Naturally Occurring Homoisoflavonoids and Their Pharmacological Activities

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Key words

- homoisoflavonoids
- phytochemistry
- biosynthesis
- pharmacological activities

Abstract

▼
Homoisoflavonoids, a special subclass of flavonoids, are rarely found in nature, mainly existing in Fabaceae and Asparagaceae families and being less common in Polygonaceae, Portulacaceae, Orchidaceae, and Gentianaceae families. Until now, approximately 240 natural occurring homoisoflavonoids have been identified from roots, barks, heartwood, bulbs, leaves, and seeds of the plants from the above mentioned families, which have often been used in traditional medicine. Homoisoflavonoids have been reported with a broad range of bioactivities, including anti-microbial, anti-mutagenic, anti-oxidant, immunomodulatory, anti-diabetic, cytotoxic, anti-angiogenic, vaso-relaxant, and anti-inflammatory effects. To organize this review, the homoisoflavonoids were classified into five groups based on their structures: sappanin-type (I), scillascillin-type (II), brazilin-type (III), caesalpin-type (IV), and protosappanin-type (V). The structures of natural occurring homoisoflavonoids are described, and their proposed biosynthetic pathway and recent pharmacological studies are discussed. The main purpose of this review is to provide a comprehensive and up-to-date state of knowledge from phytochemical and pharmacological studies performed on homoisoflavonoids during the past decades. Homoisoflavonoids might have a large potential for further investigations of their bioactivities in order to identify important leads.

Abbreviations

▼
AAF: acetylaminofluorene
Akt: protein kinase B
AMPK: adenosine monophosphate-activated protein kinase
2AN: 2-aminoanthracene
ATP: adenosine triphosphate

BAPTA-AM: 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid
Bcl-2: B-cell lymphoma 2
bFGF: basic fibroblast growth factor
BHA: butylated hydroxyanisole
BHT: butylated hydroxytoluene
CAM: chorioallantoic membrane
CD: circular dichroism
cGMP: cyclic guanosine 3',5'-monophosphate
c-src: proto-oncogene tyrosine-protein kinase sarcoma
CYP1A: cytochrome P4501A
DPPH: 2,2-diphenyl-1-picrylhydrazyl
ECD: electronic circular dichroism
EMS: ethyl methanesulfonate
EP: efflux pump
ERK1/2: extracellular regulated protein kinases 1/2
F-2,6-BP: fructose-2,6-bisphosphate
F-6-P: fructose-6-phosphate
GLUT4: glucose transporter type 4
H-6-P: hexose-6-phosphate
HTS: high-throughput screening
IC₅₀: 50% inhibitory concentration
iNOS: inducible nitric oxide synthase
IL-2: interleukin 2
IL-4: interleukin 4
MIC: minimum inhibitory concentration
MMP-9: matrix metalloproteinase-9
L-NAME: N(G)-nitro-L-arginine methyl ester
L-NMMA: N(G)-monomethyl-L-arginine acetate
LPS: lipopolysaccharide
NO: nitric oxide
NOS: nitric oxide synthase
ODQ: ¹H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one
p21: cyclin-dependent kinase inhibitor 1
p53: tumor suppressor p53
PDGF: platelet-derived growth factor
PFK-2: 6-phosphofructo-2-kinase
PI3-kinase: phosphatidylinositol 3-kinase

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PPAR γ : peroxisome proliferator-activated receptor γ
 PTKs: protein tyrosine kinases

ROS: reactive oxygen species
 VSMC: vascular smooth muscle cell

Introduction

Homoisoflavonoids are a rather uncommon subclass of flavonoids which contain one additional carbon atom. They mostly are likely to originate from chalcone precursors. Up to now, about 240 natural occurring homoisoflavonoids have been reported, distributed in various parts of plant materials. The homoisoflavonoids isolated so far could be classified into five types based on their carbon skeleton: sappanin-type (I), scillascillin-type (II), brazilin-type (III), caesalpin-type (IV), and protosappanin-type (V). Sappanin-type homoisoflavonoids are further subdivided according to the pyran ring moiety (● Fig. 1).

Since a wide range of biological and medicinal activities are attributed to them, natural occurring homoisoflavonoids have been intensively studied in the past decades. In 2007, Abegaz et al. reviewed phytochemistry, biological activities, and synthesis of homoisoflavonoids, but they did not classify the structural types of homoisoflavonoids appropriately [1]. In the past seven years, more than 70 homoisoflavonoids have been isolated and structurally elucidated, and various new pharmacological activities related to homoisoflavonoids have been reported [2–36]. This review describes the structures of the homoisoflavonoids isolated so far, discusses the biosynthesis of their different structural types and also summarizes the biological activities of naturally occurring homoisoflavonoids.

Occurrence of Homoisoflavonoids

Homoisoflavonoids are rarely found in nature, only existing in six families so far. The majority of homoisoflavonoids have been reported from Asparagaceae (*Ophiopogon*, *Scilla*, *Muscari*, *Polygonatum*, *Liriope*, *Agave*, *Chlorophytum*, *Hyacinthus*, *Pseudoprospéro*, *Drimia*, *Ornithogalum*, *Ledebouria*, *Dracaena*, *Chionodoxa*, *Veltheimia*, *Bellevalia*, *Eucomis* among others), and Fabaceae (*Hoffmannseggia*, *Caesalpinia*, *Cassia*, *Pterocarpus*, *Haematoxylum* among others). Few homoisoflavonoids have been found in Polygonaceae (*Polygonum* among others), Portulacaceae (*Portulaca* among others), Orchidaceae (*Crematstra* among others), and Gentianaceae (*Tachadenus* among others) (● Table 1 to 6). Homoisoflavonoids are widely distributed in different parts of plants, including roots, barks, heartwood, bulbs, leaves, and seeds. The greatest number of homoisoflavonoids (44 compounds) has been isolated from *Ophiopogon japonicus* [9, 14, 17, 36–42], and a notable number has also been identified in the heartwoods of *Caesalpinia sappanin* [6, 7, 15, 18, 24, 31, 34, 43–52]. All isoflavonoids are described based on their structural types.

Structural Types of Homoisoflavonoids

Sappanin-type (I)

Sappanin-type homoisoflavonoids bear a 3-benzyl chromane skeleton, in which the benzopyran and aromatic rings are connected via one carbon. Until now, 191 sappanin-type homoisoflavonoids have been isolated and structurally elucidated. Based on the substitution on C-3 and C-4, and the location of the double

bond in pyran ring, sappanin-type homoisoflavonoids could be further classified into six sub-groups: 3-benzylchroman type (Ia), 3-benzylchroman-3,4-diol type (Ib), 3-benzylchroman-4-one type (Ic), 3-benzylchroman-3-ol-4-one type (Id), $\Delta^{2,3}$ 3-benzylchroman-4-one type (Ie), and $\Delta^{3,9}$ 3-benzylchroman-4-one type (If). Chemically, sappanin-type homoisoflavonoids can be easily cyclized and decyclized to form rearranged types, including scillascillin-type, brazilin-type, caesalpin-type, and protosappanin-type [20, 50]. Additionally, the attachment of hydroxyl, methoxyl, formyl and methyl groups to the framework and the configurations of the carbons on the pyran ring contribute to structural diversity as well. Sappanin-type homoisoflavonoids account for a significant proportion of homoisoflavonoids.

3-benzylchroman type (Ia): Five 3-benzylchroman type homoisoflavonoids ([1–5], ● Table 1) have been characterized from families Fabaceae (*Caesalpinia* and *Haematoxylum*) and Asparagaceae (*Dracaena* and *Agave*). The hydroxyl groups can be found on C-5 of ring A and C-4' of ring B. Compounds 1–3 were identified with a double bond at C-3 and C-4, while 4 and 5 were saturated at the same positions and the stereochemistry of C-3 remained unresolved. 3-benzylchroman type homoisoflavonoids are speculated to be byproducts of the biosynthesis of other molecules [20].

3-benzylchroman-3,4-diol type (Ib): This sub-group consists of eighteen compounds (6–23, ● Table 1) that were identified from plants of the Fabaceae family (*Caesalpinia* and *Haematoxylum*). The hydroxy or methoxy moieties are located at C-4. The hydroxyl groups can be found on C-5 of ring A and C-4' of ring B. The hydroxyl group at C-3 is β -oriented in most compounds [15, 20, 24, 35, 48, 49] and α -oriented in only one compound (23) [15]. When the protons of the methylene (C-9) appear as singlet in the $^1\text{H-NMR}$ spectrum, the relative configuration of the hydroxyl groups on C-3 and C-4 is determined as *cis*; on the contrary, when the methylene was shown as two doublets, the relative configuration of the hydroxyl groups could be *trans* [15, 20, 24, 35, 48, 49]. The absolute configurations of C-3 and C-4 were determined by CD spectroscopy. The negative Cotton effect at 283 nm suggested absolute configurations of C-3 and C-4 to be R and S, respectively; on the other hand, the positive Cotton effect at 283 nm indicated absolute configurations of C-3 and C-4 to be

Fig. 1 Carbon skeletons of homoisoflavonoids.

Table 1 Structures of 3-benzylchroman type (1a) and 3-benzylchroman-3,4-diol type (1b) homoisoflavonoids, with their sources.

No	R1	R2	R3	R4	Source	Ref.
1	H	H			<i>Haematoxylum</i>	[20]
2	H	OH			<i>Caesalpinia</i>	[15]
3	OH	OH			<i>Haematoxylum</i>	[20]

4	OH	H			<i>Agave</i>	[5]
5	-O-CH ₂ -O-				<i>Dracaena</i>	[13]

6	H	H	β -OH	β -OH	<i>Caesalpinia</i>	[48]
7	H	H	β -OH	β -OMe	<i>Caesalpinia</i>	[49]
8	H	OH	β -OH	β -OH	<i>Caesalpinia</i>	[48]
9	H	OH	β -OH	β -OMe	<i>Caesalpinia</i>	[49]
10	H	OH	$-\beta$ -O-C(CH ₃) ₂ - β -O-		<i>Caesalpinia</i>	[15]
11	H	OMe	β -OH	β -OH	<i>Caesalpinia</i>	[48]
12	H	OMe	β -OH	β -OMe	<i>Caesalpinia</i>	[24]
13	OH	OH	β -OH	β -OH	<i>Haematoxylum</i>	[20]
14	OH	OH	β -OH	β -OMe	<i>Haematoxylum</i>	[20]
15	H	H	β -OH	α -OH	<i>Caesalpinia</i>	[49]
16	H	OH	β -OH	α -OH	<i>Caesalpinia</i>	[48]
17	H	OH	β -OH	α -OMe	<i>Caesalpinia</i>	[49]
18	H	OH	β -OH	α -OMe	<i>Caesalpinia</i>	[49]
19	H	OMe	β -OH	β -OH	<i>Caesalpinia</i>	[48]
20	H	OMe	β -OH	α -OMe	<i>Caesalpinia</i>	[35]
21	OH	OH	β -OH	α -OH	<i>Haematoxylum</i>	[20]
22	OH	OH	β -OH	α -OMe	<i>Haematoxylum</i>	[20]
23	H	OH	α -OH	β -OH	<i>Caesalpinia</i>	[15]

R [20, 49]. Compound **10** from *Caesalpinia sappan* is unusual since it contains an acetonide moiety, therefore it could be speculated that it is an artificial derivative of compound **8** [15].

3-benzylchroman-4-one type (1c): A large number of 3-benzylchroman-4-one type homoisoflavonoids have been reported. Till now, 88 compounds (**24–111**, **Table 2**) were identified, from various medicinal plants, including several families: Fabaceae (*Caesalpinia*), Polygonaceae (*Polygonum*), Asparagaceae (*Ophiopogon*, *Scilla*, *Muscari*, *Liriope*, *Polygonatum*, *Agave*, *Drimia*, *Ledebouria*, *Chionodoxa*, *Bellevallia*, and *Eucomis*), and Portulacaceae (*Portulaca*).

Of these, 49 compounds are only hydroxy-, methoxy-, acetyl- and/or methylenedioxy-substituted (**Table 2**). Their great structural diversity is due to the number and position of these oxygen functions. Two to five oxygen-bearing moieties usually locate at C-6 and C-8 in ring A, as well as C-3' and C-4' in ring B, but rarely at other positions. Besides oxygen functions, other substituents can be found in 3-benzylchroman-4-one type homoisoflavonoids, such as methyl and formyl groups, which can be found at C-5 and C-7 of ring A. Compounds substituted with

methyl and/or formyl groups have been only identified from the genera *Ophiopogon* and *Liriope* (Asparagaceae), as well as *Polygonum* (Polygonaceae). It could be considered as the chemical classification feature of these three genera.

The substitution of C-2 is uncommon in natural occurring homoisoflavonoids. Till now, there are only two such compounds with hydroxyl group at C-2 (**110** and **121**, **Table 2**), isolated from *Ophiopogon japonicus*. The configuration of the hydroxyl group was not determined [37]. Recently, the first 9-hydroxylhomoisoflavone, polygohomoisoflavanone, (**109**, **Table 2**) was isolated from *Polygonum senegalense* [23]. Homoisoflavonoids with isoprenoid-derived groups are rare; three such compounds (**106–108**, **Table 2**) were isolated from *Ledebouria floribunda* [3].

The configuration of C-3 in 3-benzylchroman-4-one type homoisoflavonoids remained in the most cases unsolved. Recently, Dai et al determined the stereochemistry at C-3 by ECD spectroscopy. They found that a positive $\pi \rightarrow \pi^*$ Cotton effect in the 280–295 nm region and a negative $n \rightarrow \pi^*$ Cotton effect in the 310–325 nm region indicated an *S* configuration of this position [7].

3-benzylchroman-3-ol-4-one type (1d): This class is represented by 24 members (**112–135**, **Table 3**), which have been identified from Fabaceae (*Caesalpinia* and *Haematoxylum*) and Asparagaceae (*Ophiopogon*, *Polygonatum*, *Liriope*, *Agave*, *Dracaena*, *Ledebouria*, *Pseudoprospiro*, *Hyacinthus*, and *Drimia*) and are shown in **Table 3**. In addition, three *O*-glycosylated homoisoflavonoids (**133–135**) were isolated from *Ornithogalum caudatum* (Asparagaceae) [69]. These compounds carry a varying number of *O*-substituents on ring A and ring B, including hydroxyl, methoxyl, and methylenedioxy groups (**Table 3**). These substituents are usually located at C-5, C-7, C-3', and C-4', and only in some cases at C-6 and C-8. Beside those, a methyl group can be found at C-6. The hydroxyl group at C-3 can be α - or β -oriented. Using ECD spectroscopy, Dai et al. found a positive $\pi \rightarrow \pi^*$ Cotton effect in the 280–295 nm region and a negative $n \rightarrow \pi^*$ Cotton effect in the 310–325 nm region indicating a *R* configuration at C-3 [7].

$\Delta^{2,3}$ 3-benzylchroman-4-one type (1e): This group of homoisoflavonoids comprises currently twenty compounds (**Table 4**). Among them, nineteen compounds (**137–155**) were identified from the genus *Ophiopogon* (Asparagaceae), and only one (**136**) was isolated from the genus *Cassia* (Fabaceae) (**Table 4**). They are all hydroxy-substituted at C-5 in ring A, and usually hydroxyl-, methoxy-, and/or methylenedioxy-substituted at C-7 in ring A, as well as at C-2', C-3', and C-4' in ring B. Additionally, methyl and/or formyl groups can be found at C-6 and C-8 in ring A in compounds isolated from the genus *Ophiopogon*. The only one with methyl group at C-7 was isolated from the genus *Cassia*, which was the first example with a methyl substituent from the Fabaceae family. Therefore, a re-authentication of the investigated plant material might be of interest.

$\Delta^{3,9}$ 3-benzylchroman-4-one type (1f): This group consists of 36 compounds (**Table 5**). Among them, most (**156–186**) have an *E*-geometry double bond at C-3 and C-9 (**Table 5**). A varying number of *O*-substituents are present on rings A and B, including hydroxyl, methoxyl, acetyl and/or methylenedioxy functions. These groups are usually located at C-5, C-7, C-8, C-3', and C-4', but can be found in some cases also at C-6 and C-2'. Interestingly, the $\Delta^{3,9}$ 3-benzylchroman-4-one type homoisoflavonoids from Fabaceae (*Caesalpinia* and *Hoffmannseggia*) have no substitution at C-5. The others, isolated from Asparagaceae (*Scilla*, *Muscari*, *Ledebouria*, *Hyacinthus*, *Chionodoxa*, and *Eucomis*) and Portulacaceae (*Portulaca*) have *O*-substituents at C-5. This difference might be considered as chemical classification feature.

Table 2 Structures of 3-benzylchroman-4-one type (Ic) homoisoflavonoids, with their sources.

No	R1	R2	R3	R4	R5	R6	R7	R8	3-H	Source	Ref.
24	H	H	OH	H	H	H	OMe	H	unknown	Agave	[5]
25	H	H	OH	H	H	OH	OH	H	unknown	Caesalpinia	[15]
26	H	H	-O-CH ₂ -O-		H	H	OMe	H	β	Chlorophytum	[53]
27	H	OH	H	H	OH	OH	H	OH	β	Caesalpinia	[2]
28	H	OH	OMe	H	H	OH	OMe	H	unknown	Pterocarpus	[54]
29	H	OMe	H	H	OH	OH	H	OH	β	Caesalpinia	[2]
30	OH	H	OH	H	H	H	OH	H	α	Ledebouria	[30]
31	OH	H	OH	H	H	H	OMe	H	α	Ledebouria	[30]
32	OH	H	OH	H	H	H	OMe	H	β	Drimia	[7]
33	OH	H	OH	H	H	OH	OH	H	α	Ledebouria	[30]
34	OH	H	OH	H	H	OH	OMe	H	unknown	Scilla	[55]
35	OH	H	OH	H	H	OMe	OH	H	α	Drimia	[56]
36	OH	H	OH	H	H	OMe	OMe	H	unknown	Scilla	[55]
37	OH	H	OH	H	OH	H	OH	H	α	Liriope	[29]
38	OH	H	OH	OMe	H	H	OH	H	unknown	Muscari	[57]
39	OH	H	OH	OMe	H	OH	OMe	H	unknown	Chionodoxa	[58]
40	OH	H	OMe	H	H	H	OH	H	unknown	Ledebouria	[59]
41	OH	H	OMe	H	H	H	OMe	H	unknown	Eucomis	[60]
42	OH	H	OMe	H	H	OH	OMe	H	unknown	Scilla	[61]
43	OH	H	OMe	H	H	OMe	OH	H	unknown	Scilla	[55]
44	OH	H	OMe	OH	H	OH	OH	H	unknown	Muscari	[62]
45	OH	H	OMe	OMe	H	H	OH	H	unknown	Bellevia	[63]
46	OH	H	OMe	OAc	H	H	OH	H	unknown	Muscari	[57]
47	OH	Me	OH	H	H	H	OH	H	α	Liriope	[29]
48	OH	Me	OH	H	H	H	OMe	H	α	Ophiopogon	[36]
49	OH	Me	OH	H	H	-O-CH ₂ -O-		H	unknown	Ophiopogon	[40]
50	OH	Me	OH	H	OH	H	OH	H	α	Ophiopogon	[9]
51	OH	Me	OH	H	OH	H	OH	H	α	Liriope	[29]
52	OH	Me	OH	Me	H	H	OH	H	α	Polygumum	[11]
53	OH	Me	OH	Me	H	H	OMe	H	α	Ophiopogon	[36]
54	OH	Me	OH	Me	H	OH	OMe	H	unknown	Polygumum	[33]
55	OH	Me	OH	Me	H	-O-CH ₂ -O-		H	α	Ophiopogon	[36]
56	OH	Me	OH	Me	H	OMe	OH	H	α	Ophiopogon	[36, 37]
57	OH	Me	OH	Me	H	OMe	OH	OMe	unknown	Ophiopogon	[37]
58	OH	Me	OH	Me	OH	H	OMe	H	unknown	Polygumum	[33]
59	OH	Me	OH	CHO	H	-O-CH ₂ -O-		H	α	Ophiopogon	[36, 39]
60	OH	Me	OH	CHO	H	H	OMe	H	α	Ophiopogon	[36]
61	OH	Me	OH	OMe	H	H	OH	H	unknown	Polygonatum	[33]
62	OH	Me	OH	OMe	H	H	OMe	H	unknown	Polygonatum	[33]
63	OH	Me	OH	OMe	OH	H	OMe	H	unknown	Ophiopogon	[37, 39]
64	OH	Me	OH	OMe	OH	OH	OMe	H	α	Ophiopogon	[14]
65	OH	Me	OMe	H	H	H	OH	H	α	Liriope	[29]
66	OH	Me	OMe	H	OH	H	OH	H	α	Liriope	[29]
67	OH	Me	OMe	Me	H	H	OMe	H	α	Ophiopogon	[36]
68	OH	Me	OMe	OMe	H	OH	OH	H	unknown	Ophiopogon	[37]
69	OH	Me	Oglc	CHO	H	-O-CH ₂ -O-		H	α	Ophiopogon	[14]
70	OH	CHO	OH	Me	H	H	OH	H	unknown	Ophiopogon	[36]
71	OH	CHO	OH	Me	H	H	OMe	H	unknown	Ophiopogon	[40]
72	OH	CHO	OH	Me	H	-O-CH ₂ -O-		H	unknown	Ophiopogon	[40]
73	OH	CHO	OMe	Me	H	-O-CH ₂ -O-		H	unknown	Ophiopogon	[40]
74	OH	OH	OMe	OMe	H	OH	OH	H	unknown	Bellevia	[64]
75	OH	OMe	OH	H	H	H	OH	H	β	Scilla	[25]
76	OH	OMe	OH	H	H	H	OMe	H	unknown	Polygonatum	[65]
77	OH	OMe	OH	H	H	OH	OH	H	β	Scilla	[25]
78	OH	OMe	OH	H	H	OH	OMe	H	unknown	Scilla	[66]
79	OH	OMe	OH	H	H	OMe	OH	H	unknown	Muscari	[62]
80	OH	OMe	OMe	H	H	H	OH	H	unknown	Ledebouria	[59]

continued

Table 2 Continued

No	R1	R2	R3	R4	R5	R6	R7	R8	3-H	Source	Ref.
81	OH	OMe	OMe	H	H	OH	OH	H	β	Scilla	[25]
82	OH	OMe	OMe	H	H	OMe	OH	H	unknown	Scilla	[55]
83	OH	OMe	OMe	H	OH	H	H	H	unknown	Portulaca	[32]
84	OH	OMe	OMe	OH	H	H	OH	H	α	Veltheimia	[67]
85	OH	OMe	OMe	OMe	H	H	OH	H	α	Veltheimia	[67]
86	OMe	H	OH	H	H	H	OH	H	α	Ledebouria	[30]
87	OMe	H	OH	H	H	OH	OH	H	α	Ledebouria	[30]
88	OMe	H	OH	H	H	OH	OMe	H	unknown	Muscari	[62]
89	OMe	H	OMe	H	H	H	OH	H	unknown	Scilla	[61]
90	OMe	H	OMe	H	H	H	OMe	H	unknown	Scilla	[61]
91	OMe	H	OMe	H	H	H	OAc	H	unknown	Scilla	[61]
92	OMe	H	OMe	H	OH	H	H	H	unknown	Portulaca	[32]
93	OMe	H	OMe	OH	H	H	OMe	H	unknown	Scilla	[55]
94	OMe	H	OMe	OMe	H	H	OH	H	unknown	Ledebouria	[59]
95	OMe	Me	OH	CHO	H	H	OMe	H	α	Ophiopogon	[36]
96	OMe	Me	OH	CHO	H	-O-CH ₂ -O-		H	unknown	Ophiopogon	[39]
97	OMe	Me	OH	OMe	OH	H	OMe	H	unknown	Ophiopogon	[37, 39]
98	OMe	Me	Oglc	OMe	OH	-O-CH ₂ -O-		H	α	Ophiopogon	[14]
99	OMe	OH	OMe	H	H	H	OMe	H	unknown	Scilla	[55]
100	OMe	OMe	OH	H	H	H	OH	H	unknown	Eucomis	[68]
101	OMe	OMe	OH	H	H	H	OMe	H	unknown	Scilla	[10]
102	OMe	OMe	OMe	H	H	H	OH	H	unknown	Scilla	[55]
103	OMe	OMe	OMe	H	H	H	OMe	H	β	Drimia	[7]
104	OMe	OMe	OMe	H	H	-O-CH ₂ -O-		H	β	Drimia	[7]
105	OMe	OMe	OMe	H	OH	H	H	H	unknown	Portulaca	[32]
106	OH	-CH=CH-C(CH ₃) ₂ -O-		H	H	H	OMe	H	unknown	Ledebouria	[3]
107	OH	OH	geranyl	H	H	H	OH	H	unknown	Ledebouria	[3]
108	OH	OH	geranyl	isopentenyl	H	H	OH	H	unknown	Ledebouria	[3]

109	H	H	H	H	OH				unknown	Polygonum	[23]
110	Me	H	OMe	OH	H				unknown	Ophiopogon	[37]
111	Me	-O-CH ₂ -O-		OH	H				unknown	Ophiopogon	[37]

Homoisoflavonoids with *Z*-geometry double bond at C-3 and C-9 are rare; there are only five such compounds reported till now (187–191, Table 5), isolated from genera *Eucomis* and *Caesalpinia* [4, 27, 60, 73]. They are all methoxy-substituted at C-4' in ring B, and usually hydroxyl- and/or methoxy-substituted at C-5, C-7, and C-8 in ring A. The *E*- and *Z*-isomers can be easily distinguished by ¹H-NMR-spectroscopy since the characteristic signals of H-2 and H-9 of the *Z*-isomer appear as a singlet at about 5.00 ppm and a broad singlet at 7.00 ppm, respectively, while those of the corresponding *E*-isomer appear as a doublet at about 5.40 ppm and a broad singlet at 7.80 ppm, respectively [8, 27].

Scillascillin-type (II)

The C-6' in ring B of sappanin-type compounds connects to C-3 in pyran ring to form a spiro four-member ring, which is classified as scillascillin-type homoisoflavonoid. Until now, 16 scillascillin-type homoisoflavonoids have been isolated and identified (192–

207, Table 6). These compounds carry *O*-substituents at C-5 and C-7 in ring A, and C-2', C-3', and C-4' in ring B, including hydroxyl, methoxyl, methylenedioxy and acetyl functions. Scillascillin-type homoisoflavonoids were only isolated from Asparagaceae (*Scilla*, *Muscari*, *Ledebouria*, and *Chionodoxa*). The stereochemistry of C-3 is mostly unsolved. Using ECD spectroscopy, recent studies determined the stereochemistry at C-3 as *R* by the positive $\pi \rightarrow \pi^*$ Cotton effect in the 290–300 nm region and the negative $n \rightarrow \pi^*$ Cotton effect in the 330–350 nm region [25, 30].

Brazilin-type (III)

Brazilin-type homoisoflavonoids result when the C-6' in ring B of sappanin-type compounds connects to C-4 in the pyran ring to form a fused five-member ring. Only nine brazilin-type homoisoflavonoids have been reported from Fabaceae (*Caesalpinia* and *Haematoxylum*) so far (208–216, Fig. 2) [20, 24, 48, 49, 81]. These compounds carry hydroxyl groups at C-7 in ring A and C-

Table 3 Structures of 3-benzylchroman-3-ol-4-one type (Id) homoisflavonoids, with their sources.

No	R1	R2	R3	R4	R5	R6	3-OH	Source	Ref.
112	H	H	OH	H	OH	OH	β	Caesalpinia	[47]
113	H	H	OH	H	OMe	OH	β	Caesalpinia	[6]
114	H	H	OH	OH	OH	OH	β	Haematoxylum	[20]
115	H	H	OMe	H	H	OMe	unknown	Agave	[5]
116	OH	H	OH	H	H	OH	β	Dracaena	[19]
117	OH	H	OH	H	H	OMe	unknown	Pseudoprospero	[16]
118	OH	H	OH	H	H	OMe	α	Ledebouria	[30]
119	OH	H	OH	H	OH	OMe	unknown	Pseudoprospero	[16]
120	OH	H	OMe	H	H	OMe	unknown	Pseudoprospero	[16]
121	OH	H	OMe	H	OMe	OH	unknown	Hyacinthus	[70]
122	OH	H	OMe	Me	H	OMe	β	Dracaena	[71]
123	OH	H	OMe	OMe	OMe	OMe	unknown	Pseudoprospero	[16]
124	OH	Me	OH	H	H	OMe	β	Dracaena	[22]
125	OH	Me	OH	Me	H	OH	α	Polygonatum	[12]
126	OH	Me	OH	Me	-O-CH ₂ -O-		β	Ophiopogon	[17]
127	OH	Me	OH	OMe	H	OH	α	Polygonatum	[12]
128	OH	Me	OMe	H	H	OH	β	Liriope	[29]
129	OH	OH	OMe	H	OH	OMe	unknown	Pseudoprospero	[16]
130	OMe	OMe	OMe	H	H	OH	β	Drimia	[7]
131	OMe	OMe	OMe	H	H	OMe	β	Drimia	[7]
132	OMe	OMe	OMe	H	-O-CH ₂ -O-		β	Drimia	[7]
133	O-β-D-glc	H	OMe	H	H	OMe	α	Ornithogalum	[69]
134	O-β-D-glc-(2-1)-α-l-rha	H	OMe	H	H	OMe	α	Ornithogalum	[69]
135	O-β-D-glc-(6-1)-α-l-rha	H	OMe	H	H	OMe	α	Ornithogalum	[69]

Table 4 Structures of Δ2,3 3-benzylchroman-4-one type (Ie) homoisflavonoids, with their sources.

No	R1	R2	R3	R4	R5	R6	Source	Ref.
136	H	Me	H	H	H	OH	Cassia	[72]
137	H	OH	H	H	H	OH	Ophiopogon	[42]
138	H	OH	Me	H	H	OH	Ophiopogon	[41]
139	H	OH	Me	H	-O-CH ₂ -O-		Ophiopogon	[41]
140	H	OH	Me	OH	-O-CH ₂ -O-		Ophiopogon	[38]
141	Me	OH	H	H	H	OH	Ophiopogon	[38]
142	Me	OH	H	H	H	OMe	Ophiopogon	[41]
143	Me	OH	H	H	-O-CH ₂ -O-		Ophiopogon	[41]
144	Me	OH	H	OH	H	OH	Ophiopogon	[9]
145	Me	OH	H	OH	-O-CH ₂ -O-		Ophiopogon	[38]
146	Me	OH	Me	H	H	OMe	Ophiopogon	[41]
147	Me	OH	Me	H	-O-CH ₂ -O-		Ophiopogon	[42]
148	Me	OH	Me	OH	-O-CH ₂ -O-		Ophiopogon	[42]
149	Me	OH	CHO	H	H	OMe	Ophiopogon	[36]
150	Me	OH	CHO	H	-O-CH ₂ -O-		Ophiopogon	[39]
151	Me	OH	OMe	OH	H	OMe	Ophiopogon	[17]
152	Me	OMe	H	H	OH	OH	Ophiopogon	[42]
153	Me	OMe	Me	H	H	OMe	Ophiopogon	[36]
154	CHO	OH	Me	H	H	OMe	Ophiopogon	[42]
155	CHO	OH	Me	H	-O-CH ₂ -O-		Ophiopogon	[42]

Table 5 Structures of $\Delta 3,9$ 3-benzylchroman-4-one type (If) homoisoflavonoids, with their sources.

<div> </div>									
No	R1	R2	R3	R4	R5	R6	R7	Source	Ref.
156	H	H	OH	H	H	H	OH	Caesalpinia	[47]
157	H	H	OH	H	H	H	Ome	Caesalpinia	[74]
158	H	H	OH	H	H	OH	OH	Caesalpinia	[47]
159	H	H	OH	H	H	-O-CH ₂ -O-		Caesalpinia	[8]
160	H	H	OH	H	H	OH	Ome	Caesalpinia	[8]
161	H	H	OH	OH	H	H	Ome	Hoffmannseggia	[75]
162	H	H	OH	OMe	H	H	Ome	Caesalpinia	[27]
163	H	H	OMe	H	H	H	OH	Caesalpinia	[76]
164	H	H	OMe	H	H	H	Ome	Caesalpinia	[8]
165	H	H	OMe	H	H	OMe	Ome	Caesalpinia	[8]
166	H	H	OMe	H	H	-O-CH ₂ -O-		Caesalpinia	[8]
167	H	H	OMe	OH	H	H	Ome	Hoffmannseggia	[75]
168	H	H	OMe	OMe	H	H	OH	Caesalpinia	[76]
169	H	Me	H	Me	H	H	OH	Polygonatum	[33]
170	H	OMe	OMe	H	H	OH	Ome	Caesalpinia	[8]
171	OH	H	OH	H	H	H	OH	Scilla	[55]
172	OH	H	OH	H	H	H	Ome	Eucomis	[60]
173	OH	H	OH	OMe	H	H	OH	Chionodoxa	[58]
174	OH	H	OH	OMe	H	H	Ome	Eucomis	[77]
175	OH	H	OH	OMe	H	OH	OH	Chionodoxa	[58]
176	OH	H	OMe	H	H	H	OH	Scilla	[55]
177	OH	H	OMe	H	H	H	Ome	Eucomis	[60]
178	OH	H	OMe	H	OH	H	H	Portulaca	[32]
179	OH	H	OMe	OH	H	OH	OH	Muscari	[78]
180	OH	H	Oglc	H	H	H	OH	Polygonatum	[33]
181	OH	OH	OH	OMe	H	H	OH	Hyacinthum	[70]
182	OH	OMe	OH	H	H	H	OH	Eucomis	[77]
183	OH	OMe	OH	H	H	H	OMe	Scilla	[55]
184	OH	OMe	OH	H	H	OH	OH	Scilla	[55]
185	OMe	H	OH	H	H	OH	OH	Muscari	[78]
186	OAc	H	OH	H	H	OH	OH	Ledebouria	[30]
<div> </div>									
187	H	OH	H					Caesalpinia	[73]
188	H	OH	OH					Caesalpinia	[27]
189	H	OH	OMe					Caesalpinia	[4]
190	OH	OH	H					Eucomis	[60]
191	OH	OMe	H					Eucomis	[60]

4' in ring B. Brazilin (**208**) and hematoxylin (**213**) were isolated as the major constituents of the heartwood of *Caesalpinia sappan* and *Haematoxylum campechianum*, respectively [20,49]. Hematoxylin (**213**) was identified to be the sweet principle of the heartwood of *H. campechianum*, while brazilin (**208**) and hematein (**216**) are tasteless [81].

Caesalpin-type (IV)

The C-6' in ring B of sappanin-type compounds connects to C-4a of the pyran ring to form a bridged six-member ring in caesalpin-type homoisoflavonoids. Only seven caesalpin-type homoisoflavonoids have been reported from families Fabaceae (*Caesalpinia* and *Haematoxylum*) and Asparagaceae (*Dracaena*) so far (**217–223**, Fig. 3) [20,35,51,82]. The compounds carry a carbonyl group at C-7 in ring A and are usually hydroxyl-substituted at C-3' and C-4' in ring B. When the hydroxyl group at C-3 is β -orient-

Table 6 Structures of scillascillin-type (II) homoisoflavonoids, with their sources.

No	R1	R2	R3	R4	R5	R6	Source	Ref.
192	H	OH	OH	H	OH	OMe	<i>Muscari</i>	[62]
193	H	OH	OH	H	OMe	OH	<i>Muscari</i>	[79]
194	H	OH	OH	H	OMe	OMe	<i>Ledebouria</i>	[59]
195	H	OH	OH	H	-O-CH ₂ -O-		<i>Muscari</i>	[79]
196	H	OH	OH	OH	OMe	OMe	<i>Scilla</i>	[25]
197	H	OH	OMe	H	OH	OH	<i>Muscari</i>	[79]
198	H	OH	OMe	H	OMe	OH	<i>Muscari</i>	[79]
199	H	OH	OMe	H	OMe	OMe	<i>Ledebouria</i>	[59]
200	H	OH	OMe	H	-O-CH ₂ -O-		<i>Scilla</i>	[80]
201	H	OH	OMe	OH	OMe	H	<i>Muscari</i>	[79]
202	H	OH	OMe	OH	OMe	OMe	<i>Ledebouria</i>	[30]
203	H	OMe	OMe	OMe	OMe	H	<i>Muscari</i>	[79]
204	OH	OH	OH	H	-O-CH ₂ -O-		<i>Chionodoxa</i>	[58]
205	OH	OH	OMe	H	-O-CH ₂ -O-		<i>Scilla</i>	[80]
206	α -OAc	OAc	OMe	H	-O-CH ₂ -O-		<i>Ledebouria</i>	[30]
207	β -OAc	OAc	OMe	H	-O-CH ₂ -O-		<i>Ledebouria</i>	[30]

Fig. 2 Structures of brazilin-type (III) homoisoflavonoids.

ed, the relative configuration of C-4 can be determined by signal appearance of H-9 in ¹H-NMR spectrum. When H-9 appears as a doublet, the methoxyl group at C-3 is β -oriented; when H-9 appears as two doublets, the methoxyl group is α -oriented [20, 35].

Protosappanin-type (V)

When the single bond between C-4 and C-4a participates in the formation of an eight-member ring, the resulting homoisoflavonoids are classified as protosappanin-type. Eleven compounds have been reported (224–234, ● Fig. 4) so far, isolated only from Fabaceae (*Caesalpinia* and *Haematoxylum*) [6, 20, 21, 31, 43, 46]. These compounds carry hydroxyl groups at C-7 in ring A and C-4' in ring B, and an O-substituent (hydroxyl or methoxyl) at C-3' in ring B. The substituents at C-3 could be hydroxyl, formyl, hydroxymethyl, and carbonyl groups. Recently, the first eight-member ring opened protosappanin-type compound (234) was identified [31].

Fig. 3 Structures of caesalpin-type (IV) homoisoflavonoids.

Fig. 4 Structures of protosappanin-type (V) homoisoflavonoids.

Miscellaneous structures

In addition, two condensation products of brazilin and protosappanin (**235** and **236**), a dimer of caesalpin-type compound (**237**), and three derivatives, brazilide A (**238**), caesalpin P (**239**), and caesalpinaphenol B (**240**) were isolated from *Caesalpinia sappan* (Fig. 5) [6, 44, 51, 52, 83].

Proposed Biosynthetic Pathway of Homoisoflavonoids

Chalcones are considered as the precursors of homoisoflavonoids in their biosynthesis [20, 50]. As shown in Fig. 6, the chalcone precursor 2'-hydroxyl chalcone could be converted into a 3-benzylchroman-4-one type homoisoflavonoid, which in turn could be a 3-benzylchroman-3-ol-4-one type. The latter compounds could be reduced to a 3-benzylchroman type, 3-benzylchroman-3,4-diol type, $\Delta^{2,3}$ 3-benzylchroman-4-one type, and $\Delta^{3,9}$ 3-benzylchroman-4-one type homoisoflavonoid, respectively. In addition, a 3-benzylchroman-4-one type homoisoflavonoid could cyclize to form a scillascillin-type, brazilin-type, or caesalpin-type compound, while the latter could further decyclize to form a protosappanin-type. For instance, all isolated homoisoflavonoids from *Haematoxylum campechianum* could be considered as precursors or byproducts of hematoxylin [20]. Through aldol condensation, dehydration, oxidation, and reduction, the chalcone precursor was finally transformed to the end product, hematoxylin. In this course, many homoisoflavonoids could be obtained as byproducts. The C-4 carbonyl group in 3-benzylchroman-4-one type homoisoflavonoids would be non-selectively reduced to a hydroxyl group that could be methylated. Cyclization between C-4a and C-6' by a nucleophilic addition would result in caesalpin-type compounds. Further oxidation of caesalpin-type compounds could yield protosappanin-type ones. Additionally, the vicinal diol in 3-benzylchroman-3,4-diol type homoisoflavonoids could be reduced to give 3-benzylchroman type compounds.

Fig. 5 Structures of miscellaneous homoisoflavonoids.

Pharmacological Activities

Homoisoflavonoids have been reported to exert wide range of biological activities. These include: anti-microbial, anti-mutagenic, anti-oxidant, immunomodulatory, anti-diabetic, cytotoxic, anti-angiogenic, vasorelaxant, and anti-inflammatory effects. In addition, homoisoflavonoids were reported to inhibit protein tyrosine kinase and showed estrogenic and anti-estrogenic activities.

Anti-microbial effects

Homoisoflavonoids have shown inhibitory activities against various kinds of microorganisms. Reddy et al. isolated four homoisoflavonoids, 4-O-methylsappanol (**8**), brazilin (**208**), caesalpin J (**217**), and protosappanin A (**224**) from *Caesalpinia sappan* and found that 4-O-methylsappanol possesses growth inhibitory activity against the fungus *Beauveria bassiana*, at a concentration of 100 µg/mL comparable to that of the standard drug dithane M-45 [84]. A homoisoflavonone, 3-(4'-methoxybenzyl)-7,8-methylenedioxy-chroman-4-one (**26**), was isolated from *Chlorophytum inornatum*, which exhibited MIC ranging from 16–256 µg/mL against growth of four strains of fast-growing mycobacteria [53]. In search for EP inhibitors from natural products, Roy et al. found that bonducellin (**157**), a homoisoflavonoid isolated from *C. digyna* roots, showing a reduction of the MIC of ethidium bromide against *Mycobacterium smegmatis* mc² 155 by eight fold to a concentration of 62.5 mg/L, also showed significant EP inhibitory activity [28].

Anti-mutagenic effects

Mutagens are physical or chemical agents that change the genetic material [85]. Homoisoflavonoids have shown anti-mutagenic activities against several mutagens. Wall et al. isolated two homoisoflavonoids, intricatin (**167**) and intricatinol (**161**), from *Hoffmannseggia intricata* and found that both compounds are able to inhibit the mutagenicity of 2AN towards *Salmonella typhimurium* [75]. Intricatinol was found to be much more active than intricatin in the inhibition of the mutagenicity of AAF toward *S. typhimurium* and the inhibition of EMS toward *S. typhimurium* [75]. A mixture containing three homoisoflavonoids (**179**, **184**, and **185**) from *Muscari racemosum* was shown to exert anti-mutagenic effects on four strains of *S. typhimurium* and the yeast strain *Saccharomyces cerevisiae*, and anti-clastogenic effect on *Vicia sativa* [86]. These results suggest that homoisoflavonoids could be included in the group of natural anti-mutagens of great

Fig. 6 Proposed biosynthetic pathway for various types of homoisoflavonoids.

pharmacological importance and might be beneficial for the prevention of cancer.

Anti-oxidant activity

ROS actively participate in a diverse array of biological processes. Imbalance between production of ROS and anti-oxidant defenses causes oxidative stress, resulting in genomic instability and tissue damage [87]. Most polyphenols exhibit anti-oxidant properties, including homoisoflavonoids. Machala et al. isolated a series of homoisoflavonoids from the endemic tropical plant *Dracaena cinnabari* Balf., which showed potential activities to inhibit CYP1A enzymes and Fe-enhanced *in vitro* peroxidation of microsomal lipids in C57Bl/6 mouse liver [88]. Calvo reported the isolation of three homoisoflavanones, namely ledebourin A (**106**), ledebourin B (**107**), and ledebourin C (**108**), from the bulbs of *Ledebouria floribunda*. Ledebourin B and ledebourin C exhibited potent anti-oxidant activity in the DPPH radical-scavenging compared to the positive controls, the well-known antioxidants BHT and BHA [3].

Immunomodulation

Brazilin (**208**), the main compound of *Caesalpinia sappan*, was reported to improve altered immune functions caused by halothane administration in mice [89]. Furthermore, brazilin decreased splenic cellularity and IL-2 production which had been augmented in mice treated with halothane (21.5% in olive oil, 10 mmol/kg) for 4 consecutive days, whereas the reduced expression of IL-2 receptors by concanavalin A was increased by brazilin treatment. These data indicate that brazilin affects the function of T cells and improves halothane-induced abnormal immune responses. Yang et al. reported that the intraperitoneal administration of brazilin for 5 consecutive days prevents the decrease of concanavalin A-induced proliferation of splenocytes and mixed lymphocyte reaction in low-dose streptozotocin-induced type I diabetic mice and increased IL-2 production without affecting

suppressor cell activity. Expression of high affinity IL-2 receptors was also enhanced by brazilin. These results indicate that brazilin augments cellular immune responses, which are suppressed in the streptozotocin-induced type I diabetic mice, by increasing IL-2 production and responsiveness of immune cells to IL-2 [90].

Anti-diabetic activities

Homoisoflavonoids have shown significant activities in regulation of glucose uptake, hepatic glucose output, and adipocytes differentiation. Moon et al. found that brazilin (**208**) remarkably lowered non-fasting plasma glucose level without any changes in plasma insulin level and increased the rate of glucose oxidation and lipogenesis only in the presence of insulin. Activities of glucose-6 phosphate dehydrogenase and fatty acid synthase, involved in glucose oxidation and lipogenesis, respectively, were significantly increased. The results suggested that brazilin might exert hypoglycemic action in insulin resistance state by regulating the enzymatic reaction process involved in glucose metabolism [91]. Khil et al. reported that brazilin (**208**) increased [³H]2-deoxy-D-glucose uptake, which was blocked by phenylarsine oxide, the inhibitor of glucose transporters translocation, or wortmannin, the inhibitor of PI3-kinase. Western blot analysis with an anti-GLUT4 antibody revealed that brazilin increased the translocation of GLUT4 from intracellular pools to the plasma membrane. Brazilin, in combination with phorbol ester, showed an additive effect on glucose transport. The stimulating effect of phorbol ester on glucose transport was inhibited by staurosporine, but the effect of brazilin remained unchanged. The study suggested that brazilin may increase glucose transport by recruitment of GLUT4 from intracellular pools to the plasma membrane of adipocytes via the activation of PI3-kinase [92]. You et al. reported that brazilin (**208**) decreases blood glucose in diabetic animals, increases the production of F-2,6-BP in hepatocytes by elevating intracellular levels of F-6-P and H-6-P and also in-

creases the activity of PFK-2 and pyruvate kinase in glucagon-treated hepatocytes, which suggests that brazilin plays a role in hepatic glucose output by regulating gluconeogenesis and glycolysis in the liver [93]. Zhang et al. reported that the EtOAc-soluble fraction of a 90% MeOH extract of the fibrous roots of *Polygonatum odoratum* was found to potentiate insulin-stimulated glucose uptake in differentiated 3 T3-L1 adipocytes. Further bioassay-guided fractionation yielded four homoisoflavonoids (**54**, **58**, **169**, and **180**), which showed effects of sensitizing adipocytes for insulin in a cell-based glucose uptake assay using 3 T3-L1 adipocytes. The results indicated that homoisoflavonoids may be potential insulin sensitizers [33]. Liang et al. reported that brazilin (**215**), a natural, biologically active compound from *Caesalpinia sappan*, inhibited intracellular lipid accumulation during adipocyte differentiation in 3 T3-L1 cells and suppressed the induction of PPAR γ , the master regulator of adipogenesis, suggesting that brazilin possesses anti-obesity effects [18]. AMPK is a major cellular energy sensor and plays a central role in studies on diabetes. Guo et al. isolated six homoisoflavonoids from the rhizomes of *Polygonatum odoratum* Druce, and found that (3R)-5,7-dihydroxyl-6-methyl-3-(4'-hydroxylbenzyl)-chroman-4-one (**47**), (3R)-5,7-dihydroxyl-6,8-dimethyl-3-(4'-hydroxylbenzyl)-chroman-4-one (**52**), and (3R)-5,7-dihydroxyl-6-methyl-8-methoxyl-3-(4'-hydroxylbenzyl)-chroman-4-one (**61**) significantly activated AMPK and acetyl-CoA carboxylase in rat liver epithelial IAR-20 cells [11].

Cytotoxicity and anti-angiogenesis

Homoisoflavonoids showed cytotoxicity against a number of cell lines from a wide range of tumors, mainly including breast cancer, lung cancer, and colon cancer. Guo et al. reported that pretreatment with brazilin (**208**) dose-dependently inhibited PDGF-stimulated VSMC proliferation and migration, which were associated with a cell-cycle arrest at G0/G1 phase, a reduction in the adhesion molecule expression and MMP-9 activation in VSMCs. Furthermore, the increase in PDGF receptor β , c-src, ERK1/2, and Akt phosphorylation induced by PDGF were suppressed by brazilin. Collectively, the study implicated that brazilin may be useful as an anti-proliferative agent for the treatment of vascular diseases [12]. Mutanyatta et al. isolated and structurally elucidated five homoisoflavonoids (**40**, **80**, **94**, **194**, and **199**) from *Ledebouria graminifolia* and submitted them to the US National Cancer Institute for investigation of *in vitro* primary cytotoxic and anti-proliferative activities using a panel of 60 different human tumor cell lines [59]. Compound **80** was noted to show some activity on MCF7 breast cancer line (GI₅₀ = 7 μ g/mL, 50% growth inhibition), while other compounds were inactive. Zhou et al. identified 13 homoisoflavonoids from the root tubers of *Ophiopogon japonicus*, including three compounds, 8-formyl-phiopogonanone B (**60**), 6-formylisoophiopogonanone B (**70**), and 8-formyl-7-hydroxy-5,4'-dimethoxy-6-methylhomisoflavone (**95**), and evaluated those for their cytotoxic activities against the human-lung-tumor A549 cell line. The study showed that four known compounds exhibited promising anti-proliferative activities [36]. Rafi et al. isolated and identified a structure specific homoisoflavone (**53**) from Vietnamese coriander (*Polygonatum odoratum*) root which induces Bcl-2 phosphorylation, thereby causing mitotic arrest in breast cancer cells. Compound **53** induced Bcl-2 phosphorylation in breast tumor cells, caused G2/M cell cycle arrest, up regulated the expression of p21 and p53 proteins and decreased cell viability demonstrated by a clonogenic assay [26]. Dai et al. reported six homoisoflavonoids (**32**, **104**,

105, and **130–132**) from the South African plant *Drimys depressa* Baker and discovered their anti-proliferative activity against the A2780 ovarian cancer, A2058 melanoma, and H522-T1 human non-small-cell lung cancer cells [7]. Nguyen et al. isolated a homoisoflavonone, disporopsin (**37**), from cytotoxic extracts of the roots of *Disporopsis aspera* (Asparagaceae). The homoisoflavonone was found to be cytotoxic against a series of human cancer cell lines (HCT15, T24S, MCF7, Bowes, A549, and K562) with IC₅₀ ranging from 15 to 200 μ M [94].

Anti-angiogenesis is a promising way for treatment of cancer [95]. Shim et al. isolated a homoisoflavonone, 7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-6-methoxychroman-4-one (**78**), from the bulb of *Cremastra appendiculata* (Orchidaceae) as a potent inhibitor of angiogenesis. It inhibited bFGF-induced *in vitro* angiogenesis and *in vivo* angiogenesis of the CAM of chick embryo without showing any toxicity [96].

Anti-inflammatory activities

Long-term inflammation has been considered as a cause of several diseases, such as type 2 diabetes, cardiovascular diseases and neuro-degenerative diseases [97–99], while overproduction of NO is responsible for inflammation [100]. Many studies have shown that homoisoflavonoids inhibit NO production in macrophage cells. Hung T. et al. isolated compounds **64**, **69** and **98** from the roots of *Ophiopogon japonicus* (Asparagaceae) and discovered that these compounds suppressed IL-4-induced inflammatory chemokine eotaxin release in BEAS-2B cells [14]. Moreover, Li et al. who report the isolation of ophiopogonone E (**151**) and ophiopogonanone H (**126**) from the tuberous roots of *Ophiopogon japonicus* found that ophiopogonanone H is effective in the inhibition of NO production induced by lipopolysaccharide in the murine microglial cell line BV-2, with an IC₅₀ value of 20.1 μ M [17]. Min et al. isolated thirteen phenolics from the heartwood of *Caesalpinia sappan*. Among them, protosappanin A (**224**) and 3-deoxysappanchalcone showed strong inhibitory activities toward the LPS-induced NO production in macrophage RAW264.7 cells, with IC₅₀ values of 12.5 and 8.1 μ M, respectively. In addition, these two compounds inhibited the induction of iNOS mRNA in dose-dependent manner, indicating that these compounds attenuated the synthesis of these transcripts at the transcriptional level [24].

Protein tyrosine kinase inhibition

PTKs play crucial roles in cell differentiation, proliferation, and apoptosis. More than 70% of the known oncogenes and proto-oncogenes involved in cancer code for PTKs [101]. Lin et al. identified hematoxylin (**213**), the major constituent of *Haematoxylum campechianum*, as one of the most remarkable c-Src inhibitors in an orthogonal compound-mixing library (32 200 compounds) by using an ELISA-based automated HTS strategy [20]. Furthermore, hematoxylin was found to be an ATP competitive broad-spectrum PTK inhibitor *in vitro*, with IC₅₀ values ranging from nanomolar to micromolar level, and the inhibition was associated with the PTK phosphorylation and subsequent downstream signaling pathways. Additionally, a series of hematoxylin analogues were isolated from *H. campechianum* with potent PTK inhibitory activity [20,21]. The structure-activity relationship assessment of the PTK inhibitory potency was in good agreement with the result of the concurrent molecular docking simulation. Hematoxylin and its natural analogues were substantially validated to serve as a new class of PTK inhibitors.

Other activities

Hu et al. investigated the vasorelaxant activity of brazilin (208) in isolated rat aorta and human umbilical vein endothelial cells [102]. In isolated rat aorta, *Caesalpinia sappan* extract and brazilin relaxed phenylephrine-induced vasoconstriction and increased cGMP content. Induction of vasorelaxation of brazilin was endothelium-dependent and could be markedly blocked by pretreatment with NOS inhibitor, L-NAME; L-NMMA and guanylyl cyclase inhibitor, methylene blue; ODQ and NO scavenger, hemoglobin. The increasing cGMP content induced by brazilin was also blocked by pretreatment with L-NAME, methylene blue, and the removal of extracellular Ca^{2+} . In human umbilical vein endothelial cells, brazilin dose-dependently induced an increase in NO formation and NOS activity, which was greatly attenuated by either the removal of extracellular Ca^{2+} or the chelating of intracellular Ca^{2+} with BAPTA-AM. Moreover, brazilin dose-dependently induced the influx of extracellular Ca^{2+} in human umbilical vein endothelial cells. These results suggested that brazilin induces vasorelaxation by increasing intracellular Ca^{2+} concentration in endothelial cells of blood vessels and hence activating Ca^{2+} /calmodulin-dependent NO synthesis, resulting in vasorelaxation. Urbancikova et al. extracted a homoisoflavonoid-enriched fraction from *Muscari racemosum* and found estrogenic activity. The mixture enlarged the proliferation activity of MCF7 cells in a dose-dependent manner at concentrations up to 5 $\mu\text{g/mL}$. A concentration of 5 $\mu\text{g/mL}$ caused the highest increase of proliferation activity representing 181% of the control. Additionally, the extract exhibited a dose-dependent anti-estrogenic effect in the presence of estradiol in MCF7 cells [103]. Tsai et al. isolated eight homoisoflavonoids from the roots of *Liriope platyphylla*, and found that (3R)-3-(4'-hydroxybenzyl)-5,7-dihydroxychroman-4-one (30) and 3-(40-hydroxybenzylidene)-5,7-dihydroxychroman-4-one (117) exhibited the most potent estrogenic activity, and (3R)-3-(2',4'-dihydroxybenzyl)-5,7-dihydroxychroman-4-one (37) and (3R)-3-(2',4'-dihydroxybenzyl)-5,7-dihydroxy-6-methyl-chroman-4-one (51) showed the highest inhibitory activity in platelet aggregation assay [29].

Conclusions

Homoisoflavonoids have received much attention in the literatures over the past 30 years. The structure diversity of homoisoflavonoids has attracted research interest of natural product chemists. Until now, 240 homoisoflavonoids have been isolated and identified, which could be classified into five structural categories, sappanin-type, scillascillin-type, brazilin-type, caesalpin-type, and protosappanin-type. Homoisoflavonoids have become of interest in the research and development of natural bioactive compounds over the past decades. A broad range of activities have been reported, including anti-microbial effects, anti-mutagenic effects, anti-oxidant activities, immunomodulation, anti-diabetic activities, cytotoxic and anti-angiogenic effects, and anti-inflammatory activities. However, most of the research involves *in vitro* studies; it is still a long way from drawing definite conclusions about the usefulness of homoisoflavonoids as drug candidates or lead compounds. More investigations on pharmacology and chemistry, as well as toxicological researches, should be done for better validation of the therapeutic potential of homoisoflavonoids.

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Conflict of Interest

The authors declare no conflict of interest.

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