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Review

Proceedings of Chemistry, Pharmacology, Pharmacokinetics and Synthesis of Biflavonoids

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Abstract: Biflavonoids, composed of two monoflavonoid residues, occur naturally in angiosperms, bryophytes, ferns, and gymnosperms. More than 592 biflavonoids have been structurally elucidated, and they can be classified into two groups of C-C and C-linear fragments-C, based on whether the linker between the two residues contains an atom. As the linker can be established on two arbitrary rings from different residues, the C-C type contains various subtypes, as does the C-linear fragment-C type. Biflavonoids have a wide range of pharmacological activities, including anti-inflammatory, antioxidant, antibacterial, antiviral, antidiabetic, antitumor, and cytotoxic properties, and they can be applied in Alzheimer's disease and Parkinson's disease. This review mainly summarizes the distribution and chemistry of biflavonoids; additionally, their bioactivities, pharmacokinetics, and synthesis are discussed.

Keywords: biflavonoids; chemistry; pharmacology; pharmacokinetics; synthesis

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1. Introduction

Flavonoids, one of the main classes of secondary metabolites in plants, and have representative scaffolds as flavones, chalcones, isoflavones, aurones, and xanthones. Biflavonoids, as members of the flavonoid family, are comprised of two monoflavonoids by a direct connection, or a linear linker. In 2017, Gontijo et al., summarized 139 biflavonoids and their medical applications [1]. In the same year, Sheng Yu et al. [2] also reviewed the phytochemistry, pharmacology, and pharmaceutics of amentoflavone in biflavonoids, including a comprehensive description and summary of the source and current situation of amentoflavone derivatives. It is known that amentoflavone can be obtained from different parts of 127 plants, 45 kinds of derivatives that belong to the same type of connection with amentoflavone. The pharmacological effects of amentoflavone are summarized, including its anti-inflammatory, antioxidation, antitumor, antiaging, antidiabetes, antiviral, central nervous, cardiovascular system, antifungal, and other pharmacological effects. The amentoflavone family is recorded in detail.

In this report, 592 biflavonoids, as well as their distribution, structural scaffolds, and chemical subtype are reviewed. In addition, the pharmacology and synthesis of biflavonoids are summarized.

2. Distribution of Biflavonoids

A total of 592 biflavonoids are widely distributed in angiosperms, ferns, gymnosperms, and bryophytes, but most of them are found in angiosperms, including: Anacardiaceae, Apiaceae, Aristolochiaceae, Asteraceae, Balsaminaceae, Berberidaceae, Caprifoliaceae, Chloranthaceae, Clusiaceae (especially Garcinia), Daphniphyllaceae, Ephedraceae, Ericaceae, Euphorbiaceae, Gentianaceae, Juglandaceae, Lanariaceae, Leguminosae, Liliaceae, Lythraceae, Menispermaceae, Moraceae, Myrtaceae, Ochnaceae, Polygonaceae, Rosaceae,

Rubiaceae, Theaceae, Thymelaeaceae, Velloziaceae, and Vitaceae. The vast majority of biflavonoids are come from Clusiaceae, Thymelaeaceae, Ochnaceae, and Selaginellaceae, which account for approximately 50% of the biflavonoids in all families. The standard names of the plant families are from The Plant List (2013), which was published in http://www.theplantlist.org/ (accessed on 21 October 2020).

3. The Scaffold of Biflavonoids

In these 592 biflavonoids, according to the C6-C3-C6 combination pattern, flavan (A), flavone (B), anthocyanidin (C), isoflavan (D), isoflavone (E), neoflavan (F), chalcone (G), aurone (H), and xanthone (I) were the main monoflavonoid scaffolds. According to the different monomer combination types, 592 biflavonoids were divided into 17 kinds, including: AA (flavan-flavan), AB (flavan-flavone), AC (flavan-anthocyanidin), AD (flavan-isofalvan), AE (flavan-isoflavone), AG (flavan-chalcone), AH (flavan-aurone), BB (flavone-flavone), BD (flavone-isoflavan), BE (flavone-isoflavone), BG (flavone-chalcone), CC (anthocyanidin-anthocyanidin), EE (isoflavone-isoflavone), EG (isoflavone-chalcone), FF (neoflavan-neoflavan), GG (chalcone-chalcone), HH (aurone-aurone), and II (xanthone-xanthone) (Figure 1). Among them, AA type biflavonoids are abundant in natural plants, and have good development prospects.

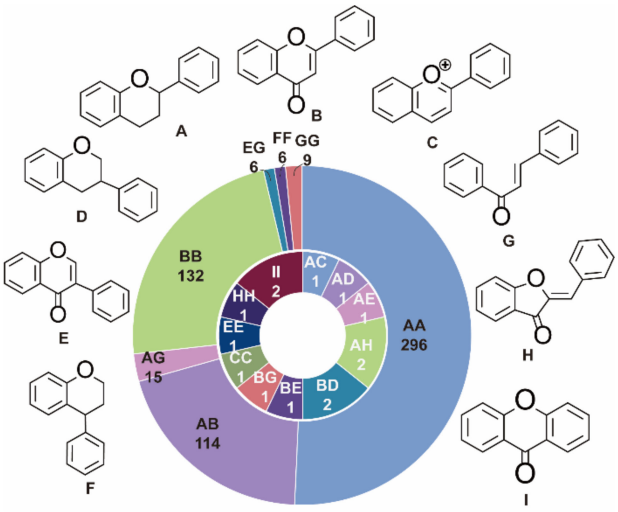


Figure 1. The scaffold of biflavonoids.

4. Subtypes of Biflavonoids

4.1. C-C Type

According to the connection mode of biflavonoids, they are divided into three major groups.

Group A is about C-C linkages (Tables 1–8); C-C type biflavonoids have a large number, so they can according the positions of their combinations, divide into: 2-3″, 2′-2‴, 2′-6″, 2′-8″, 3-3″, 3-3‴, 3′-3‴, 3′-4‴,3′-5″, 3-6″, 3′-6″, 3-7″, 3′-7″, 3-8″, 3′-8″ , 4-6″, 4-8″, 4′-8″, 5-5″, 6-6″, 6-γ, 6-8″, 7-7″, and 8-8″.

The detailed data about subtypes, No., monomer types, origin families and references of 2-3″, 2′-2‴, 2′-6″, 2′-8″, 3-3″ type biflavonoids were showed in Table 1, the structure of them were drew in Figure 2.

Table 1. The 2-3″, 2′-2‴, 2′-6″, 2′-8″, and 3-3″ subtypes of biflavonoids.

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
2-3″	**1**	Linobiflavonoid	AH	Thym	[1]
2′-2‴	**2**	I-3,II-3,I-5,II-5,I-7,II-7,I-4′,II-4′-octahydroxy[I-2′,II-2′]biflavone	BB	Clus	[3]
	3	I-3,II-3,I-5,II-5,I-7,II-7,I-4′,II-4′-octamethoxy[I-2′,II-2′]biflavone	BB	Clus	[3]
	4	3,3″-di-*O*-α-L-rhamnopyranoside,2′,2‴-bimyricetin	BB	Myrt	[4]
	5	Acuminatanol	AA	Anac	[5]
	6	Theasinensin A	AA	Thea	[6]
	7	Theasinensin B	AA	Thea	[6]
2′-6″	**8**	2′,6″-Biapignin	BB	Sela	[7]
2′-8″	**9**	2′,8″-Biapignin	BB	Sela	[7]
3-3″	**10**	Chamaejasmine	AA	Thym, Legu	[8]
	11	7-methoxychamaejasmin	AA	Thym	[8]
	12	Ruixianglangdu B	AA	Thym	[8]
	13	Isosikokianin	AA	Thym	[8]
	14	7,4′,7″,4″-tetramethylisochamaejasmin	AA	Ochn	[9]
	15	7,7″-di-*O*-methylchamaejasmin	AA	Legu	[10]
	16	Campylospermone A	AA	Ochn	[10,11]
	17	Campylospermone B	AA	Ochn	[11]
	18	Isochamaejasmine	AA	Thym	[12]
	19	7,7″-di-*O*-glucosylisochamaejasmin	AA	Thym	[13]
	20	Neochamaejasmin A	AA	Thym	[8]
	21	Chamaejasmenin B	AA	Thym	[8]
	22	Chamaejasmenin C	AA	Thym	[8]
	23	Sikokianin A	AA	Thym	[8]
	24	7-methoxyneochamaejasmin A	AA	Thym	[8]
	25	Chamaejasmenin D	AA	Thym	[8]
	26	Isoneochamaejasmin A	AA	Thym	[8]
	27	Isochamaejasmine B	AA	Thym	[8]
	28	Neochamaejasmin B	AA	Thym	[8]
	29	Sikokianin B	AA	Thym	[12]
	30	Chamaejasmenin A	AA	Thym	[8]
	31	Sikokianin C	AA	Thym	[8,12]
	32	Ruixianglangdu A	AA	Thym	[8]
	33	Isosikokianin A	AA	Thym	[8]
	34	Asteryomenin	AA	Aste	[14]
	35	Wikstaiwanone C	AA	Thym	[12]
	36	Sikokianin D	AA	Thym	[15]
	37	2‴-dehydroxy-2,2″-bisteppogenin	AA	Thym	[1]
	38	2,2″-bisteppogenin 7-*O*-β-glucopyranoside	AA	Thym	[1]
	39	2,2″-bisteppogenin	AA	Thym	[1]
	40	Apigenil-(I-3,II-3)-naringenin	AA	Legu	[1]
	41	6-aminoacryloylchamaejasmin	AA	Legu, Thym	[1,16]
	42	Ormocarpin	AA	Legu	[1,13,17]
	43	(−)-7,7″-di-*O*-glucosylchamaejasmin	AA	Legu	[1,13]
	44	(−)-(2S, 3S, 2″S, 3″R)-7-*O*-glucosylchamaejasmin	AA	Legu	[1]
	45	(2S, 3R, 2″S, 3″R)-7-*O*-glucosylchamaejasmin	AA	Legu	[1,17]
	46	Campilospermone B	AA	Ochn	[1]
	47	Neochamaejasmin C	AA	Thym	[1]
	48	7-methoxyneochamaejasmin B	AA	Thym	[1]
	49	2‴-dehydroxy-2,2″-bisteppogenin 7-*O*-β-glucopyranoside	AA	Thym	[1]
	50	3″-epidiphysin	FF	Legu	[1]
	51	5,5″-di-*O*-methyldiphysin	FF	Legu	[1,17]
	52	Diphysin	FF	Legu	[1]
	53	2,3-didehydro-(+)-chamaejasmin	AA	Thym	[16]
	54	3,3′-biliquiritigenin	AA	Ochn, Legu	[17]
	55	Euchamaejasmin A	AA	Thym	[18]

Table 1. *Cont.*

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
	56	7-*O*-β-D-glucopyranoside-diphysin	FF	Legu	[17]
	57	3-Epimer, 5,5′-dideoxy-diphysin	FF	Anac	[19]
	58	3,3′-diepimer, 5,5′-dideoxy-diphysin	FF	Anac	[19]
	59	6‴-hydroxylophirone	AG	Ochn	[20]

* Anac: Anacardiaceae; Aste: Asteraceae; Clus: Clusiaceae; Legu: Leguminosae; Myrt: Myrtaceae; Ochn: Ochnaceae; Sela: Selaginellaceae; Thea: Theaceae; and Thym: Thymelaeaceae.

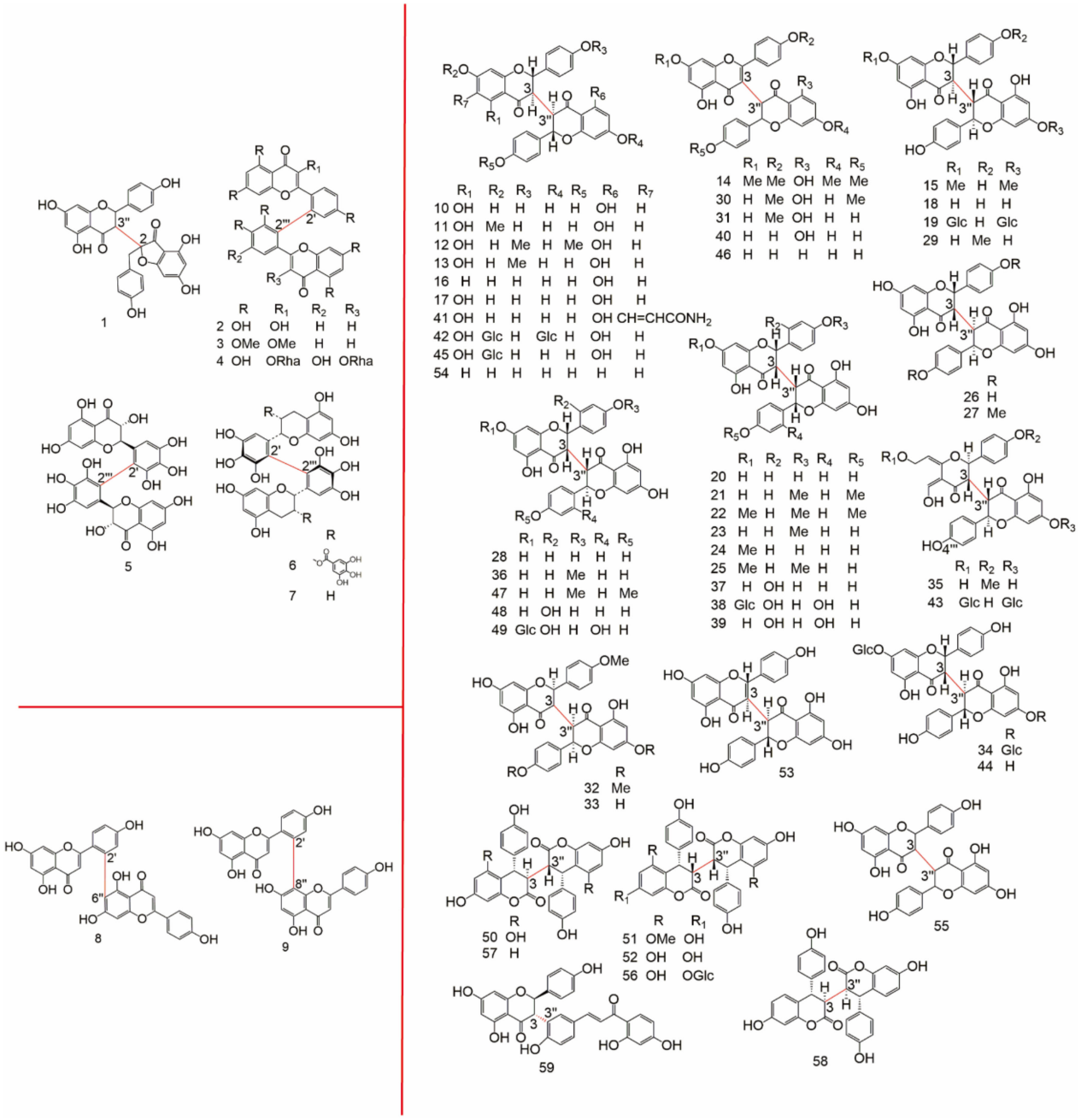


Figure 2. The structure of 2-3″, 2′-2‴, 2′-6″, 2′-8″, and 3-3″ type.

The detailed data of 3-3‴, 3′-3‴, 3′-4‴,3′-5″, 3-6″, 3′-6″, 3-7″, 3′-7″ type biflavonoids were showed in Table 2, the structure of them were drew in Figure 3.

Table 2. The 3-3‴, 3′-3‴, 3′-4‴, 3′-5″, 3-6″, 3′-6″, 3-7″, and 3′-7″ subtypes of biflavonoids.

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
3-3‴	**60**	Taiwaniaflavone	BB	Cupr, Sela, Taxo	[21–23]
	61	7-*O*-methyltaiwaniaflavone	BB	Taxo	[23]
	62	4‴,7-di-*O*-methyltaiwaniaflavone	BB	Taxo	[23]
	63	Lupinabisone A	AB	Legu	[24]
3′-3‴	**64**	2,3-dihydro-3′,3‴-biapigenin	BB	Sela	[7]
	65	3′,3″-binaringenin	BB	Sela	[7,25]
	66	Thuidinin	BB	Thui	[25]
	67	Kudzuisoflavone A	EE	Faba	[26]
3′-4‴	**68**	Chrysocauloflavone III	AB	Sela	[7]
	69	Japoflavone D	BB	Capr	[27]
3′-5″	**70**	Aulacomniumbiaureusidin	HH	Aula	[28]
3-6″	**71**	Daphnodorin K1	AB	Thym	[29]
	72	Daphnodorin K2	AB	Thym	[29]
	73	Wikstaiwanone A	AB	Thym	[12]
	74	Wikstaiwanone B	AB	Thym	[12]
	75	Stephaflavone A	BB	Meni	[30]
	76	Stephaflavone B	BB	Meni	[30]
	77	Isomanniflavone	AA	Clus	[1]
	78	Ridiculuflavone	BB	Aris	[1]
	79	Afzelone B	AA	Ochn	[31]
	80	Ridiculuflavone A	BB	Aris	[32,33]
	81	Ridiculuflavone B	BB	Aris	[32,33]
	82	Ridiculuflavone D	BB	Aris	[32]
	83	Ridiculuflavone C	BB	Aris	[32]
	84	4‴,5,5″,7″-tetrahydroxy-3‴,4′,7-trimethoxy-3,6″-biflavone	BB	Aris	[32,34]
3′-6″	**85**	Robustaflavone	BB	Anac, Arau, Clus, Sela	[35,36]
	86	7″-*O*-methylrobustaflavone	BB	Sela	[7]
	87	4′-*O*-methylrobustaflavone	BB	Sela	[7,35,37]
	88	7,4′-di-*O*-methylrobustaflavone	BB	Sela	[7,38]
	89	4′,4‴-di-*O*-methylrobustaflvone	BB	Sela	[7,39]
	90	4′,7″-di-*O*-methylrobustaflavone	BB	Sela	[7,37]
	91	7,4′,4‴-tri-*O*-methylrobustaflvone	BB	Sela	[7,39]
	92	Imbricataflavone A	AB	Podo, Sela	[7,35,40]
	93	Caesalflavone	AB	Legu, Sela	[7,41,42]
	94	Uncinatabiflavone D	AB	Sela	[7,43,44]
	95	7,4′,7″-tri-*O*-methyl-2,3-dihydrorobustaflavone	AB	Sela	[7,39]
	96	5-*O*-methyl-2,3-dihydrorobustaflavone	AB	Sela	[7,42]
	97	Macrophylloflavone	AB	Sela	[45]
	98	2,3-dihydrorobustaflavone 7,7″-dimethyl ether	AB	Sela, Thym	[1]
	99	Imbricataflavone B	AB	Podo	[40]
	100	4′-*O*-methyl-2″,3″-dihydrorobustaflavone	AB	Sela, Thym	[7,43]
	101	7,4′-di-*O*-methyl-2″,3″-dihydrorobustaflvone	AB	Arau, Sela, Thym	[7,37]
	102	4′,7″-di-*O*-methyl-2″,3″-dihydrorobustaflavone	AB	Arau, Sela, Thym	[36]
	103	7,4′,7″-tri-*O*-methyl-2″,3″-dihydrorobustaflavone	AB	Sela, Thym	[7,37]
	104	Robustaflavanone	AA	Sela, Thym	[7,38]
	105	Uncinatabiflavone A	AA	Sela	[7,43,44]
	106	Uncinatabiflavone B	AA	Sela	[7,43,44]
	107	Uncinatabiflavone C	AA	Sela	[7,43,44]
	108	7,4′,7″-tri-*O*-methyl-2,3,2″,3″-tetrahydrorobustaflavone	AA	Sela	[7,35]
	109	Abiesin	BB	Pina	[46]
	110	5′-hydroxyrobustaflavone	BB	Hylo	[47]
	111	2″,3″-dihydro-5‴-hydroxyrobustaflavone	AB	Mnia	[48]
	112	5′,6″-biluteolin	BB	Hylo, Dicr	[49]

Table 2. *Cont.*

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
	113	2,3-dihydro-5′,6″-biluteolin	AB	Dicr	[49]
	114	2″,3″-dihydro-5′,6″-biluteolin	AB	Mnia	[50]
3-7″	**115**	5,5″,6″,7,8-pentahydroxy-2,2″-bis(p-hydroxyphenyl)-4H,4″H(3,7″-bichromene)-4,4″-dione	BB	Anac	[51]
3′-7″	**116**	Lophirone M	AB	Ochn	[52]
	117	Lophirone M hexa-acetate	AB	Ochn	[52]

* Aula: Aulacomniaceae; Arau: Araucariaceae; Aris: Aristolochiaceae; Capr: Caprifoliaceae; Cupr: Cupressaceae; Faba: Fabaceae; Meni: Menispermaceae; Podo: Podocarpaceae; Taxa: Taxaceae; Taxo: Taxodiaceae; and Thui: Thuidiaceae.

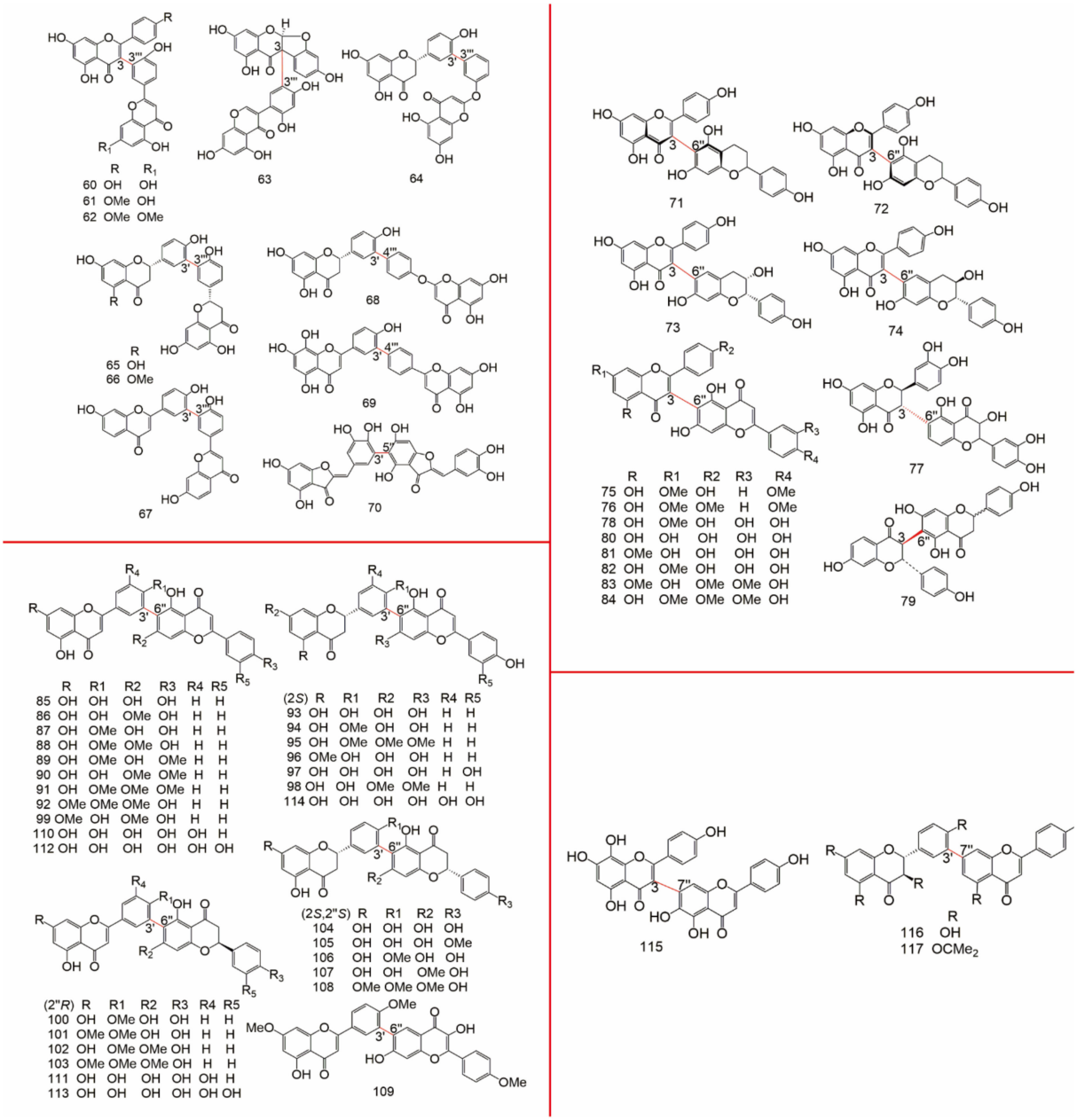


Figure 3. The structure of 3-3‴, 3′-3‴, 3′-4‴,3′-5″, 3-6″, 3′-6″, 3-7″, and 3′-7″type.

The data of 3-8″ type biflavonoids were showed in Table 3, the structure of them were drew in Figure 4.

Table 3. The 3-8″ subtype of biflavonoids.

No.	Compounds Name	Monomer Type	Origin (Family *)	References
118	Garciniaflavone E	AB	Clus	[1]
119	Garciniaflavone F	AB	Clus	[1]
120	Morelloflavone-7″-*O*-β-D-glucosíde	BB	Clus	[1]
121	(+)-4‴-*O*-methylmorelloflavone	AB	Clus	[1]
122	Biapigenin	BB	Clus	[1]
123	4‴-*O*-methyl-I3,II8-binaringenin	AA	Clus	[1,53]
124	Volkensiflavone	AB	Clus	[54]
125	Morelloflavone	AB	Clus	[55]
126	Spicataside	AB	Clus	[55]
127	Fukugiside	AB	Clus	[55]
128	3‴-*O*-methylfukugetin	AB	Clus	[1]
129	Garcinianin	AB	Clus	[55–57]
130	Madrunoudeaside	AB	Clus	[58]
131	Morelloflavone-7′-sulfate	AB	Clus	[59]
132	(2R,3S)-morelloflavone	AB	Mora	[60]
133	7,4′,7″,3‴,4‴-penta-*O*-acetylmorelloflavone	BB	Mora	[60]
134	7,4′,7″,3‴,4‴-penta-*O*-methylmorelloflavone	BB	Mora	[60]
135	7,4′,7″,3‴,4‴-penta-*O*-butanoylmorelloflavone	BB	Mora	[60]
136	Talbotaflavone	BB	Clus	[1,61]
137	Balsamiside A	AB	Bals	[62]
138	Balsamiside B	AB	Bals	[62]
139	Balsamiside C	AB	Bals	[62]
140	Balsamiside D	AB	Bals	[62]
141	Daphnodorin D1	AB	Thym	[29]
142	Daphnodorin D2	AB	Thym	[29]
143	Wikstrol A	AB	Thym	[63]
144	Wikstrol B	AB	Thym	[63]
145	II-3,I-5, II-5,II-7,I-4′,II-4′-hexahydroxy-(I-3,II-8)-flavonylflavanonol	BB	Clus	[1]
146	GB-1a	AA	Clus	[54,64]
147	GB-2a	AB	Clus	[65]
148	GB-1a-7″-*O*-glycoside	AA	Clus	[55]
149	Xanthochymuside	AA	Clus	[55,66]
150	Kolaflavanone	AA	Clus	[55,64]
151	GB-1	AA	Clus	[55,64]
152	GB-2	AA	Clus	[55,64]
153	Manniflavanone	AA	Clus	[54,64]
154	GB-2a-II-4′-OMe	BB	Clus	[65]
155	Buchananiflavone	AA	Clus	[1,67]
156	Manniflavone-7″-*O*-β-D-glucopyranoside	AB	Clus	[1]
157	(2R,3S,2″R)3,8″-binaringenin-7″-*O*-β-glucoside	AA	Clus	[1,68]
158	(2R, 3S, 2″R, 3″R)GB1-7″-*O*-β-glucoside	AA	Clus	[1,68]
159	Ent-naringenil-(I-3α,II-8)-4′-*O*-metilnaringenin	BB	Clus	[1,53]
160	3,8″-biapigenin	BB	Poly, Clus	[69,70]
161	Sumaflavone	BB	Anac	[7,71]
162	4′-methoxydaphnodorin D1	AB	Thym	[72]
163	4′-methoxydaphnodorin D2	AB	Thym	[72]
164	Pancibiflavonol	AB	Clus	[73]
165	Volkensiflavone 7-sulfate	AB	Clus	[74]
166	8-(3′,4′,5,7-tetrahydroxyflavanon-3-yl)-4′,5,7-trihydroxyflavone	AB	Clus	[75]
167	GB-3	AA	Clus	[64]
168	GB-4	AA	Clus	[76]
169	GB-2b	AA	Clus	[64]
170	GB-4a	AA	Clus	[76]
171	4‴-*O*-methylfukugetin	AB	Clus	[77]
172	Lupinalbisone B	AB	Legu	[24]

* Bals: Balsaminaceae; Dicr: Dicranaceae; Hylo: Hylocomiaceae Mnia: Mniaceae; Mora: Moraceae; Poly: Polygonaceae; and Pina: Pinaceae.

The data of 3′-8″ type biflavonoids were showed in Table 4, the structure of them were drew in Figure 5.

Table 4. The 3′-8″ subtype of biflavonoids.

No.	Compounds Name	Monomer Type	Origin (Family *)	References
173	Amentoflavone	BB	Anac, Capr, Clus, Cupr, Gink, Pina, Podo, Pter, Sela, Taxa, Taxo	[2]
174	Isoginkgetin	BB	Gink, Sela	[2,7]
175	3′,8″-biisokaempferide	BB	Pter, Vell	[1,2]
176	7,7″-di-*O*-methylamentoflavone	BB	Arau, Cupr, Podo, Sela, Taxo	[2,7]
177	4′,7″-di-*O*-methylamentoflavone	BB	Arau, Sela, Taxo	[2,7]
178	5′-methoxybilobetin	BB	Gink, Mnia	[2]
179	7,4,7″,4‴-tetra-*O*-methylamentoflavone	BB	Sela	[2,7]
180	7,4′,7″-tri-*O*-methylamentoflavone	BB	Arau, Ceph, Cupr, Taxa	[2]
181	Acetyl ginkgetin	BB	Gink	[78]
182	Acetyl isogenkgetin	BB	Gink	[78]
183	Acetyl sciadopitysin	BB	Gink	[78]
184	6-C-methyl-7-*O*-methylamentoflavone	BB	Ceph	[79]
185	3‴-hydroxy-4‴,7-dimethylamentoflavone	BB	Aris, Taxa	[80]
186	Anacarduflavone	BB	Anac	[81]
187	Bilcarobetin	BB	Gink, Sela	[2,7]
188	CGY-1	BB	Lili	[82]
189	Ginkgetin	BB	Arau, Gink, Sela, Taxa, Taxo	[2,7]
190	Ginkgetin 7-*O*-D-glucopyranoside	BB	Gink	[83]
191	Heveaflavone	BB	Euph, Sela	[2,7]
192	7-*O*-gluamentoflavone	BB	Cupr, Gink	[84]
193	Isoginkgetin 7-*O*-D-glucopyranoside	BB	Gink	[83]
194	Amentoflavone 7″-*O*-β-D-glucopyranoside	BB	Cupr, Gink	[84]
195	Kayaflavone	BB	Podo, Sela, Taxa, Taxo	[2,7]
196	Oliveriflavone	BB	Taxa	[79]
197	Oliveriflavone B	BB	Taxa	[85]
198	Oliveriflavone C	BB	Taxa	[85]
199	Podocarduflavone B	BB	Podo	[2]
200	Podocarpusflavone A	BB	Podo, Sela	[2,7]
201	Sciadopitysin	BB	Cupr, Gink, Podo, Taxa, Taxo	[2]
202	Sequoiaflavone	BB	Sela, Taxo	[2,7]
203	Sotetsuflavone	BB	Cyca, Sela, Taxo	[2,7]
204	Taiwaniaflavone A	BB	Ceph	[2]
205	Dulcisbiflavonoid A	BB	Clus	[59]
206	Putraflavone	BB	Euph, Podo	[1]
207	(2S,2″S)-2,3-di-hydroisoginkgetin	AB	Cyca	[86]
208	2,3-dihydro-6-methylginkgetin	AB	Ceph	[1]
209	2,3-dihydrosciadopitysin	AB	Gink, Taxo	[83]
210	4′,7″-di-*O*-methyl-2,3-dihydroamentoflavone	AB	Sela	[7]
211	(2S)-2,3-dihydroamentoflavone	AB	Sela	[7]
212	7,4′-di-*O*-methyl-2,3-dihydroamentoflavone	AB	Cupr, Sela	[7]
213	7,4′,7″-tri-*O*-methyl-2,3-dihydroamentoflavone	AB	Arau, Sela, Taxa	[7]
214	2,3-dihydro-4-*O*-methylamentoflavone	AB	Cyca, Sela	[87]
215	(2S)-4′-*O*-methyl-2,3-tetrahydroamentoflavone	AB	Cyca, Sela	[7]
216	Garciniaflavone A	AB	Clus	[1,2]
217	Garciniaflavone B	AB	Clus	[1,2]
218	Garciniaflavone C	AB	Clus	[1,2]
219	Garciniaflavone D	AB	Clus	[1,2]
220	6″-hydroxy-2,3-dihydroamentoflavone	AB	Sela	[7]
221	Selamariscina A	AB	Sela	[36]

Table 4. *Cont.*

No.	Compounds Name	Monomer Type	Origin (Family *)	References
222	2″,3″-dihydroamentoflavone	AB	Anac, Cyca, Sela, Taxo	[7]
223	4′-*O*-methyl-2″,3″-dihydroamentoflavone	AB	Cyca, Sela	[1,7]
224	(2S,2″S)-2,3,2″,3″-tetrahydroisoginkgetin	AA	Arau, Cyca, Podo	[86]
225	(2S,2″S)-2,3,2″,3″-tetrahydroamentoflavone	AA	Anac, Cyca, Sela	[7,86]
226	(2S,2″S)-4′-*O*-methyl-2,3,2″,3″-tetrahydroamentoflavone	AA	Sela	[7]
227	Taxusbiflavone A	BB	Capr	[88]
228	3‴-methoxyamentoflavone	BB	Anac	[89]
229	3‴,5′-dihydroxyamentoflavone	BB	Dicr	[49]
230	(2S,2″S)-3′,4′,4‴,5,5″,7″-hexahydroxy-8,3‴-biflavanone	AA	Anac	[81]
231	3′,5,5″-trihydroxy-4′,4‴,7″-trimethoxy-8,3‴-biflavanone	AA	Anac	[90]
232	5,5″-dihydroxy-3′,4′,4‴,7″-tetramethoxy-8,3‴-biflavanone	AA	Anac	[91]
233	Anacarduflavanone	AA	Anac	[92]

* Capr: Caprifoliaceae; Ceph: Cephalotaxaceae; Cyca: Cycadaceae; Euph: Euphorbiaceae; Gink: Ginkgoaceae; Lili: Liliaceae; Pter: Pteridiaceae; and Vell: Velloziaceae.

The data of 4-6″ type biflavonoids were showed in Table 5, the structure of them were drew in Figure 6.

Table 5. The 4-6″ subtype of biflavonoids.

No.	Compounds Name	Monomer Type	Origin (Family *)	References
234	Sarcandrone D	AA	Chlo	[1]
235	Procyanidin B5	AA	Dava, Malv, Pina, Rosa, Sapi	[93,94]
236	Epicatechin 3-*O*-gallate-(4β→6)-epicatechin 3-*O*-(4-hydroxybenzoate)	AA	Myro	[95]
237	3′-*O*-galloylprocyanidin B5	AA	Vita	[95,96]
238	3,3′-di-*O*-galloylprocyanidin B5	AA	Poly	[97]
239	Epigallocatechin 3-*O*-gallate-(4β→6)-epicatechin 3-*O*-gallate	AA	Thea	[98]
240	Epicatechin 3-*O*-gallate-(4β→6)-epigallocatechin 3-*O*-gallate	AA	Thea	[98]
241	Epigallocatechin-(4β→6)-epigallocatechin 3-*O*-gallate	AA	Cist	[99]
242	3,3′-di-*O*-galloylprodelphinidin B5	AA	Myri	[100]
243	Epiafzelechin 3-*O*-gallate-(4β→6)-epigallocatechin 3-*O*-gallate	AA	Thea	[98]
244	Procyanidin B6	AA	Cupr, Eric, Rosa	[93]
245	Procyanidin B7	AA	Cupr, Eric	[93]
246	Procyanidin B8	AA	Eric, Rosa, Sali	[93]
247	Ent-epicatechin-(4α→6)-ent-epicatechin	AA	Malp	[101]
248	Fisetinidol-(4β→6)-fisetinidol-4β-ol	AA	Legu	[102]
249	Fisetinidol-(4β→6)-fisetinidol	AA	Legu	[103]
250	Fisetinidol-(4β→6)-fisetinidol-4α-ol	AA	Legu	[102]
251	Fisetinidol-(4β→6)-ent-epifisetinidol	AA	Legu	[103]
252	Fisetinidol-(4α→6)-fisetinidol-4β-ol	AA	Legu	[102]
253	Fisetinidol-(4α→6)-fisetinidol	AA	Legu	[103]
254	Fisetinidol-(4α→6)-fisetinidol-4α-ol	AA	Legu	[102]
255	Fisetinidol-(4α→6)-ent-epifisetinidol	AA	Legu	[103]
256	Globiflorin 3B1	AA	Legu	[104]
257	Globiflorin 3B2	AA	Legu	[104]
258	Guibourtinidol-(4α→6)-afzelechin	AA	Legu	[105]
259	ent-Guibourtinidol-(4β→6)-catechin	AA	Rosa	[106]
260	Epicatechin-(4β→6)-epicatechin-(4β→2)-phloroglucinol	AA	Legu, Pina, Rosa	[107–109]
261	Guibourtinidol-(4α→6)-epicatechin-8-carboxylic acid	AA	Legu	[104]
262	Guibourtinidol-(4α→6)-catechin-8-carboxylic acid	AA	Legu	[104]
263	Epioritin-(4β→6)-epioritin-4α-ol	AA	Legu	[110]

Table 5. *Cont.*

No.	Compounds Name	Monomer Type	Origin (Family *)	References
264	Epioritin-(4β→6)-epioritin-4β-ol	AA	Legu	[110]
265	Epioritin-(4β→6)-oritin-4α-ol	AA	Legu	[111]
266	Epioritin-(4β→6)-ent-oritin-4α-ol	AA	Legu	[110]
267	Ent-Oritin-(4β→6)-epioritin-4α-ol	AA	Legu	[110]
268	Ent-Oritin-(4α→6)-epioritin-4α-ol	AA	Legu	[111]
269	Ent-Oritin-(4α→6)-epioritin-4β-ol	AA	Legu	[111]
270	Ent-Oritin-(4β→6)-oritin-4α-ol	AA	Legu	[110]
271	Ent-Oritin-(4α→6)-oritin-4α-ol	AA	Legu	[111]

* Chlo: Chloranthaceae; Cist: Cistaceae; Dava: Davalliaceae; Eric: Ericaceae; Malv: Malvaceae; Malp: Malpighiaceae; Myri: Myricaceae; Myro: Myrothamnaceae; Rosa: Rosaceae; Sali: Salicaceae; and Sapi: Sapindaceae.

The data of 4-8″ type biflavonoids were showed in Tables 6 and 7, the structure of them were drew in Figure 7.

Table 6. The 4-8″ subtype of biflavonoids.

No.	Compounds Name	Monomer Type	Origin (Family *)	References
272	Juglbiflavone A	AB	Jugl	[112]
273	Sarcandrone	AA	Chlo	[1]
274	Procyanidin B2	AA	Aizo, Rosa, Sapi	[94,113,114]
275	Procyanidin B2 7′-xyloside	AA	Legu	[115]
276	3′-galloylprocyanidin B2	AA	Poly,Vita	[6]
277	3,3′-digalloylprocyanidin B2	AA	Poly, Thea, Rosa	[6,114]
278	3′-*O*-(3,4-di-*O*-methylgalloyl)procyanidin B2	AA	Poly	[94]
279	Epicatechin-(4α→8)-epicatechin	AA	Rosa	[116]
280	Procyanidin B1	AA	Legu	[114]
281	3′-(4-hydroxybenzoyl)procyanidin B1	AA	Hama	[117]
282	3-galloylprocyanidin B1	AA	Poly	[114,118]
283	3′-*O*-(1-hydroxy-6-oxo-2-cyclohexene-1-carboxylate)procyanidin B1	AA	Sali	[119]
284	Procyanidin B4	AA	Rosa	[113]
285	3-*O*-β-D-glucopyranoside, 3′-*O*-(6-*O*-E-cinnamoyl-β-D-glucopyranoside)Procyanidin B4	AA	Legu	[120]
286	3′-galloylprocyanidin B4	AA	Euph	[6]
287	Procyanidin B3	AA	Sali	[113,121]
288	3-rhamnoside-procyanidin B3	AA	Faga	[122]
289	3-glucoside-procyanidin B3	AA	Faga	[122]
290	3-*O*-β-D-glucopyranoside, 3′-*O*-(2-*O*-E-cinnamoyl-β-D-glucopyranoside)procyanidin B3	AA	Legu	[120]
291	Procyanidin B3 3′-rhamnoside	AA	Faga	[122]
292	Procyanidin B3 3′-*O*-glucoside	AA	Rosa	[123]
293	Procyanidin B3 7-glucoside	AA	Poly	[124]
294	Catechin-(4α→8)-catechin 7-xyloside	AA	Betu	[125]
295	3-galloylprocyanidin B3	AA	Rosa	[126]
296	3,3′-di-Ac-3‴-*O*-β-D-glucopyranoside procyanidin B3	AA	Poly	[127]
297	3′-*O*-(1-Hydroxy-6-oxo-2-cyclohexene-1-carboxylate)procyanidin B3	AA	Sali	[119]
298	Epicatechin-(4β→8)-ent-epicatechin	AA	Arec	[128]
299	Ent-epicatechin-(4α→8)-epicatechin	AA	Arec	[128]
300	Ent-epicatechin-(4α→8)-catechin	AA	Arec	[128]
301	Ent-epicatechin-(4α→8)-ent-epicatechin	AA	Arec	[128]
302	3-*O*-(3,4,5-trihydroxybenzoyl)ent-epicatechin-(4α→8)-ent-epicatechin	AA	Malp	[101]
303	3′-*O*-(3,4,5-trihydroxybenzoyl)ent-epicatechin-(4α→8)-ent-epicatechin	AA	Malp	[101]
304	3,3′-bis-*O*-(3,4,5-trihydroxybenzoyl)ent-epicatechin-(4α→8)-ent-epicatechin	AA	Malp	[101]
305	Auricassidin	AA	Legu	[129]

Table 6. *Cont.*

No.	Compounds Name	Monomer Type	Origin (Family *)	References
306	3,3′,4′,5,7-pentahydroxyflavan-(4→8)-3,4′,5,7-tetrahydroxyflavan	AA	Legu	[130]
307	Epicatechin-(4β→8)-epiafzelechin	AA	Legu	[131,132]
308	Catechin-(4α→8)-epiafzelechin	AA	Legu	[133]
309	Epicatechin-(4β→8)-ent-epiafzelechin	AA	Legu	[134]
310	Ent-epicatechin-(4α→8)-epiafzelechin	AA	Legu	[134]
311	Ent-epicatechin-(4α→8)-ent-epiafzelechin	AA	Legu	[134]
312	Epiguibourtinidol-(4β→8)-epicatechin	AA	Legu	[135]
313	Guibourtinidol-(4β→8)-epicatechin	AA	Legu	[105]
314	Guibourtinidol-(4β→8)-epiafzelechin	AA	Legu	[105]
315	Guibourtinidol-(4α→8)-epicatechin	AA	Legu	[104]
316	Guibourtinidol-(4α→8)-epiafzelechin	AA	Legu	[105]
317	Guibourtinidol-(4β→8)-catechin	AA	Legu	[104]
318	Guibourtinidol-(4α→8)-catechin	AA	Legu	[104]
319	Calodenin C	AA	Legu	[136]
320	Ent-guibourtinidol-(4β→8)-epicatechin	AA	Legu	[105]
321	Epiafzelechin-(4β→8)-epicatechin	AA	Legu, Poly	[134,137]
322	3′-*O*-(3,4,5-trihydroxybenzoyl)epiafzelechin-(4β→8)-epicatechin	AA	Poly	[137]
323	3,3′-bis-*O*-(3,4,5-trihydroxybenzoyl)epiafzelechin-(4β→8)-epicatechin	AA	Poly	[137]
324	Ouratea proanthocyanidin A	AA	Cela, Ochn	[138]
325	Ouratea proanthocyanidin B	AA	Cela, Ochn	[138]
326	Epiafzelechin-(4ξ→8)-epicatechin	AA	Poly	[94]
327	3′-*O*-(4-hydroxybenzoyl)epiafzelechin-(4ξ→8)-epicatechin	AA	Poly	[94]
328	3′-*O*-(3-hydroxy-4,5-dimethoxybenzoyl)epiafzelechin-(4ξ→8)-epicatechin	AA	Poly	[94]
329	Gambiriin C	AA	Rubi	[139]
330	Afzelechin-(4α→8)-epicatechin	AA	Rhiz	[140]
331	3′-*O*-(4-hydroxy-3-methoxybenzoyl), 3-*O*-α-L-rhamnopyranoside-afzelechin-(4α→8)-epicatechin	AA	Euph	[141]

* Arec: Arecaceae; Aizo: Aizoaceae; Betu: Betulaceae; Faga: Fagaceae; Hama: Hamamelidaceae; Jugl: Juglandaceae; and Vita: Vitaceae.

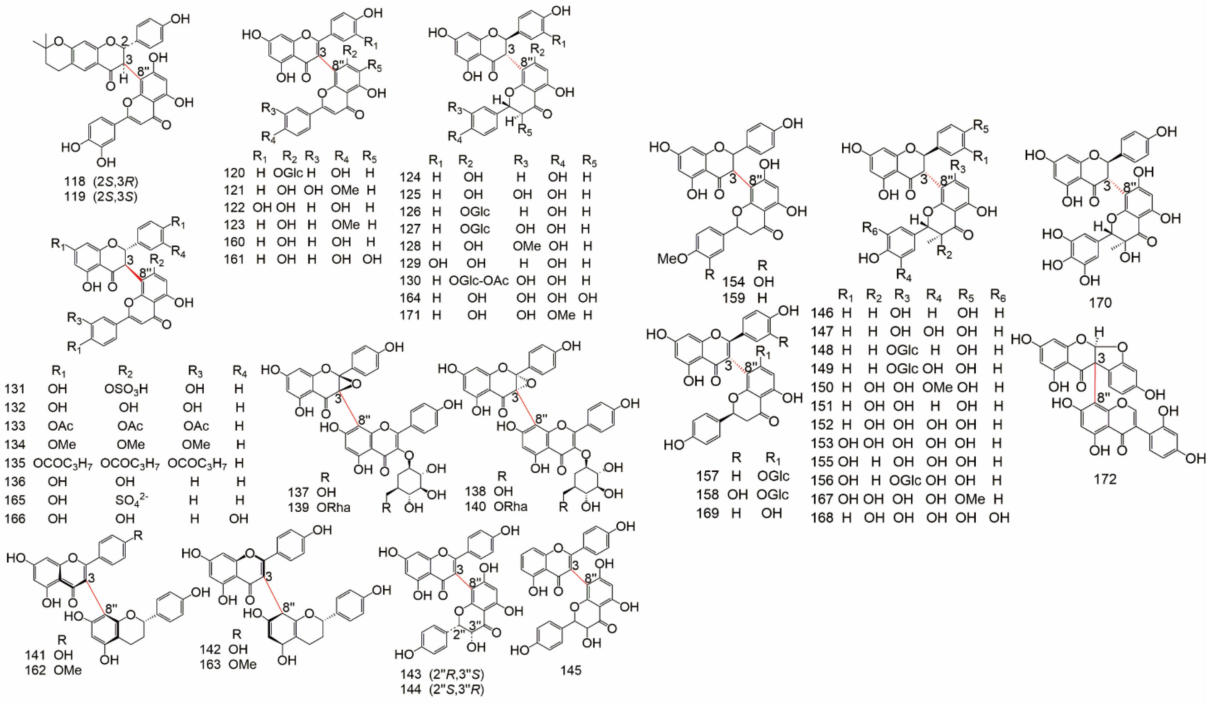


Figure 4. The structure of 3-8″ type biflavonoids.

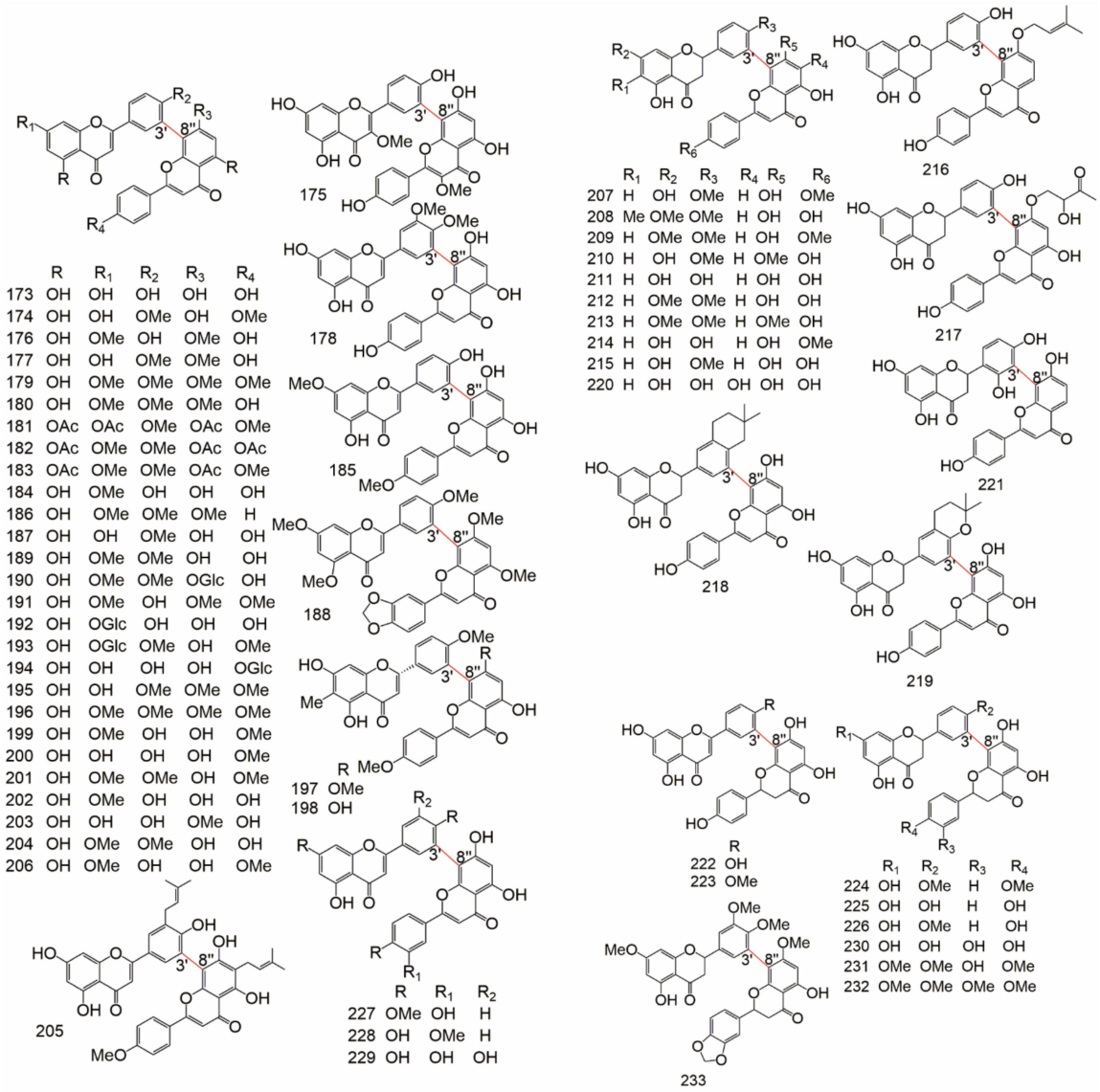


Figure 5. The structure of 3′-8″ type biflavonoids.

Table 7. The 4-8″ subtype of biflavonoids.

No.	Compounds Name	Monomer Type	Origin (Family *)	References
332	3′-*O*-(4-hydroxy-3,5-dimethoxybenzoyl), 3-*O*-α-L-rhamnopyranoside-afzelechin-(4α→8)-epicatechin	AA	Euph	[141]
333	afzelechin-(4α→8)-catechin	AA	Rhiz, Rosa	[121,140]
334	3-*O*-α-L-rhamnopyranoside-afzelechin-(4α→8)-catechin	AA	Faga	[142]
335	3-*O*-β-D-glucopyranoside-afzelechin-(4α→8)-catechin	AA	Faga	[142]
336	Epiafzelechin-(4β→8)-ent-epicatechin	AA	Legu	[132]
337	Ent-epiafzelechin-(4α→8)-epicatechin	AA	Legu	[132]
338	Ent-epiafzelechin-(4α→8)-ent-epicatechin	AA	Legu	[134]
339	Ichangol	AA	Adox	[143]
340	Epicatechin-(4β→8)-epicatechin-(4β→2)-phloroglucinol	AA	Legu, Pina	[109,144]
341	Epigallocatechin-(4β→8)-epicatechin-(4β→2)-phloroglucinol	AA	Legu	[109]
342	Epigallocatechin-(4β→8)-epigallocatechin-(4β→2)-phloroglucinol 3,3′-digallate	AA	Cist	[145]
343	Catechin-(4α→8)-epicatechin-(4β→2)-phloroglucinol	AA	Pina	[144]
344	Gallocatechin-(4α→8)-epigallocatechin-(4β→2)-phloroglucinol	AA	Cist	[145]

Table 7. *Cont.*

No.	Compounds Name	Monomer Type	Origin (Family *)	References
345	Epirobinetinidol-(4β→8)-catechin	AA	Legu	[146]
346	Robinetinidol-(4β→8)-epigallocatechin	AA	Mimo	[147]
347	Robinetinidol-(4β→8)-epigallocatechin-3′-gallate	AA	Mimo	[147]
348	Robinetinidol-(4α→8)-epigallocatechin	AA	Mimo	[147]
349	Robinetinidol-(4α→8)-epigallocatechin-3′-gallate	AA	Mimo	[147]
350	Robinetinidol-(4β→8)-catechin	AA	Legu	[148]
351	Robinetinidol-(4α→8)-gallocatechin	AA	Legu	[149]
352	Robinetinidol-(4α→8)-catechin	AA	Legu	[149]
353	Prodelphinidin B2	AA	Phyl, Legu, Myri	[100]
354	3′-*O*-(4-hydroxybenzoyl)prodelphinidin B2	AA	Legu	[150]
355	3-*O*-galloylprodelphinidin B2	AA	Cist, Poly	[99,151]
356	3′-galloylprodelphinidin B2	AA	Cist, Myri, Thea	[6,99,100, 152]
357	Rhodisin	AA	Myri, Cras	[100,153]
358	Rhodisinoside	AA	Cras	[153]
359	Epicatechin-(4β→8)-epigallocatechin-3-*O*-gallate	AA	Thea	[98]
360	Epicatechin-3-*O*-gallate-(4β→8)-epigallocatechin-3-*O*-gallate	AA	Thea	[98]
361	Epicatechin-(4β→8)-4′-*O*-methylepigallocatechin	AA	Cela	[154]
362	Epigallocatechin-(4β→8)-epicatechin-3-*O*-gallate	AA	Thea	[155]
363	Prodelphinidin B1	AA	Cist, Legu	[150,156]
364	3-galloylprodelphinidin B1	AA	Cist, Hama	[117,156]
365	3,3′-digalloylprodelphinidin B1	AA	Myri	[100]
366	Epigallocatechin-(4β→8)-4′-*O*-methylgallocatechin	AA	Legu	[157]
367	Epicatechin-(4β→8)-gallocatechin	AA	Phyl	[158]
368	Epicatechin-(4β→8)-4′-*O*-methylgallocatechin	AA	Legu	[157]
369	Epigallocatechin-(4β→8)-catechin	AA	Legu, Pina	[117,159]
370	3‴-Deoxy, 3-*O*-(3,4,5-trihydroxybenzoyl)epigallocatechin-(4β→8)-catechin	AA	Hama	[117]
371	Prodelphinidin B4	AA	Thea, Phyl, Gros	[160]
372	Gallocatechin-(4α→8)-epigallocatechin-3-*O*-(4-hydroxybenzoate)	AA	Mimo	[150]
373	3′-galloylprodelphinidin B4	AA	Thea	[98]
374	4″,4‴-di-me ether-prodelphinidin B4	AA	Legu	[150]
375	Catechin-(4α→8)-epigallocatechin	AA	Thea	[161]
376	Catechin-(4α→8)-epigallocatechin-3-*O*-gallate	AA	Thea	[161]
377	Gallocatechin-(4α→8)-epicatechin	AA	Thea	[161]
378	Prodelphinidin B3	AA	Faga, Rham	[162,163]
379	4″,4‴-di-*O*-methylprodelphinidin B3	AA	Legu	[157]
380	Catechin-(4α→8)-gallocatechin	AA	Cist	[156]
381	Prodelphinidin C	AA	Hama, Myri, Faga, Sali	[117,160,163, 164]
382	Epifisetinidol-(4β→8)-epicatechin	AA	Legu	[135]
383	Epifisetinidol-(4β→8)-catechin	AA	Legu	[165]
384	Fisetinidol-(4β→8)-epicatechin	AA	Legu	[166]
385	Fisetinidol-(4α→8)-epicatechin	AA	Legu	[166,167]
386	Fisetinidol-(4β→8)-catechin	AA	Legu	[166]
387	Fisetinidol-(4α→8)-catechin	AA	Legu	[168]
388	Fisetidinol-(4α→8)-3-*O*-galloylcatechin	AA	Legu	[166]
389	Ent-fisetinidol-(4β→8)-epicatechin	AA	Anac	[149]
390	Ent-fisetinidol-(4β→8)-catechin	AA	Anac, Legu	[149,169]
391	Ent-fisetinidol-(4α→8)-catechin	AA	Anac, Legu	[149]

* Adox: Adoxaceae; Cela: Celastraceae; Cras: Crassulaceae; Gros: Grossulaceae; Mimo: Mimosaceae; Phyl: Phyllanthaceae; Rhiz: Rhizophoraceae; and Rubi: Rubiaceae.

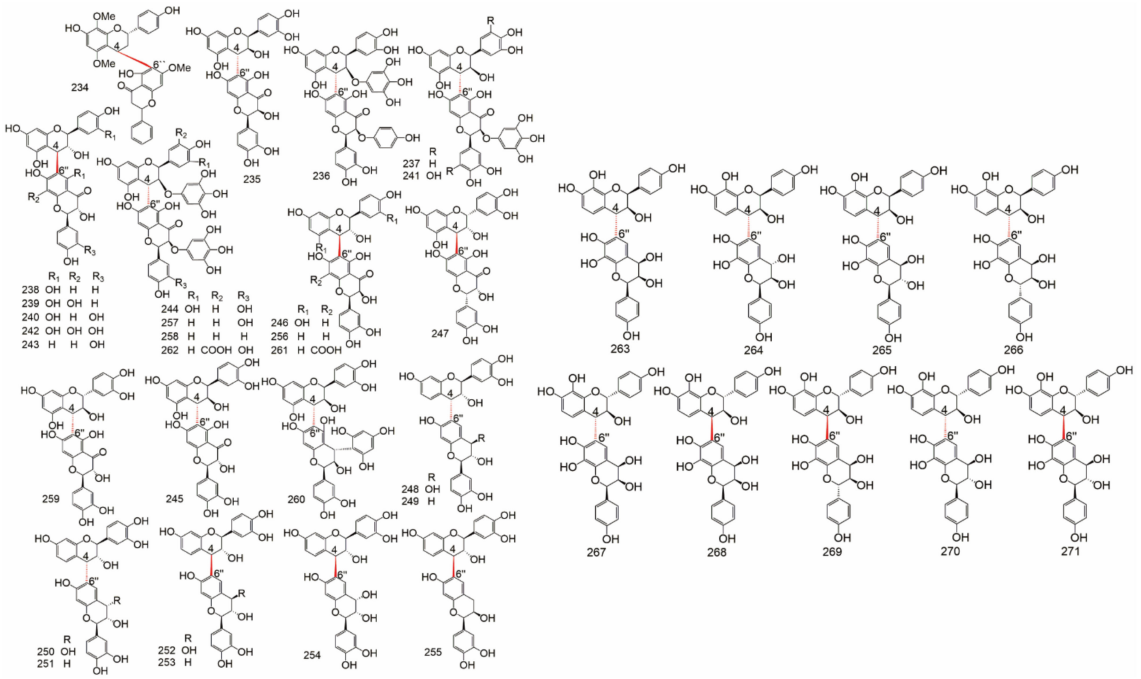


Figure 6. The structure of 4-6″ type biflavonoids.

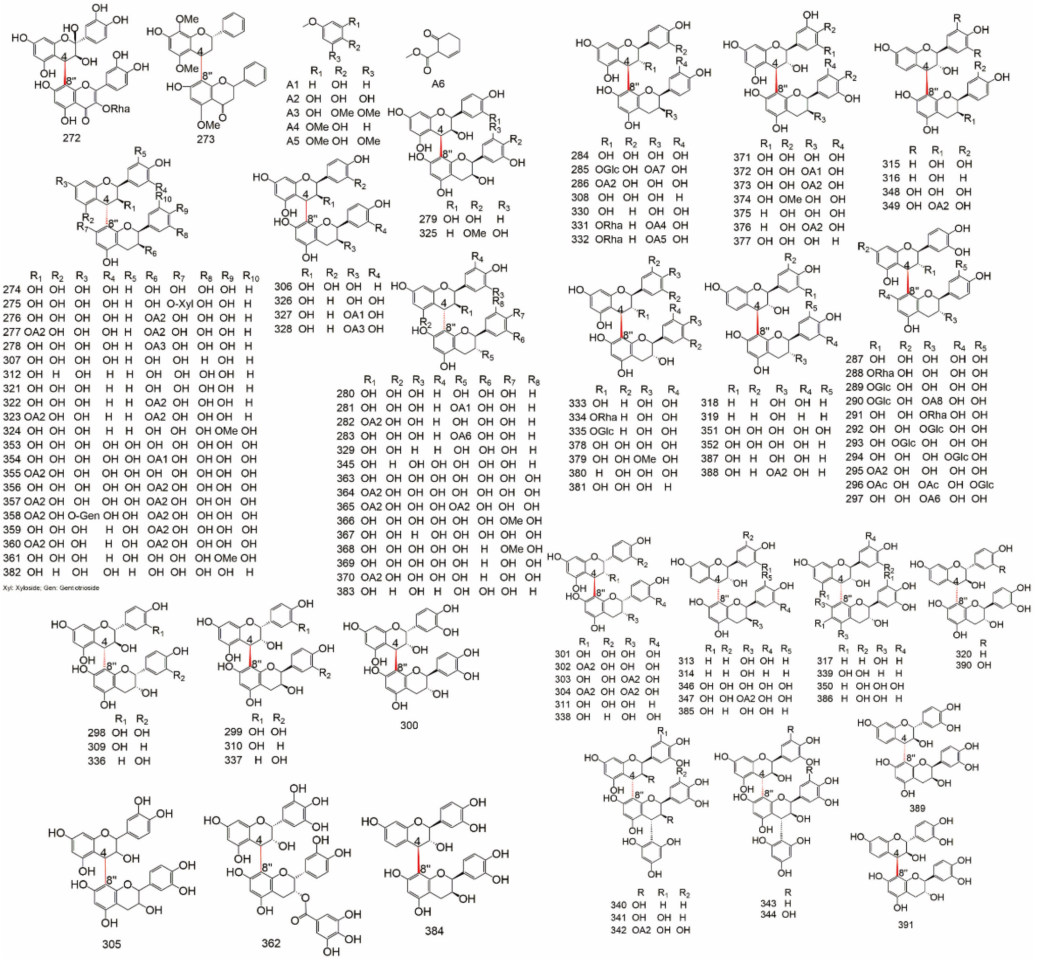


Figure 7. The structure of 4-8″ type biflavonoids.

The data of 4′-8″, 5-5″, 6-6″, 6-γ, 6-8″, 7-7″, and 8-8″ type biflavonoids were showed in Table 8, the structure of them were drew in Figure 8.

Table 8. The 4′-8″, 5-5″, 6-6″, 6-γ, 6-8″, 7-7″, and 8-8″ subtypes of biflavonoids.

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
4′-8″	**392**	5,3′,5″,4‴-tetrahydroxy-3‴,5‴-dimethoxy-biflavone(4′→8″)-7-*O*-(2-rhamnoside)rhamnoside	BB	Apia	[170]
5-5″	**393**	8,8′-bis(7,8-dihydroxy-2-C-methyl-2H-1-benzopyran-5-yl)-4,4′-dimethoxy-[5,5′-bi-6H-furo[3,2-h][1]benzopyran]-6,6′-dione	BB	Legu	[171]
	394	3-C-(6-deoxy-α-L-mannopyranosyl)-3′-C-α-D-glucopyranosyl-2,2′-bis(4-hydroxyphenyl)-7,7′-dimethyl-[5,5′-bi-4H-1-benzopyran]-4,4′-dione	BB	Legu	[171]
6-6″	**395**	Succedaneaflavanone	AA	Anac	[1]
	396	6,6″-bigenkwanin	BB	Ochn	[172]
6-γ	**397**	8-methylsocotrin-3′-methoxy-4′-ol	AG	Drac	[1]
	398	8-methylsocotrin-4′-methoxy-3′-ol	AG	Drac	[1]
	399	8-methylsocotrin-3-methoxy-4-ol	AG	Drac	[1]
	400	8-methylsocotrin-4-methoxy-3-ol	AG	Drac	[1]
	401	8-methylsocotrin-4-ol	AG	Drac	[1]
6-8″	**402**	6,8″-bigenkwanin	BB	Arau, Ochn	[172,173]
	403	Agathisflavone	BB	Anac, Ochn	[173]
	404	7,7″,4‴-tri-*O*-methylagathisflavone	BB	Arau	[1,174]
	405	7,4‴-di-*O*-methylagathisflavone	BB	Arau	[1]
	406	Agathisflavone A	BB	Arau	[173,174]
	407	Ouratine A	BB	Ochn	[1,175]
	408	Agatisflavone	AB	Ochn	[1]
	409	7,4′,7″,4‴-tetra-*O*-methylcupressuflavone	AB	Sela	[7]
	410	7,4′,7″-tri-*O*-methylcupressuflavone	AB	Arau	[1]
	411	7,7″-di-*O*-methylcupressuflavone	AB	Arau	[1]
	412	Rhusflavone	AB	Anac	[176]
	413	Lateriflavanone	AB	Clus	[1]
	414	4‴-*O*-methylagatisflavone	AB	Clus, Ochn	[54,177]
	415	Rhusflavanone	AA	Anac	[178]
	416	6,8″-binaringenin	AA	Clus	[178]
	417	3‴,4′,4‴,5,5″,7,7″-hepta-me ether-3,3″,3‴,4′,4‴,5,5″,7,7″-nonahydroxy-6,8″-biflavanone	AA	Ochn	[179]
	418	Ouratine B	BB	Ochn	[175]
	419	4‴-*O*-methylagathisflavone	BB	Ochn	[177]
	420	7″-*O*-methylagathisflavone	BB	Ochn	[180]
	421	Agathisflavone B	BB	Arau	[174]
7-7″	**422**	4′-methoxy-7,7″-biflavone	BB	Legu	[181]
8-8″	**423**	Cupressuflavone	AA	Anac, Arau, Cupr	[182]
	424	3,3″-dihydroxycupressuflavone	BB	Thea	[183]
	425	4′-*O*-methylcupressuflavone	BB	Clus	[54]
	426	Mesuaferrone B	AB	Anac, Clus	[178,184]
	427	4′,4‴-di-*O*-methylcupressuflavanone	AA	Comp	[185]
	428	(R)4′-*O*-β-D-glucopyranoside-cupressuflavone	AA	Cupr	[186]
	429	(S)4′-*O*-β-D-glucopyranoside-cupressuflavone	AA	Cupr	[186]
	430	7-me ether-cupressuflavone	BB	Arau	[173,187]
	431	8,8″-bigenkwanin	BB	Arau, Cupr	[186,187]
	432	W11	BB	Arau, Phyl	[188]
	433	4′,7,7″-tri-*O*-methylcupressuflavone	BB	Arau	[187]
	434	WB1	BB	Arau	[173,187]
	435	Moghatin	BB	Malv	[189]
	436	Neorhusflavanone	AA	Anac, Calo	[184,190]

* Apia: Apiaceae; Calo: Calophllaceae; Comp: Compositae; Drac: Dracaenaceae; and Rham: Rhamnaceae.

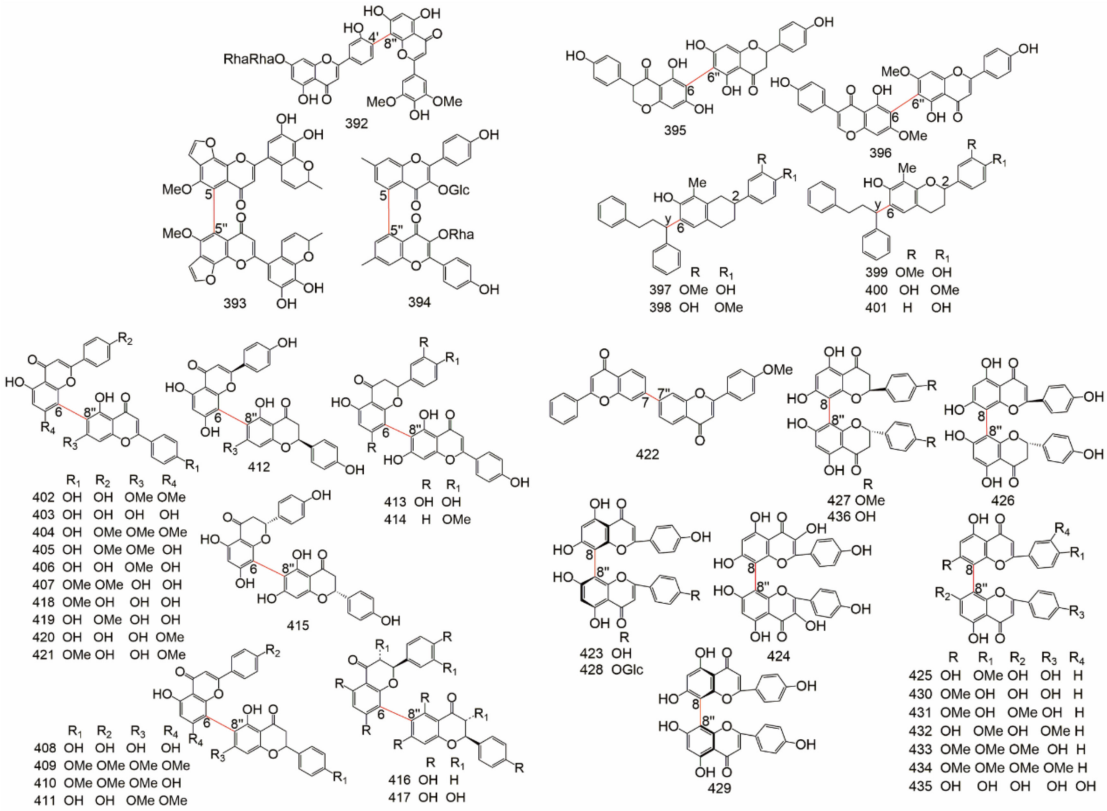


Figure 8. The structure of 4′-8″, 5-5″, 6-6″, 6-γ, 6-8″, 7-7″, and 8-8″ type biflavonoids.

4.2. C-Linear Fragment-C Type

Group B (Table 9) is consist of C-*O*-C connections, C-C-C connections and other linear fragment connections, including: 3′-*O*-3‴, 3-*O*-4″, 3-*O*-4‴, 3′-*O*-4‴, 3-*O*-7″, 3′-*O*-7″, 4-*O*-4″, 4′-*O*-4‴, 4′-*O*-6″, 4′-*O*-7″, 4′-*O*-8″, 5-*O*-5″, 6-*O*-7″, 7-*O*-7″, 6-C-8″, and 8-C-8″. The structure of C-linear fragment-C biflavonoids were showed in Figures 9 and 10.

Table 9. The C-linear fragment-C subtypes of biflavonoids.

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
3′-*O*-3‴	**437**	Sparinaritin	AB	Chry	[191]
3-*O*-4″	**438**	Epioritin(4β-3)-epioritin-4β-ol	AA	Legu	[20]
3-*O*-4‴	**439**	Delicaflavone	BB	Sela	[7]
	440	5,7,4′,5″-tetrahydroxy-7″-metroxy-[3-*O*-4‴]-biflavone	BB	Sela	[7]
	441	Chrysocauloflavone I	AB	Sela	[7]
	442	Chrysocauloflavone II	AB	Sela	[7]
	443	Baeckein E	AB	Myrt	[192]
	444	Baeckein C	AB	Myrt	[192]
	445	Baeckein D	AB	Myrt	[192]
3′-*O*-4‴	**446**	Ochnaflavone	BB	Ochn	[7,193]
	447	Ochnaflvone 7″-*O*-β-D-glucopyranoside	BB	Ochn	[194]
	448	2″,3″-dihydroochnaflavone	AB	Ochn	[7,195]
	449	2,3-dihydro-4′,7,7″-tri-*O*-methylochnaflavone	AB	Ochn	[7,196]
	450	Sulcatone A	AB	Ochn	[197]
	451	4′-me ether-ochnaflavone	BB	Ochn	[193]
	452	7-*O*-methylochnaflavone	BB	Ochn	[198]
	453	7″-*O*-methylochnaflavone	BB	Ochn	[199]
	454	4′,7-di-*O*-methylochnaflavone	BB	Ochn	[193]
	455	2,3-dihydroochnaflavone	AB	Ochn	[200]
	456	2,3-dihydro-7-*O*-methylochnaflavone	AB	Ochn	[200]
	457	2,3-dihydro-7″-*O*-methylochnaflavone	AB	Ochn	[9]

Table 9. *Cont.*

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
	458	2″,3″-dihydro-7″-*O*-methylochnaflavone	AB	Ochn	[9]
	459	2,2″,3,3″-tetrahydroochnaflavone	AA	Para	[201]
	460	2,2″,3,3″-tetrahydro-7-*O*-methylochnaflavone	AA	Ochn, Para	[201]
	461	2,2″,3,3″-tetrahydro-7,7″-di-*O*-methylochnaflavone	AA	Para	[202]
	462	3‴-hydroxyochnaflavone	BB	Rubi	[203]
	463	6,6″-dimethylochnaflavone	BB	Sela	[1]
	464	2,3-dihydro-6,6″-dimethylochnaflavone	AB	Sela	[196]
	465	Hypnumbiflavanoid B	AA	Hypn, Ochn	[197,204,205]
3-*O*-7″	**466**	3-*O*-7″-biluteolin	BB	Aste	[206]
3′-*O*-7″	**467**	Lophirone L	BB	Ochn	[52]
	468	Lophirone penta-acetate	BB	Ochn	[52]
	469	5,7,4′,5″,3‴,4‴′-hexahydroxy-3″-*O*-β-glucosyl-3′,7″-*O*-biflavone	BB	Legu	[207]
	470	5,7,4′,5″,3‴,4‴′-hexahydroxy-3,3″-di-*O*-β-glucosyl-3′,7″-*O*-biflavone	BB	Vita	[208]
4-*O*-4″	**471**	Epimesquitol(4β-4)-epioritin-4β-ol	AA	Legu	[20]
4′-*O*-4‴	**472**	Achyrobichalcone	GG	Aste	[209]
	473	Loniflavone	BB	Capr	[1]
	474	3′-*O*-methylloniflavone	BB	Capr	[210]
	475	Oniflavone	BB	Capr	[210]
	476	Ericoside	AB	Eric	[211]
4′-*O*-6″	**477**	Hinokiflavone	BB	Cupr, Psil, Sela, Taxo, Cyca	[212–216]
	478	Isocryptomerin	BB	Cupr, Sela, Taxo	[7,213–215,217]
	479	Neocryptomerin	BB	Podo	[7]
	480	Cryptomerin B	BB	Taxo	[7,214,218]
	481	Chamaecyparin	BB	Cupr, Sela	[7,217,219]
	482	2,3-dihydrohinokiflavone	AB	Cupr, Cyca	[7,215,216]
	483	(2S)-2,3-dihydroisocryptomerin	AB	Sela	[7,37]
	484	2″,3″-dihydrohinokiflavone	AB	Sela	[7,220]
	485	2″,3″-dihydroisocryptomerin	AB	Sela	[7,221]
	486	7-*O*-methyl-2″,3″-dihydroisocryptomerin	AB	Sela	[221]
	487	Taiwaniaflavone B	AB	Capr	[7,79]
	488	(2S,2S″)-2,3,2″,3″-tetrahydrohinokiflavone	AA	Cyca	[7,222]
	489	7″-*O*-methyl-2,3,2″,3″-tetrahydrohinokiflavone	AA	Sela	[7]
	490	7,4″-di-*O*-methyl-2,3,2″,3″-tetrahydrohinokiflavone	AA	Sela	[7]
	491	Oliveriflavone A	AA	Capr	[85]
	492	Cryptomerin A	BB	Taxo	[215,218]
	493	2,2″,3,3″-tetrahydro-7,7″-di-*O*-methylhinokiflavone	AA	Cyca	[223]
	494	2,3-dihydrochamaecyparin	AB	Sela	[39]
4′-*O*-7″	**495**	Brevipedicelone E	BB	Clus	[224]
4′-*O*-8″	**496**	Lanaroflavone	BB	Anac, Lana	[225,226]
	497	7-*O*-methyllanaroflavone	BB	Ochn	[227]
	498	4‴,7-di-*O*-methyllanaroflavone	BB	Ochn	[227]
	499	7,7″-di-*O*-methyllanaroflavone	BB	Ochn	[228]
5-*O*-5″	**500**	Potifulgene	AA	Rosa	[1]
6-*O*-7″	**501**	Masazinoflavanone	AA	Anac	[229]
7-*O*-7″	**502**	(myricetin-3-*O*-α-L-rhamnoside(C7I-*O*-C7II)myricetin-3-*O*-α-L-rhamnoside	BB	Legu	[230]
6-C-8″	**503**	Bosistoabiflavanone	AA	Ruta	[231]
8-C-8″	**504**	Ttrianguletin	BG	Adia	[20]
	505	Pentagrametin	AB	Adia	[20]
	506	Di(8-catechinyl)methane	AA	Malv	[232]
	507	3-*O*-β-D-glucopyranoside-malvidin 8-(8-ethylcatechin)	AC	Red wine	[233]
	508	3,3′-bis-*O*-[β-D-xylopyranosyl-(1→2)-[4-hydroxy-3,5-dimethoxy-E-cinnamoyl-(→6)-β-D-glucopyranosyl-(1→6)]-β-D-galactopyranoside]	CC	Apia	[234]
Others	**509**	Carinoside A	BE	Gent	[235]
	510	Mesuferrol A	II	Clus	[236]
	511	Mesuferrol B	II	Clus	[236]

* Adia: Adiantaceae; Chry: Chrysobalanaceae; Gent: Gentianaceae; Hypn: Hypnaceae; Para: Paracryphiaceae; Lana: Lanariaceae; Psil: Psilotaceae and Ruta: Rutaceae.

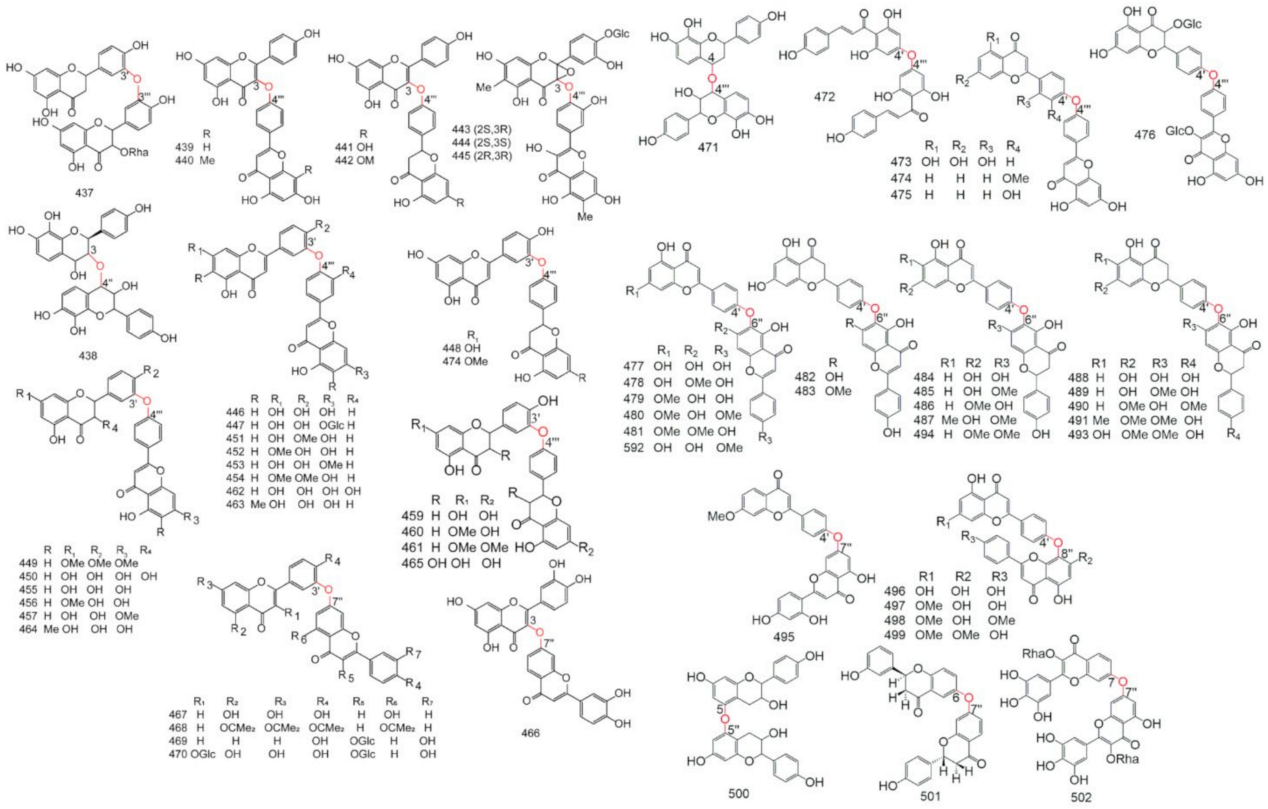


Figure 9. The structure of C-*O*-C type biflavonoids.

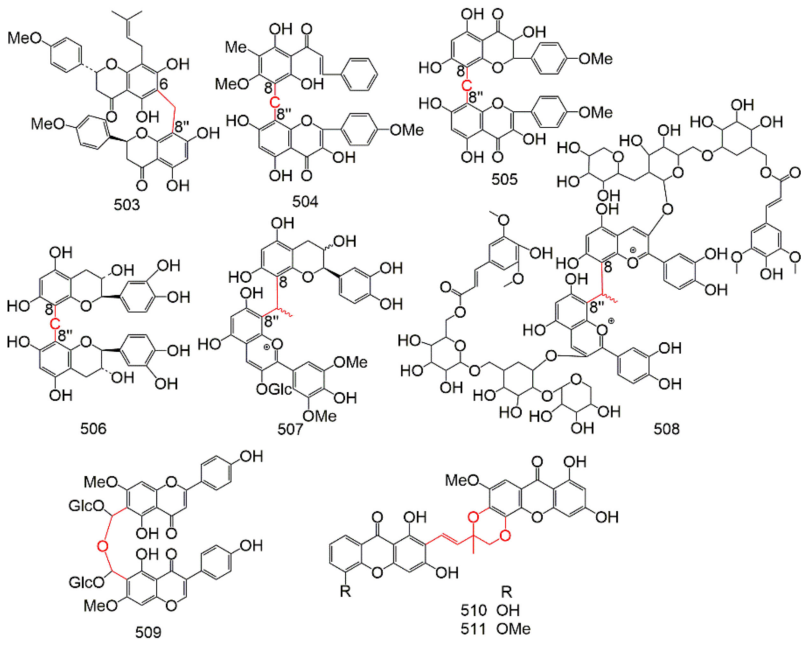


Figure 10. The structure of C-C-C and others type biflavonoids.

4.3. Complex Biflavonoids

Group C belongs to the complex biflavonoids (Tables 10 and 11). They include the simple-ring type (C-C & C-C, C-C & C-C-C, C-C & C-*O*-C, C-*O*-C & C-*O*-C), the bicyclic type, the atom-shared type, and spirobiflavonoids. The structure of complex biflavonoids were showed in Figure 11.

Table 10. Complex biflavonoids. (Simple-ring type).

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
C-C & C-C	**512**	Licobichalcone	GG	Legu	[237]
C-C & C-C-C	**513**	Selacyclicbifkavone A	AB	Sela	[7]
C-C & C-*O*-C	**514**	Licoagrodin	AD	Legu	[20]
	515	Daphnodorin A	AG	Thym	[29,238]
	516	Daphnodorin B	AG	Thym	[29,238]
	517	Dihydrodaphnodorin B	AG	Thym	[239]
	518	Daphnodorin J	AG	Thym	[29,238,240]
	519	Daphnodorin E	AA	Thym	[29]
	520	Daphnodorin H	AA	Thym	[29]
	521	4′-methoxydaphnodorin E	AA	Thym	[241]
	522	Daphnodorin F	AA	Thym	[29]
	523	Daphnodorin G	AA	Thym	[29]
	524	Lawsonia biflavone A	AB	Lyth	[230]
	525	3′-*O*-methyldaphnodorin G	AA	Thym	[242]
	526	4″-*O*-methyldaphnodorin E	AA	Thym	[241]
	527	3-*O*-methyldaphnodorin H	AA	Thym	[242]
	528	3′-*O*-methyldaphnodorin H	AA	Thym	[242]
	529	Daphnogirin A	AA	Thym	[243]
	530	Daphnogirin B	AA	Thym	[243]
	531	Ephedrannin B	AB	Ephe, Daph	[244,245]
	532	Ephedrannin A	AB	Ephe, Daph, Vita	[244,245]
	533	Ent-epiafzelechin-(2α→7, 4α→8)-quercetin	AB	Rosa	[246]
	534	Proanthocyanidin A5′	AA	Ephe, Rosa	[247,248]
	535	3-*O*-α-L-arabinopyranosylproanthocyanidin A5′	AA	Malv	[248]
	536	3-*O*-β-D-galactopyranosylproanthocyanidin A5′	AA	Malv	[248]
	537	Pavetannin A2	AA	Ephe, Rosa, Rubi	[249]
	538	3-*O*-α-L-arabinopyranosylpavetannin A2	AA	Malv	[232]
	539	Ent-epicatechin-(2α→7,4α→8)-ent-catechin	AA	Rubi	[250]
	540	Ent-epicatechin-(2α→7,4α→8)-ent-epicatechin	AA	Ephe	[248]
	541	Proanthocyanidin A2	AA	Sapi, Legu, Laur	[251–253]
	542	3′-*O*-trans-cinnamoylproanthocyanidin A2	AA	Legu	[254]
	543	Proanthocyanidin A1	AA	Sapi, Legu, Laur	[253]
	544	Proanthocyanidin A4	AA	Sapi, Rubi	[250]
	545	Baeckein F	AB	Myrt	[1]
	546	Baeckein G	AB	Myrt	[255]
	547	Baeckein H	AB	Myrt	[1]
	548	Baeckein I	AB	Myrt	[255]
	549	Lophirone C	GG	Ochn	[256,257]
	550	Dihydrolophirone C	GG	Ochn	[257]
	551	Isolophirone C	GG	Ochn	[257]
	552	Lophirone K	GG	Ochn	[258]
	553	Lophirone F	GG	Ochn	[259]
	554	Lophirone G	GG	Ochn	[259]
	555	Lophirone L‡	GG	Ochn	[260]
C-*O*-C & C-*O*-C	**556**	Dysoverine D	AB	Berb	[261]
	557	Dysoverine F	AB	Berb	[261]
	558	Dysoverine A	AB	Berb	[261]
	559	(2R,2′R,3S,3′S,4α,4′α)-3′,4′,7-trihydroxyflavan-(3→*O*→4)(4→*O*→3)-3′,4′,7-trihydroxyflavan	AA	Legu	[262]

* Berb: Berberidaceae; Daph: Daphniphyllaceae; Ephe: Ephedraceae; Laur: Lauraceae; and Lyth: Lythraceae.

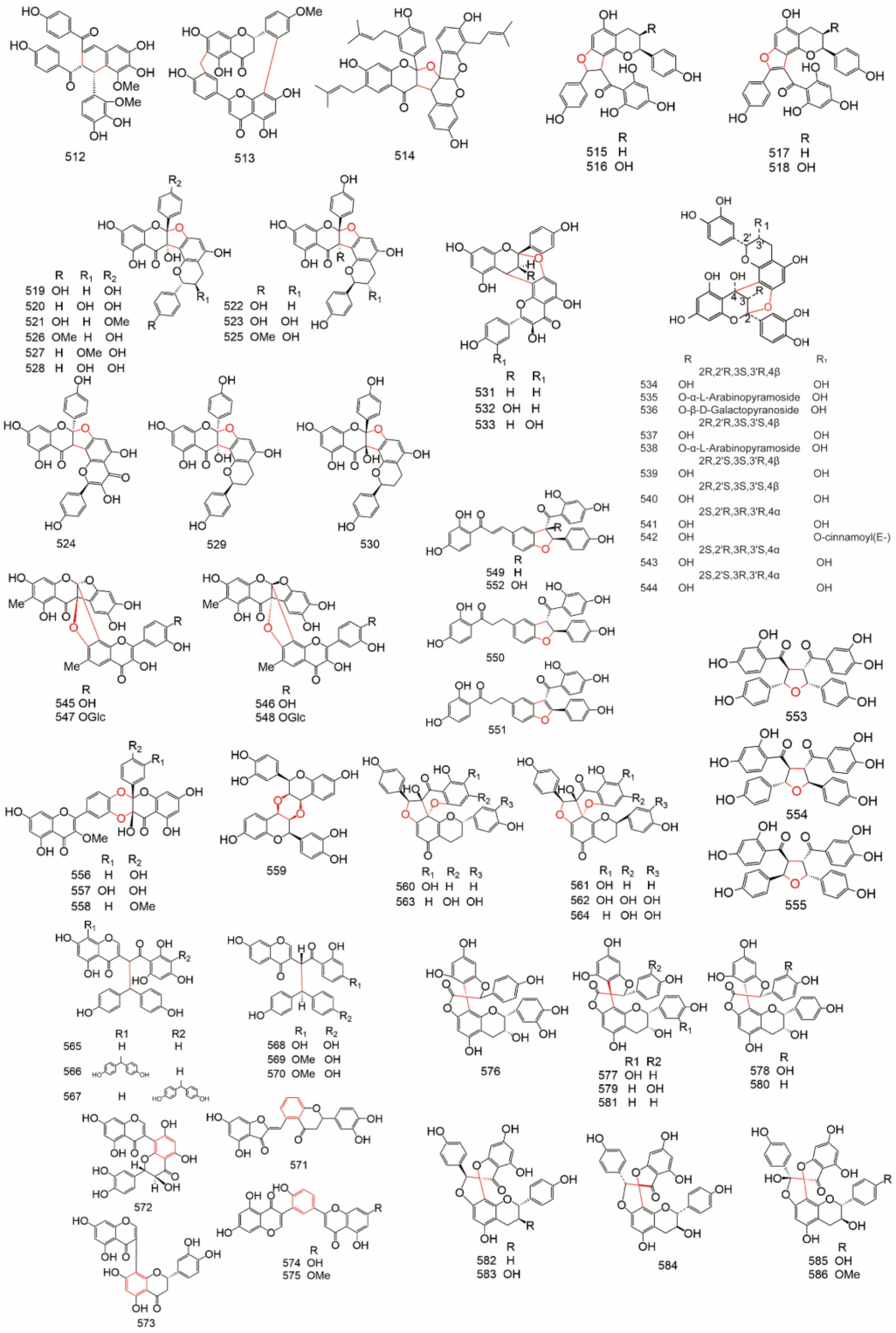


Figure 11. The structure of Complex biflavonoids.

Table 11. The other types of bioflavonoids.

Subtype	No.	Compounds Name	Monomer Type	Origin (Family *)	References
Bicyclic type	**560**	Daphnodorin M	AG	Thym	[29]
	561	Daphnodorin N	AG	Thym	[29]
	562	Stelleranol	AG	Thym	[1]
	563	Genkwanol B	AG	Thym	[1]
	564	Genkwanol C	AG	Thym	[1]
Atom-shared type	**565**	Chamaechromone	EG	Thym	[63]
	566	Mohsenone	EG	Thym	[63]
	567	Isomohsenone	EG	Thym	[63]
	568	Lophirone A	EG	Ochn	[263]
	569	Calodenone	EG	Ochn, Anac	[264]
	570	Afzelone D	EG	Ochn	[265]
	571	Campylopusaurone	AH	Clus	[266]
	572	Preussianone	AB	Clus	[267]
	573	Paucinervin K	AE	Clus	[268]
	574	Lancedatin A	BD	Legu	[20]
	575	Lancedatin B	BD	Legu	[20]
Spirobiflavonoids	**576**	Absienol A	AA	Mora	[60]
	577	Absienol B	AA	Pina	[1]
	578	Absienol C	AA	Mora	[60]
	579	Absienol D	AA	Pina	[1]
	580	Absienol E	AA	Mora	[60]
	581	Absienol F	AA	Pina	[1]
	582	Daphnodorin C	AA	Thym	[29]
	583	Daphnodorin I	AA	Thym	[29]
	584	Genkwanol A	AA	Thym	[269]
	585	2″-hydroxygenkwanol A	AA	Thym	[1]
	586	4′-methylgenkwanol A	AA	Thym	[1]
	587	Olgensisinol A	AA	Pina	[270]
	588	Olgensisinol B	AA	Pina	[270]
	589	Olgensisinol C	AA	Pina	[270]
	590	Olgensisinol D	AA	Pina	[270]
	591	Vitisinol	AA	Pina	[270]
	592	Larixinol	AA	Pina	[271]

5. Pharmacology of Biflavonoids

5.1. Antioxidant

Andrade et al. [272] conducted an antioxidant test on agathisflavone in 2018. Trolox was used as a control, and agathisflavone was extracted and isolated from the fresh leaves of Caesalpinia pyramidalis Tull. In the experiment of DPPH radical scavenging, it was found that agathisflavone scavenged DPPH free radicals in a concentration-dependent manner; the EC_{50} of agathisflavone was 0.474 mM, and for Trolox it was 0.149 mM, within the 95% confidence interval. The ABTS scavenging assay data found that agathisflavone was EC_{50} = 0.179 mM, while for Trolox, it was EC_{50} = 0.311 mM. In the OH radical scavenging assay, agathisflavone also showed a concentration-dependent hydroxyl radical scavenging ability, while agathisflavone and Trolox both showed a concentration-dependent reduction in the three iron ions to ferrous iron. Through structural analysis of agathisflavone, it was found that the hydroxyl groups at positions 4′,7,7″,4‴ in its structure can provide free radical hydrogen to reduce free radicals. In addition, agathisflavone can also inhibit the production of TBARS, and has a significant ability to protect against oxidative damage, indicating that agathisflavone is likely to be a good antioxidant.

The antioxidant effect of Garcinia kola is mainly based on the biflavonoids in the extract. Through the DPPH method and the ATBS method, Lixian et al., studied the antioxidant capacity of garcinianin, kolaflavanone, GB1a, GB2, and panciflavanon. The antioxidant activity of different compounds determined by the DPPH method was garcinianin > panciflavanon > GB2 > kolaflavanone > GB1a, and the antioxidant activity of

different compounds determined by the ABTS method was garcinianin > panciflavanon > GB1a > kolaflavanone > GB2. Among them, the antioxidant effect of garcinianin was more obvious [273].

In a study of the antioxidant mechanism of the neuroprotective biflavonoids, hinokiflavone, isocryptomerin, amentoflavone, ginkgetin, amentoflavone, and ginkgetin have good antioxidant capacities, can inhibit the activity of SOD, GR, Gpx, CAT, and other oxidases, reduce the content of GSH, and achieve an antioxidant effect. Ginkgetin can also act on the ERK1/2 target for antioxidants [274]. In 2013, Jia et al. [192] extracted baeckein E from Baeckea frutescens and six other known compounds, and its IC_{50} value ranged from 11.8–16.1 μM in the DPPH free radical scavenging test. Baeckein A and B (IC_{50} = 23.5 μM, IC_{50} = 26.2 μM) showed cytotoxicity and could not be used in H_2O_2-induced oxidation experiments. The treatment rates of biflavonoid baeckein E, baeckein C, and baeckein D were 31.8%, 34.8%, and 36.0%, respectively, which were lower than those of nonbiflavonoids (43.0~44.7%).

5.2. Anti-Inflammatory Properties

The anti-inflammatory activity of biflavonoids is mainly detected by inhibiting the expression of cyclooxygenase 2 (COX-2) and iNOS. In 2006, Park et al. [275] looked for C-C linked biflavonoids as anti-inflammatory drugs and examined the production of PGE2 and nitric oxide (NO) of synthetic biflavonoids in RAW cells treated with lipopolysaccharide (LPS). The results showed that 3′-6″, 6-6″, and 3-4‴ linked biflavonoids showed resistance to COX-2 -mediated significant inhibition of PGE2 production (IC_{50} = 17.3 μM; IC_{50} = 3.7 μM; IC_{50} = 7.0 μM, respectively). Western blot and reverse transcription-polymerase chain reaction analyses showed that these compounds are not COX-2 down-regulation mediated, but are instead COX-2 inhibition mediated. Among them, 6-6″ biflavonoids have the strongest PGE2 production inhibitory activity. To ensure accuracy, PGE2 and NO tests were performed after LPS pretreatment. The IC_{50} of the 6-6″ is < 3.0μM, and it can be used as a synthetic leader of new anti-inflammatory agents. However, the biflavonoids 4′-6″ and 3-4‴ can have cytotoxic effects on RAW cells.

In 2002, the anti-inflammatory mechanism of amentoflavone as a natural biflavonoid was studied. Banerjee et al. [276] found that amentoflavone can inhibit TNF-α-mediated COX-2 expression through the NF-κB pathway, thereby showing anti-inflammatory effects. In 2019, Li et al. [277] also studied the anti-inflammatory mechanism of the natural biflavonoid ginkgetin, and found that it can produce anti-inflammatory effects through the TLR4/NF-κB signaling pathway and improve ischemia/regeneration perfusion injury.

Jia et al. [255] extracted and separated root products from Baeckea frutescens in 2014 and discovered four new natural biflavonoids of baeckeins F-I. It was found that the four biflavonoids are the cyclic biflavonoids. The conformations of baeckein F, baeckein H (2S, 3S), baeckein G, and baeckein I (2R, 3R) are different, while baeckein H and baeckein I are glycosyl substituted biflavonoids. An anti-inflammatory activity test was performed in the RAW264.7 cell line induced by LPS to produce NO. It was found that the IC50 values of baeckein F, baeckein G, baeckein H, and baeckein I were 54.7 ± 5.26 μM, 25.4 ± 2.78 μM, 43.8 ± 3.30 μM, and 15.2 ± 1.34 μM, respectively, while the IC_{50} of the control indomethacin was 13.8 ± 1.29 μM, and there was no cytotoxicity. Data analysis showed that baeckein H and baeckein I had glycosylated biflavonoids that had more anti-inflammatory activity than the nonglycosylated biflavonoids. The anti-inflammatory activity of baeckein I was not much different from that of indomethacin, and it can be developed as a new anti-inflammatory drug.

There are many mechanisms for the anti-inflammatory activity of biflavonoids. There have been reviews summarizing the anti-inflammatory targets of natural biflavonoids including: ICAM-1, PPAR-γ, COX-2, NF-κB, iNOS, ERK1/2, MMP-9, TIMP-1, and PI3K/Akt, etc. [278]. These are all targets of conventional anti-inflammatory pathways. In addition, predictive pathways such as arachidonic acid metabolism are also new anti-inflammatory mechanisms of biflavonoids.

5.3. Antiviral Activities

To find new molecules against dengue fever virus (DV), Coulerie et al. [279] extracted four biflavonoids from the ethyl acetate extract of *Dacrydium balansae*, including amentoflavone, podovarpusflavone A, isoginkgetin, and hinokiflavone, and found that the biflavonoid compounds were the strongest inhibitors of the full activity of DV-NS5 RDRP and DV-NS5, with IC_{50}s lower than 3.1 and 5.3 μM. The IC_{50} values were as follows: hinokiflavone (IC_{50} = 0.26 μM) > podovarpusflavone A (IC_{50} = 0.75 μM) > amentoflavone (IC_{50} = 1.40 μM) > isoginkgetin (IC_{50} = 3.10 μM). Hinokiflavone was the most active biflavonoid with IC_{50} = 0.26μM, but podocarpusflavone A was the strongest non-cytotoxic DV-NS5 inhibitor and could inhibit polymerase activity in the DV replicon, so podocarpusflavone A can be used as a template for the development of drugs against dengue fever virus. In addition, amentoflavone can also be developed as an antiviral drug for herpes simplex virus (HSV-1) [280], and agathisflavone can produce an anti-influenza virus effect [281].

5.4. Antibacterial and Antifungal Activities

Although the antibacterial and antifungal effects are different in mechanism, this review describes them to facilitate the summary of biflavonoids. Tang et al. [282] isolated six biflavonoids from the bark of *Ochna macrocalyx*. Dehydroxyhexaspermone C, and hexaspermone C are the C-C linked biflavonoids, and ochnone, cordigol, calodenin B, and 2,3-dihydrocalodenin B are all different from general biflavonoids. Calodenin B and 2,3-dihydrocalodenin B have a certain cytotoxicity, but also show strong antibacterial effects. Compared with the control drug, the antibacterial activities of calodenin B and 2,3-dihydrocalodenin B were more obvious. In addition, fukugiside can inhibit the activity of *Streptococcus pyogenes* [283].

The antifungal activity test mainly uses *Candida albicans* to test the antifungal effect of the biflavonoids. Lee et al. [284] used bis-(1,3-dibutylbarbituric acid) trimethine oxonol [DiBAC4(3)], a traditional membrane potential dye, in a regeneration test with fungal protoplasts to study the mechanism of isocryptomerin by depolarization. In this study, amphotericin B was used as a positive control, and isocryptomerin had an MIC value of 18.11 μM, which showed antifungal activity against human pathogenic fungi (such as *Candida albicans* and *Trypanosoma beige*). The cumulative amount of the DiBAC4(3) in isocryptomerin is small and less than the value of amphotericin B, which proves that it destroys the plasma membrane of Candida albicans and causes cell death. In addition, fungal arthritis, caused by *Candida albicans*, and ochnaflavone can promote the expression of IL-2 and IL-10 through the T cell immune system, and inhibit the expression of inflammatory mediators such as IFN-γ and IL-2, but it does not cause hemolysis, kill redundant macrophages, or improve fungal arthritis [285].

5.5. Anti-Diabetic and Anti-Atherosclerosis

A biflavonoid composed of two molecules of kaemferol was isolated from the seeds of *Semecarpus anacardium* and its antihyperglycemic mechanism in diabetic mice induced by a high-fat diet plus streptozotocin, was studied showing it could reduce the content of plasma glucose and increase the level of plasma insulin [286]. At a dose of 80 mg/kg b.wt, the biflavonoid's effect is basically the same as that of metformin, and when the biflavonoid is combined with metformin, they can significantly increase liver and muscle glycogen content, maintain hemoglobin levels, and restore the glycosynthase and glycogen phosphorylase close to normal levels. The glucose metabolism is also maintained at a normal level, and it can significantly increase enzymatic antioxidants (SOD, CAT, GPx, and GST) and nonenzymatic antioxidants (vitamin C, vitamin E, and GSH) and improve the activity of enzymes, thereby curing hyperglycemia. Liu et al. [287] indicated that biflavonoids (isoginkgetin, bilobetin, ginkgetin, and sciadopitysin), which are extracted from *Ginkgo biloba*, have the potential to become pancreatic lipase inhibitors. Four natural biflavonoids had a strong inhibitory effect on pancreatic lipase, and their residual

activities were isoginkgetin = 35.7%, bilobetin = 22.3%, ginkgetin = 41.6%, and sciadopitysin = 58.6%. Through the lipase of a concentration-dependent inhibitor of 4-MUO hydrolysis, each IC_{50} value was isoginkgetin = 2.90 ± 0.98 μM, bilobetin = 3.57 ± 0.53 μM, ginkgetin = 6.90 ± 1.60 μM, and sciadopitysin = 12.78 ± 2.30 μM, showing a degree of medium to strong inhibition. Isoginkgetin can also improve the healing of foot ulcer wounds in diabetic rats [288].

There are many pathological mechanisms of atherosclerosis, but they are related to hypertension, hyperlipidemia, and other mechanisms. Therefore, the treatment of atherosclerosis is basically inseparable from the antioxidant and anti-inflammatory effects [289]. Tabares-Guevara et al. performed oxygen radical absorbance capacity (Orac) and lDl oxidation inhibition assays on three natural biflavonoids: morelloflavone, volkensiflavone, and fukugiside, and found that all of them were effective reactive oxygen scavengers, inhibited the production of reactive oxygen species and the secretion of proinflammatory factors (IL-6, IL-12p70, MCP-1, TNF-α, MIP-1α, and NLRP3, etc.) in macrophages, and they reduced the circulating levels of cholesterol and the lipid peroxidation product propylene glycol, showing the antioxidation, anti-inflammatory, hypolipidemic, and anti-atherosclerotic effects of biflavonoids in the body [290].

5.6. Alzheimer's Disease and Parkinson's Disease

Alzheimer's disease in terms of anti-inflammatory, antioxidative stress, and neurodegenerative damage overlaps to a large extent with the treatment pathway of biflavonoids [291] so biflavonoids have great potential in the treatment of Alzheimer's disease [292]. Moreover, due to the aromatic interaction of biflavonoids, their therapeutic effect is better than that of a flavonoid [293], indicating that biflavonoids can be used as lead compounds for the development of treatments for Alzheimer's disease. In particular, the amentoflavone type includes amentoflavone (1) and its monomethoxy derivatives. They can inhibit the formation and accumulation of amyloid β, thereby preventing Alzheimer's disease [294].

Choi et al. used the peptide of Aβ1-42 to inhibit the aggregation of Aβ1-42 in vitro by thioflavin T fluorescence analysis of biflavonoids (amentoflavone, bilobetin, sequoiaflavone, sotetsuflavone, podocarpuflavone, ginkgetin, isoginkgetin, and sciadopitysin), and found that amentoflavone has the strongest comprehensive strength in inhibiting the formation of Aβ1-42 fibers and reducing the formation of Aβ1-42 fibers among the eight biflavonoids, and it has great potential as a lead compound for treating Alzheimer's disease [295]. CGY-1 [82], GB1, and other gambogic biflavonoids [296] also have the potential to treat Alzheimer's disease.

Biflavonoids extracted from Impatiens balsamina can prevent the production of NO, have neuroprotective activity, and improve neurodegenerative diseases [61]. Amentoflavone can improve Parkinson's disease through the PI3K/Akt and ERK signaling pathways [297], while ginkgetin can improve Parkinson's disease nerve damage through neuroprotection [298].

5.7. Cytotoxic Activity and Antitumor Activities

The cytotoxicity of flavonoids with different structures is also different. A review had summarized that the flavonoids with flavone(B) units (galangin, kaempferol, quercetin, myricetin, apigenin, and chrysin) had the ability to antihepatoma; the flavonoids with chalcone(G) units (flavokavain C) could cause hepatic failure; the flavonoid with isoflavone(E) units (genistein) had an antiestrogen, increasing the risk of breast cancer and the flavonoids with flavan(A) units (catechin) had no effect on tumor cells, but had the hemolytic anemia thrombocytopenia [299]. Biflavonoids are composed of two flavone monomers, so the toxicity study of flavonoids is also helpful to the toxicity activity of biflavonoids. The structure of these flavonoids are shown in Figure 12.

For the toxicity of biflavonoids, a study found that amentoflavone, sciadopitysin, ginkgetin, isoginketin, and bilobetin extracted from ginkgo can reduce the cell viability of

human renal tubular epithelial cells (HK-2 cells) in a dose-dependent manner. Ginkgetin, isoginkgetin, and bilobetin showed the cell viability of HK-2 cells were less than 50% at 10 and 100 μg/mL. At the dose of 100 μg/mL, amentoflavone, ginkgetin, isoginkgetin, and bilobetin injured the human normal hepatocytes (L-02 cells), moreover, the cell viability of isoginkgetin and bilobetin were less than 50%. After HE staining of mouse liver sections, it was found that bilobetin and ginkgetin were more toxic to hepatocytes. In renal tissue, these five biflavonoids caused acute renal injury, and renal interstitial hemorrhage was a common pathological phenomenon [300]. Therefore, *Ginkgo biloba* extract preparation should pay attention to its hepatorenal toxicity. A study found that hinokiflavone, as the cytotoxic principle, its ED_{50} value was 2.0 μg/mL in KB cells. It was proven that the ether bond between the two flavonoid monomers had a significant cytotoxicity. However, other biflavonoids with C-C linkages, being hexamethyl ethers of ring C/A-linked dimers between two flavonoid units, also showing the cytotoxic activity (the ED_{50} value was 3.0~4.0 μg/mL) [301]. A non-clinical toxicological study in 2019 revealed that there were no reported fatalities after agethisflavone acted on the female mice, and it has an LD_{50} larger than 2000 mg/kg [302].

Adem et al. [10] used the caspase-Glo assay to test the cytotoxicity of three biflavonoids (chamaejasmin, 7,7″-di-*O*-methylchamaejasmin, and campylospermone A) and other compounds. The cell cycle, apoptosis, mitochondrial membrane sites, and reactive oxygen species were analyzed by flow cytometry. The model cells were CCRF-CEM leukemia cells and CEM/ADR5000 cells and seven other cancer cells including U87MG. = EGFR glioblastoma, HepG2 liver cancer cells, U87MG. = EGFR cells, MDA-MB-231/BCRP breast cancer cells, MDA-MB-231 cells, and HepG2 cells. The IC_{50} values of chamaejasmin in CCRF-CEM cells and CEM/SDR5000 cells were both greater than 61 μM, and the IC_{50} value of campylospermone A to CEM/ADR5000 cells was also greater than 61 μM. Therefore, chamaejasmin and campylospermone A were considered to be less cytotoxic. However, 7, 7″-di-*O*-methylchamaejasmin had an IC_{50} = 3.58 ± 0.09 μM for CCRF-CEM cells, and an IC_{50} = 5.69 ± 0.51 μM for CEM/ADR5000 cells, and the IC_{50} values of the other cancer cells were less than 8 μM, indicating that it had greater cytotoxicity, and could inhibit the growth of cancer cells.

Due to the cytotoxicity of biflavonoids, they have great potential in the treatment of cancer. For example, delicaflavone can inhibit the PI3K/Akt/mTOR and Ras/MEK/Erk signaling pathways in rectal cancer cells through the mitochondrial ROS pathway [303], inhibit the MSPK signaling pathway in HeLa cervical cancer cells, and induce cell apoptosis in G2/M phase [304]; hinokiflavone inhibits the induction of apoptosis of the NF-κB signaling pathway in liver cancer cells by activating the mitochondrial ROS/JNK/caspase pathway [305]. However, the spirobiflavonoids of abiesinolA-F extracted from Abies sachalinensis can effectively inhibiting the activation of NOR1, thereby inhibiting the activity of skin cancer [306]. In the literature on the toxicology of biflavonoids, only the toxicological experiments of biflavonoids with Aunits, B units, and spirobiflavones were included. For instance, 6-8″ linkage biflavonoid (agathisflavone) had no cytotoxic activity [302], but 3′-8″ linkage biflavonoids (amentoflavone, ginkgetin, isoginkgetin, and bilobetin) impaired the liver and renal cells [300] and 3-3″ linkage biflavonoids (chamaejasmin, 7,7″-di-O-methylchamaejasmin, and campylospermone A) had the capacity to inhibit the growth of cancer cells [10]. The biflavonoids with the ether bond between two flavonoid monomers (delicaflavone [301,304], hinokiflavone [305], and spirobiflavone [306]) had the ability of anticancer. Additionally, the biflavonoids with the hexamethyl ether substituents could reduce cell activity [301].

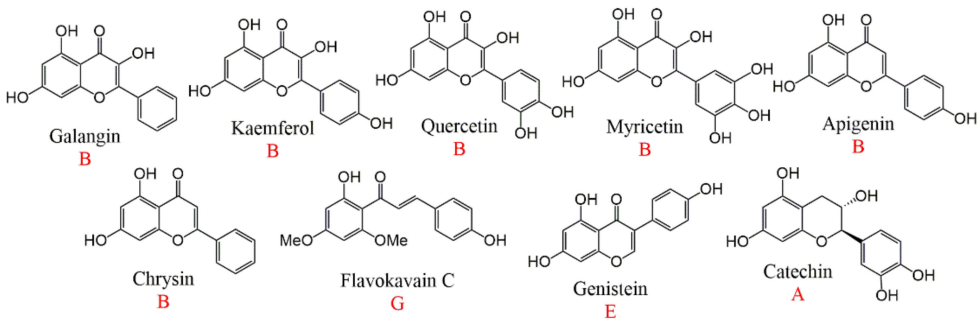


Figure 12. The structure of flavonoids.

5.8. Anti-Angiogenesis

Li et al. [307] correlated zebrafish angiogenesis measurement with ultra-performance liquid chromatography-quadrupole-time of flight-mass spectrometry (UPLC-Q-TOF/MS) as the base chemometric analysis to identify the potential antiangiogenic active compounds of *Garcinia xanthochymus*. Preliminary biological activity results showed that amentoflavone can significantly inhibit the growth of subintestinal vessels at 10 and 20 μM, and down-regulate the expression of the Angpt2 and Tie2 genes in zebrafish embryos. In addition, the zebrafish model was used to evaluate the structure-activity relationship of seven biflavonoids (volkensiflavone, fukugetin, fukugeside, GB 1a, GB 1a with glycosides, GB 2a and GB 2a with glycosides) isolated from *Garcinia*. Fukugetin, which has anticancer effects, and can effectively inhibit the growth of subintestinal vessels. Both amentoflavone and fukugetin showed antiangiogenic effects on zebrafish for the first time [308].

5.9. Other

In addition, the other pharmacological effects of biflavonoids are: morelloflavone has 63% preventive inhibition of PLA2-induced myotoxic activity, its 38% cure rate inhibits myotoxicity, and it can inhibit edema formation and anticoagulation in a concentration-dependent manner, proving that morelloflavone can be developed as an inhibitor of secretory PLA2 such as in snake venom [309]; GB1 can inhibit α-glucosidase (IC_{50} = 0.90 ± 0.01 mM) and aromatase (IC_{50} = 0.28 ± 0.02 mM), and produce anti-plasmodium activity [310]; robustaflavone-4′-dimethyl ether can inhibit the accumulation of inflammatory cells by inhibiting the AKT and APK pathways, improve lung tissue damage, and reduce pulmonary edema [311]; rhusflavone, from Rhus parviflora, has a sedative and hypnotic effect, significantly binds to the GABAA-BZD receptor (IC_{50} = 0.045 mM), and induces sleep [178]; II-3, I-5, II-5, II-7, I-4′,II-4′-hexahydroxy-(I-3,II-8)-flavonylflavanonol, from G arcinia nervosa var. pubescens King can produce 73.9% in 18.2 μg/mL Platelet-Activating-Factor Inhibition (IC_{50} = 20.4 μM) [312]; and GB-2a-II-4′-OMe has a certain analgesic effect on the pain sensation induced by Marfrine, and its mechanism from analgesic effect is different of morphine [64]; amentoflavone can reduce the influence of gamma rays [313], and six biflavonoids of *Araucaria angustifolia* can improve DNA damage caused by ultraviolet radiation, including: amentoflavone, mono-*O*-methylamentoflavone, di-*O*-methylamentoflavone, ginkgetin, tri-*O*-methylamentoflavone, and tetra-*O*-methylamentoflavone [314]; GB-2a can inhibit the formation of melanin [315]; studies have shown that isoginkgetin is an inhibitor of mRNA splicing [316]; and chamaejasmine and ginkgetin can improve chronic dermatitis through anti-inflammatory effects [317–319]. All of the above are the pharmacological effects discovered and studied in recent years for biflavonoids, indicating that biflavonoids have great developmental prospects.

6. Pharmacokinetics

LC-MS/MS is a sensitive method used in pharmacokinetics, and it is also used in the pharmacokinetics of biflavonoids. It is used in the study of amentoflavone pharmacokinetics by different drug intake modes, including oral gavage (p.o.), intravenous (i.v.), or intraperitoneal (i.p.) injection in rat models. As a result, 90.7% ± 8.3% of the total amount of amentoflavone (300 mg/kg) by p.o., 73.2% ± 6.29% of amentoflavone (10 mg/kg) by i.v., and 70.2% ± 5.18% of the total amentoflavone (10 mg/kg) by i.p. could be detected. The total amentoflavone was found to circulate as conjugated metabolites in the plasma of rats after different modes of administration [320].

Amentoflavone was used as the standard of the study of pharmacokinetics of biflavonoids in LC-MS/MS. For instance, the pharmacokinetics of total hinokiflavone in rat plasma was studied by LC-MS/MS. It was discovered that $T_{1/2}$ was 6.10 ± 1.86 h [321].

However, there are other ways to calculate the main index of pharmacokinetics. The main components of *Platycladus orientalis* leaf extract include amentoflavone and hinokiflavone. Therefore, their pharmacokinetics in the plasma of a rat model were evaluated by UFLC-MS/MS. Their $T_{1/2}$ and Tmax were 2.60 ± 1.34 h and 1.5 ± 0.00 h (amentoflavone), and 2.11 ± 0.29 h and 1.92 ± 0.20 h (hinokiflavone), respectively [322]. All the pharmacokinetics data of biflavonoids were showed in Table 12.

Table 12. The pharmacokinetics of biflavonoids.

Name	Testline	Delivery Route	Doses(mg/kg)	Method	$T_{1/2}$(h)	References
Amentoflavone	Rat plasma	i.p.	10	LC-MS/MS	3.42 ± 1.45	[320]
Amentoflavone	Rat plasma	i.v.	10	LC-MS/MS	5.88 ± 1.78	[320]
Amentoflavone	Rat plasma	p.o.	300	LC-MS/MS	11.3 ± 3.61	[320]
Amentoflavone	Rat plasma	p.o.	4.31	UFLC-MS/MS	2.60 ± 1.34	[322]
Hinokiflavone	Rat plasma	p.o.	4.30	UFLC-MS/MS	2.11 ± 0.29	[322]
Hinokiflavone	Rat plasma	i.v.	1.0	LC-MS/MS	6.10 ± 1.86	[321]

7. The Biosynthesis and Synthesis of Biflavonoids

7.1. The Biosynthesis of Biflavonoids

There were few references about the biosynthesis of biflavonoids, but it involves the oxidative coupling of two flavonoid units; therefore, the biosynthesis of flavonoids was a significant step to shape biflavonoids in plants. Alzand et al. [323] had reviewed the major pathways of flavonoid biosynthesis. Starting from phenylpropanoid metabolism and then giving the chalcone (trihydroxychalcone and tetrahydroxychalcone). The tetrahydroxychalcone is isomerised to naringenin, a key intermediate, which can transform to several end-flavonoids (Figure 13).

Furthermore, promoting the biosynthesis of biflavonoids can improve the yield of biflavonoids in plants by changing different catalytic enzymes or elicitors. Kicia Karinne Pereira Gromes-Copeland et al. [324] had converted the elicitors of 30 g/L of sucrose and 5 mg/L of 2,4-dichlorophenoxyacetic acid in *Poincianella pyramidalic*. Providing a higher accumulation of amentoflavone (16.44 mg/L) and agathisflavone (0.58 mg/L). Subsequently, they found that the amentoflavone biosynthesis is superior to agatisflavone. It seems to be related to the linkage type between two flavonoid units.

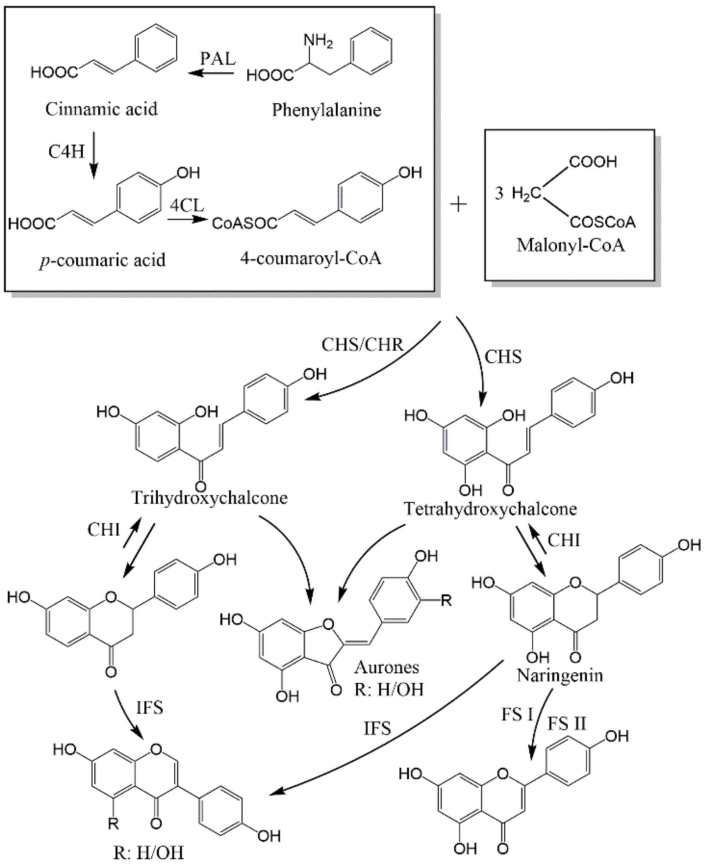


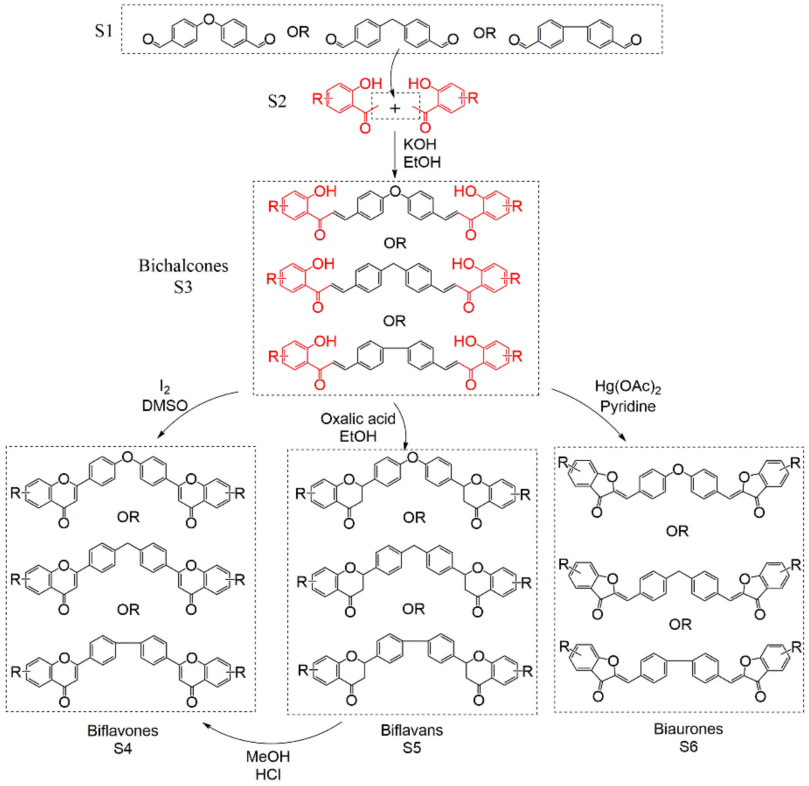
Figure 13. The biosynthesis of flavonoids. Enzyme names are abbreviated as follows: cinnamate-4-hydroxylase (C4H), chalcone isomerase (CHI), chalcone reductase (CHR), chalcone synthase(CHS), 4-coumaroyl:CoA-ligase (4CL), flavone synthase (FS I and FS II), isoflavone synthase (IFS), and Phe ammonia-lyase (PAL).

7.2. The Synthesis of Biflavonoids

Biflavonoids have great medicinal value and great development prospects. Therefore, the quantity needed in treatment and research will increase. However, it is impossible to obtain a large number of single and high-quality biflavonoids by simply extracting and separating the biflavonoids. In the process of synthesizing biflavonoids, Xue Ying et al. [325] reviewed the previous synthesis methods of biflavonoids in 2010, compared the differences between the various methods, and concluded that the synthesis method of biflavonoids is mainly to synthesize a flavonoid monomer. Then, two molecules of flavonoids coupled with boron-containing flavonoids are chosen by Suzuki or iodide-biflavonoids to obtain the final product, or the two molecules are coupled with the catalyst. The related C-C biosynthesis and reverse synthesis analysis, and the Ullmann ether condensation reaction of C-*O*-C, are also introduced. In the case of the literature that has been previously summarized, this review will conduct a general analysis of the new biflavonoid synthesis method, and compare the old method with the new one, so that readers can be more intuitive.

Until 2017, the syntheses of biflavonoids were the construction of a biflavonoid skeleton, and different types of dimers were synthesized under different synthesis conditions. First, the biflavonoid skeleton, bichalcones (S3) is obtained by Claisen–Schmidt aldol condensation from the different dialdehyde molecules (S1) with the corresponding acetophenone (S2). Second, the bichalcone skeleton can obtain biflavones (S4), through iodine-mediated or produce biaurones (S6) by mercury acetate oxidation [27]. Biflavans can be obtained by oxalic acid with EtOH [326], but biflavans will change to biflavones in MeOH with HCl [327]. (Scheme 1). These methods can synthesize different types of biflavonoids as long as different dialdehydes can be provided. For example, the di-

aldehydes S1 are 4,4′-biphenyldicarboxaldehyde, 4,4′-diaryletherdicarboxaldehyde, or 4,4′-bitoluenedicarboxaldehyde, and the biflanonoids are C-C, C-*O*-C, or C-C-C. It can be said that this Claisen–Schmidt aldol condensation of dialdehyde and acetophenone can be the synthesis route of most symmetric biflavonoids. According to the difference in the final product, bichalcones, biflavones, biflavans, and biaurones can also be obtained by autonomously controlling the conditions.



Scheme 1. Total synthesis of C-*O*-C, C-C-C, and C-C biflavonoids.

Due to the large number and types of biflavonoids connected to C-C, there are many related synthetic studies. Among them, Chen et al., achieved the synthesis of C-C biflavonoids through the construction of two flavonoid analogs in 2006: one flavonoid analog substituted by a halogen atom (bromide), and the other substituted by a group coupled by a transition metal-catalyzed cross-coupling method, namely two typical methods: the Suzuki coupling reaction and the Stille coupling reaction. The two flavonoid monomers are connected through the biaryl group. In addition, they synthesized a series of C-C 4′-4′linkage biflavonoids a–f and compared the inhibition of sPLA2-IIA among them. Amentoflavone and ochnaflavone were used as controls. Subsequently, they found that the inhibitory potency of the synthesis biflavonoid a(IC50 = 3.0 + 0.9 M) was slightly better than ochnaflavone(IC50 = 3.5 + 0.6 M), the biflavonoids b(IC50 = 15.5 + 3.7 M), d(IC50 = 19.9 + 4.6 M), and f(IC50 = 23.2 + 3.1 M) possessed the comparative inhibitory potency with amentoflavone(IC50 = 23.8 + 3.4 M) [328]. The C-C 4′-4′ linkage biflavonoids a–f are shown in Figure 14.

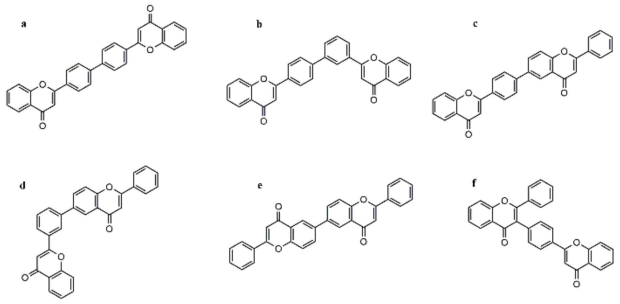
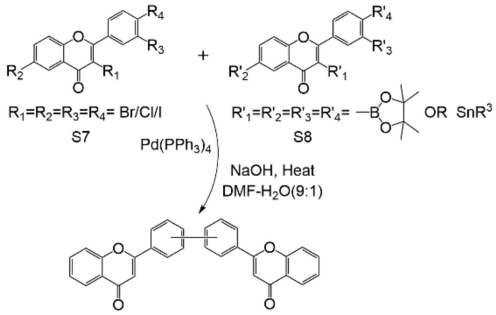


Figure 14. The structure of C-C 4′-4′ linkage biflavonoids.

However, due to the low yield of the above method, it is impossible to obtain high-yield biflavonoids on a large scale; as a result, researchers have found other ways to synthesize C-C type biflavonoids. Brominated, iominated, or chlorine substituted flavones (S7) and commercially available bis(pinacolato) diboron are reacted to obtain the corresponding pinacolato boronates (S8), and then S8 (120 mol%) and S7 under standard conditions ($Pd(PPh_3)_4$ (5 mol%), NaOH (400 mol%), and DMF-water (9:1), 100 °C) are reacted to obtain C-C biflavones. R1, R2, R3, R4, R′1, R′2, R′3, and R′4 are the positions attacked by brominated, iominated, chlorine, or bis(pinacolato) diboron. Moon et al., adjusted the reaction conditions to catalytic $PdCl_2$(dppf) and K_2CO_3 in DMF at 90 °C, to reduce the loss of products [329] (Scheme 2).

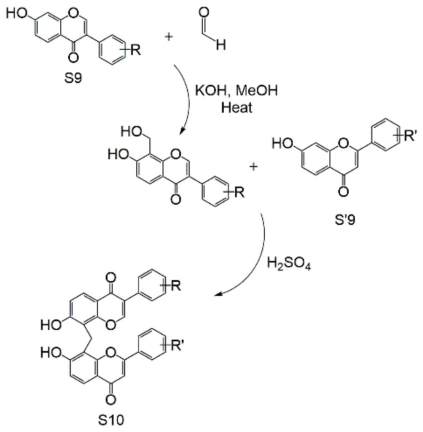


Scheme 2. The synthesis of C-C biflavonoids.

According to the above method, Lim et al., processed chrysin into the precursor product required for the reaction and then performed the relevant synthesis under standard conditions to obtain a C-C (6-6″) anti-inflammatory biflavonoid G168 [330], which had the potency of inhibiting COX-2 mediated PGE2 production. For G168, the IC_{50} value of inhibiting PGE2 production and againsting iNOS-mediated NO production were 0.1 μM and 50 μM. Furthermore, 5 mg/kg G168 was able to inhibit the paw edema in mice (30% inhibition) and 1~5 mg/kg G168 had the capacity to inhibit writhing in mice (57.3~82.9%). It has been proven that this method can synthesize amentoflavone-type biflavonoids [331] and Wikstrol A and B [332].

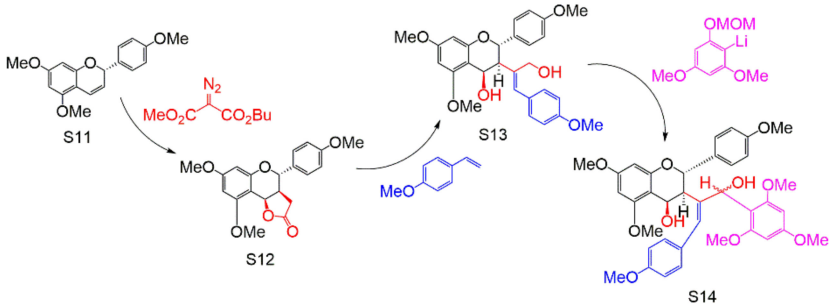
In addition to the synthesis shown in Scheme 1, C-C-C-type biflavonoids can be obtained by the Ullmann condensation reaction of the corresponding flavonoid monomers; assuming the relevant conditions are controlled, and the yield is generally high. For instance, the flavonoid monomer chrysin was used to obtain 7-hydroxy-8-hydroxymethyl-4′-methoxyisoflavonoid [333]. Therefore, the synthesis of C-C-C can be summarized as follows: flavone monomer S9 reacts with formaldehyde to form an intermediate, and then it reacts with another flavone monomer S′9 to form C-C-C type biflavone S10 (Scheme 3). However, the yield of the synthesis in the above conditions is low. Thus, Xue Ying et al., modified the method in 2010; they used daidzein as the raw material, the catalyst was concentrated sulfuric acid, and the feed ratio of the raw material was daidzein. When the amount of catalyst was 10% of the molar ratio of daidzein, and the reaction temperature

was 80 °C for 24 h, the highest yield of daidzein biflavonoid derivative was obtained [334]. Later, in 2011, Xue Ying et al., further improved the method: using 9% Lewis acid as a catalyst, isoflavones and formaldehyde as raw materials, and controlling the reaction temperature to 90 °C for 20 h; the yield can reach 82~85% [335].



Scheme 3. The synthesis of C-C-C biflavonoids.

In 2015, Baron and Mead first synthesized 3-benzylidene-dihydrofurochromen2-ones (S14), a flavan-chalcone type biflavonoid [336]. This was the first time de novo synthesis was attempted. The raw material of this synthetic route was flavonoids and chromene (S11). In the presence of catalytic Rh2(S-TBSP)4, the researchers treated S11 with a diazo derivative to obtain the donor-acceptor cyclopropane, and then used $Sn(OTf)_2$ to rearrange the donor-acceptor cyclopropane to obtain the α-carbomethoxy lactone (S12). Then, removal from the hydroxyl protection and treatment with enolate lithium will result in a mixture of stereoisomers with a high hydroxyl alcohol ratio. The alcohol base was protected by TESCl and oxidized by DDQ to selectively oxidize the protected allyl alcohol to obtain aldehyde S13. After adding the aryl lithium reagent, 71% of the final product S14 was obtained, which was an inseparable isomer mixture, but it had all of the functions of target biflavonoids (Scheme 4). Compared with the synthetic methods of Scheme 1, the required conditions are more difficult to control, but it may become one kind of synthetic method that can control the separation of intermediate stereoisomers to better obtain a pure single product and heterobiflavonoids with different types of flavonoid monomers.



Scheme 4. The de novo synthesis of biflavonoids.

8. Conclusions

In recent years, the method of extracting active ingredients from herbs and using them in research experiments has been a key research direction, and also a huge challenge. As the components in plants are complex, there are many metabolites, and current extraction and separation technologies are still insufficient. A suitable method to efficiently extract, purify, and apply the required active ingredients is the goal we need to achieve. There are many

kinds of biflavonoids, and there is an increasing number of synthetic biflavonoids; they are used as anti-inflammatory and antioxidant therapeutics, as treatments for Alzheimer's disease and Parkinson's disease, and for other therapeutic applications. Their use is more significant in anticancer and antiviral treatment. Moreover, Qiu-xia et al. [337] developed and applied amentoflavone based on antisolvent freeze-drying technology, and studied its stability during storage and the stable type of drug efficacy to solve the problem of poor water solubility of amentoflavone micropowder, and improve the oral availability of the drug. In particular, *Ginkgo biloba* has been proven to be useful in clinical treatment [338]. In summary, there is still much room for developing the pharmacology and synthesizing of biflavonoids, but there is a large gap in the research on dosage forms that needs to be supplemented by additional research. This review mainly provides a more detailed report on the classification, pharmacology, pharmacokinetics, synthesis, and other aspects of biflavonoids, to assist researchers in exploring biflavonoids.

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