which participates in electron dislocation.
2. The 2, 3-double bond, in conjugation with a 4-oxo function, responsible for electron dislocation from the B-ring.
3. The presence of both 3-(a)-and 5-(b)-hydroxyl groups (Fig.5(c)).

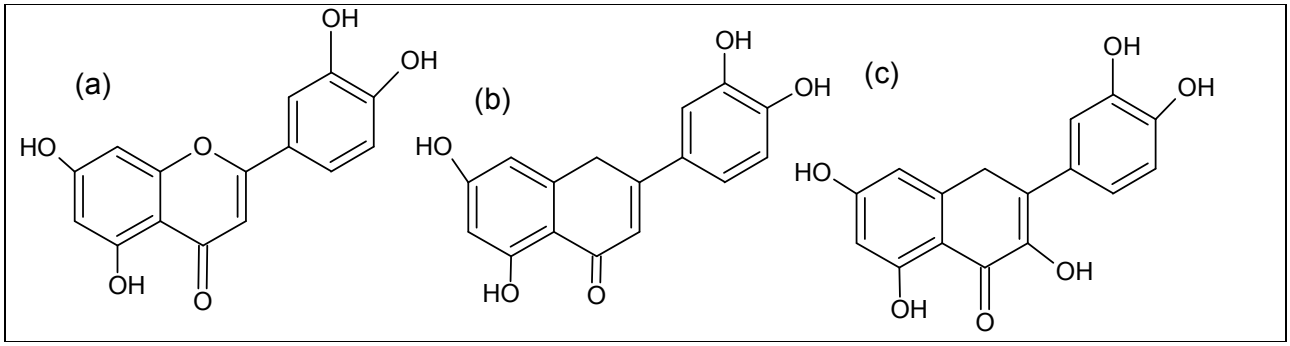

Figure 5: Structural groups responsible for antioxidant activity

3', 4'-catechol structure in B-ring strongly enhances lipid peroxide inhibition and this arrangement is an important characteristic of most potent scavengers of peroxyl, superoxide and peroxynitrite radicals [59] and its absence decreases antioxidant activity. The absence of the hydroxyl group at position 3 in flavanones and flavones decreases their antioxidant ability [58].

Biflavonoids in Treatment of Cancer:

Biflavonoids are potent bioactive molecules that possess anti carcinogenic effects since they can interfere with the initiation, development and progression of cancer by the modulation of cellular proliferation, differentiation, apoptosis, angiogenesis and metastasis [62] as shown in fig 6.

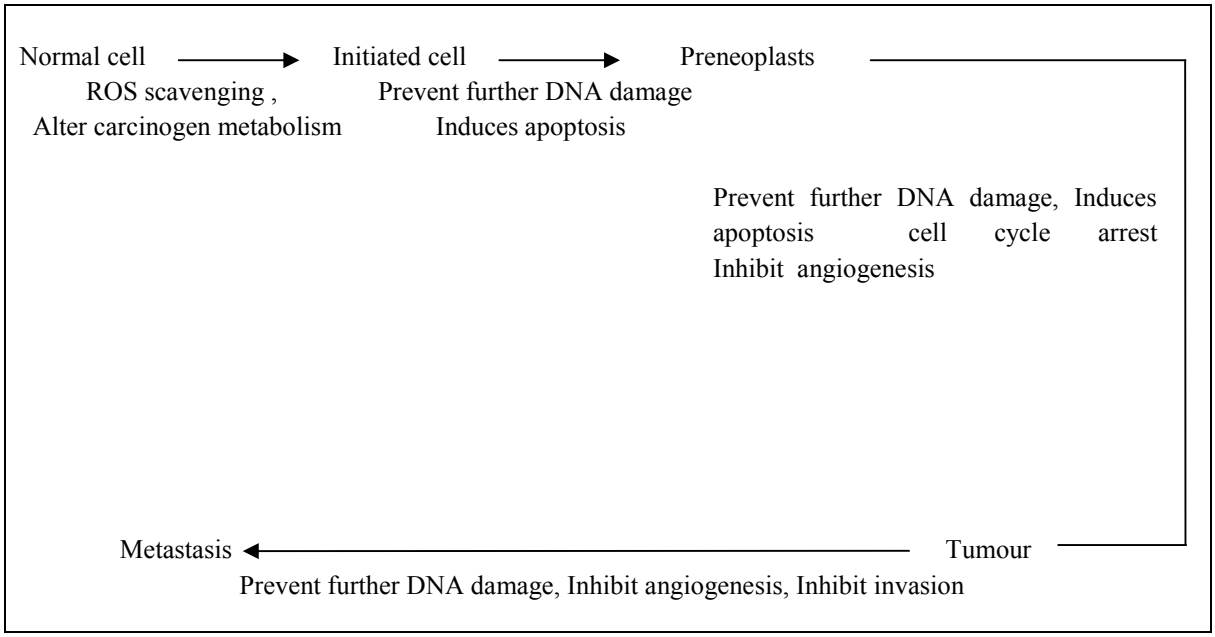

Figure 6: Multistage of carcinogenesis and potential effects of polyphenols on cancer progression

Biflavonoids 7, 7"-dimethyllanaraflavone, agathisflavone, and 7²-methylagathisflavone from *Ouratea hexasperma* (leaves) have been found to possess cytotoxic and antitumor activitiesas well as the ability to inhibit DNA topoisomerases [63]. Amentoflavone, a biflavonoid from Selaginella tamariscina, is known to possess several bioactivities such as antitumor, anti-inflammatory, and antifungal effects. However, the mechanism of the anticancer effects of amentoflavone on human cervical cancer cells has not been studied in detail. In the study, demonstrated that amentoflavone induces apoptosis in SiHa and CaSki cervical cancer cells by suppressing human papillomavirus protein E7 expression [64].

Anti-inflammatory activity:

Inflammation is the integrated response of many defence systems of the body to the invasion of a foreign body. Inflammation involves action of the complement system, blood coagulation, humoral and cellular immunity, cytokines, tissue hormones,

angiogenesis, and repair processes. It is both a free radical generating and free-radical producing process. Biflavonoids were described such as inhibition of histamine release from mast cells and inhibition of lymphocyte proliferation, suggesting the anti-inflammatory/antiallergic potential of the biflavonoids. Furthermore, several natural biflavonoids including ochnaflavone and ginkgetin inhibit phospholipase A_2. Most importantly, certain biflavonoids exhibit anti-inflammatory activity through the regulation of proinflammatory gene expression *in vitro* and *in vivo*. Recently, several synthetic approaches yielded new biflavonoid molecules with anti-inflammatory potential. These molecules also exhibit phospholipase A_2 and cyclooxygenase-2 inhibitory activity. Although the bioavailability needs be improved, certain biflavonoids may have potential as new anti-inflammatory agents [66].

A number of biflavonoids are reported to possess anti-inflammatory activity. Volkensiflavone, I3-naringenin-II8-eriodictyol (GB-2a), GB-1a, fukugetin [67] and fukugiside [68, 69], possesses significant anti inflammatory and analgesic effects. In contrast to other class of flavonoids, studies on the anti inflammatory activities of biflavonoids are limited [70]. Certain biflavonoids were previously reported to inhibit mast cell histamine release and lymphocyte poliferation [71]. Several biflavonoids such as amentoflavone, onchaflavone and gingetin were found to inhibit group II secretory phospholipase A_2 [72]. Morelloflavone, a flavone-flavonone dimmer, was also found as a phospholipase A2 inhibitor [73]. Importantly, certain natural biflavonoids such as ginkgetin exerted inhibitory activity against COX-2 mediated PGE_2 production [74].

Hepatoprotective activity:

Many biflavonoids have also been found to possess hepato-protective activity. Kolaviron, GB1, GB2 and agathisflavone investigated for their anti hepatoprotective activities. Their anti hepatotoxic properties have been evaluated using four experimental toxins, namely carbon tetrachloride, galactosamine, alpha-amanitin and phalloidin. Kolaviron, a fraction of the defatted ethanol extract, and two biflavones of Garcinia kola seeds (GB1 and GB2) significantly modified the action of all these hepatotoxins. At 100 mg/kg orally, the test substances reduced thiopental-induced sleep in CCl4-poisoned rats. The microsomal enzyme levels in the serum of mice poisoned with phalloidin were significantly protected by treatment with Garcinia extractives [75]. The biflavonoid agathisflavone from Canarium manii (Burseraceae) is reported in doses 50.0 mg and 100.0 mg orally exhibited dose-dependent hepatoprotective activity against experimentally-induced carbon tetrachloride-hepatotoxicity in rats and mice [76].

Antimicrobial activity

Biflavonoids investigated for their antibacterial, antifungal and antiviral activities. All samples were active against the fungal and gram-positive bacterial test strains and most showed antiviral activity.

Antibacterial Activity:

Antibacterial activity has been displayed by a number of biflavonoids. Amentoflavone and 4' mono methoxy amentoflavone from Garcinia livingstonei leaves had good activities (MIC 6 and 8 µg/ml) against some nosocomial bacteria [77]. Volkensiflavone, fukugetin, fukugiside, GB2a-I-7-*O*-glucoside and epicatechin from *Rheedia gardneriana* were reported as good antibacterial agents [78].

Antifungal Activity:

The antifungal activity of biflavones from T. baccata and Ginkgo biloba, namely amentoflavone, 7-O-methylamentoflavone, bilobetin, ginkgetin, sciadopitysin and 2, 3-dihydrosciadopitysin towards the fungi Alternaria alternata, Fusarium culmorum, Cladosporium oxysporum was reported [79].

Antiviral Activity:

Recent investigations of antiviral compounds have suggested that biflavonoids may be a group of compounds which cause powerful inhibition to a broad spectrum of viral pathogens. The incidence and severity of HSV-related pathologies have increased recently and the illness is usually more severe in patients with reduced cellular immunity, as in bone marrow transplant recipients or patients with acquired immunodeficiency syndrome (AIDS), who receive treatments with antiviral agents that may result in the selection of resistant variants.

"Table 1: Antibacterial, antifungal and antiviral activity of various flavonoids"

Organism	Biflavonoids	plant	References
Antibacterial activity Mycobacterium smegmatis	Amentoflavone and 4'monomethoxy amentoflavone	Garcinia livingstonei	77
Staphylococcus aureus	calodenin B and dihydrocalodenin B	Ochna macrocalyx	80
Enterobacter cloaceae, E. aerogenes Pseudomonas aeruginosa	Bartramiaflavone.	mosses	81
brine shrimp larvae	volkensiflavone, fukugetin, fukugiside , GB2a-I-7-*O*-glucoside and epicatechin	*Rheedia gardneriana*	78
Staphylococcus aureus	tetrahydroisoginkgetin	*Cycas circinalis* and *Cycas revoluta*	82
Antiviral activities			83
influenza A and B viruses	volkensiflavone , hexamethyl ether , rhusflavanone hexa acetate, succedaneflavanone hexaacetate	*Garcinia multiflora*	
Respiratory syncytial virus (RSV)	Genkwanol B, genkwanol C and stelleranol, which are	Radix Wikstroemiae	84

Antifungal Activity Alternaria alternata, Fusarium culmorum, Cladosporium oxysporum	stereo isomers of spirobiflavonoids, Bilobetin and 4-O-methylamentoflavone	**Taxus baccata and Ginkgo biloba**	79

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