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Review: The traditional uses, secondary metabolites, and pharmacology of *Symplocos* species

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Abstract. *Ethnopharmacological relevance*: The genus *Symplocos* (Symplocaceae family) includes 500 accepted names and is distributed in tropical and subtropical regions. Some *Symplocos* species are used in traditional medicines for the treatment of bacterial diseases, hemorrhage, gynecological disorders, and live diseases.

Aim of the study: This review focuses on the phytochemistry and pharmacology of the *Symplocos* genus to understand the link between the traditional medicinal uses, phytochemistry, and bioactivities. Thus, they provide a scientific basis for further research on its phytochemical and pharmacological activities.

Materials and methods: Information about the *Symplocos* genus was collected using various databases such as Web of Science, SciFinder, Google Scholar, PubMed, Wiley, ACS publications, Elsevier, and SpringerLink between 1980 and 2024. Plant names were validated by "World of Flora Online" (www.worldfloraonline.org).

Results: Up to now, a total of 202 compounds have been reported from *Symplocos* species, including triterpenoids, flavonoids, iridoids, lignans, steroids, phenolics, and athraquinones. The extracts and phytochemical constituents of the *Symplocos* genus are a rich source of biological activities, including anti-cancer, antioxidant, anti-inflammatory, antibacterial, hypoglycemic, and other activities.

Conclusions: The review indicates that the *Symplocos* genus is a promising source of biological compounds, particularly the anti-cancer activity of chromanes. The results of this review confirm the great potential of *Symplocos* species. Thus, it will be helpful for further research on the phytochemistry and pharmacology of the *Symplocos* genus.

Keywords: Symplocos, Euphorbiaceae, anti-cancer, anti-inflammatory, triterpenoid, flavonoid.

Classification numbers: 1.1.1.; 1.2.2.

1. INTRODUCTION

Nowadays, researchers around the world are increasingly interested in new drugs from plant sources due to their low cost and their ability to provide safer medicines than synthetic drugs, which are often more expensive and associated with many adverse side effects. Consequently, there is a growing interest in understanding the structure-activity relationships of secondary metabolites from plants, which could have potential pharmacological activity.

Symplocos (Symplocaceae family) is a large genus, from shrubs to trees, distributed mainly in tropical and subtropical regions such as Asia, America, and Australia. Some species of the genus have been used in traditional medicine. Phytochemical analyses of the genus have revealed many triterpenoids, flavonoids, iridoids, lignans, steroids, phenolics, and anthraquinones. Moreover, the plants in this genus exhibit various biological activities, such as cytotoxic, antioxidant, anti-inflammatory, antibacterial, and hypoglycemic properties. This review aims to consolidate the existing literature on phytochemistry and biological activities of the *Symplocos* genus, offering a comprehensive overview of its traditional medicinal applications in conjunction with structural and pharmacological insights.

2. MATERIALS AND METHODS

The review was carried out using scientific publication databases , such as Web of Science, SciFinder, PubMed, Google Scholar, Wiley, Elsevier, ACS publications, and SpringerLink, using the keyword "*Symplocos"*. The related articles were collected from 1980 to 2024. "World of Flora Online" (www.worldfloraonline.org) was used to confirm species names.

3. RESULTS AND DISCUSSION

3.1. Ethnopharmacology properties

Species of the genus *Symplocos* have many traditional medicinal values. Many species are used to treat bacterial diseases, diarrhea, dysentery, eye diseases, hemorrhage, menorrhagia, intestinal pain, infections, snake bites, vaginal discharge and miscarriage [1, 2]. In Chinese folk medicine, local people used the roots of *S. caudata* for treating jaundice, dysentery, and uterine bleeding [3]. In Indian medicine, *S. racemosa* is widely used as a Hindu remedy, treating diseases of the liver, eyes, leprosy, dropsy and bleeding, gynecological disorders, miscarriage and inflammation, vaginal ulcers [4]. Recently, some species of the genus *Symplocos* have been studied for their ability to inhibit HIV and many types of cancer cells, including liver cancer, lung cancer, gastric carcinoma, etc. [5 - 7].

In Viet Nam, many species of the genus *Symplocos* are used as medicine. The leaves of *S. racemosa* are used to make tea to prevent flatulence, help digestion, treat bronchitis, diabetes, renal failure and liver damage, ulcers, and uterine bleeding. *S. cochinchinensis* species is used to treat burns, bile deficiency, hemostasis, and gonorrhea [8].

3.2. Phytochemistry

To date, chemical constituents of the *Symplocos* genus have been widely studied, but with more focus on the following seventeen species: *S.paniculata, S.glomerata, S. cochinchinensis, S. chinensis, S. spicata, S. caudata, S.anomala, S. laurina, S. racemosa, S. lancifolia, S. microcalyx,*

S. vacciniifolia, *S. setchuensis*, *S. sumuntia*, *S. glauca*, *S.lucida*, and *S. unijlora*. From this genus, 202 compounds have been reported, belonging to oleananes (**1-58**), ursanes (**59-90**), lupanes and hopanes (**91-93**), phenolics (**94-125**), lignans and neolignans (**126-146**), flavonoids (**147-163**), iridoids (**164-177**), steroids (**178-184**), athraquinones (**185-191**) and other compounds (**192-202**) (Tables 1-2, Figures 1-2). The parts of the *Symplocos* genus have been studied, including leaves, branches, barks, roots, and whole plants.

3.2.1. Triterpenoids

Triterpenoids are an important class of substances in the *Symplocos* genus. The compounds mainly belong to the oleananes (**1-58**) (*Table 3* and *Figure 3*) and ursanes (**59-90**) (*Table 4* and *Figure 4*), and a few belong to the lupanes and hopanes (**91-93**) (*Table 5* and *Figure 5*).

Table 6. Oleananes from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
1	oleanolic acid	trunks	*S. setchuensis*	[6]
		barks	*S. racemosa*	[9]
		trunks	*S. setchuensis*	[10]
		tree	*S. racemosa*	[11]
2	3*β*,28-dihydroxyolean-12-ene	trunks	*S. setchuensis*	[10]
3	12-oleanene-3*β*,11*β*-diol	trunks	*S. setchuensis*	[10]
4	12-oleanen-3-one	trunks	*S. setchuensis*	[10]
5	24-hydroxyolean-12-en-3-one	barks	*S. racemosa*	[9]
6	*β*-amyrin	tree	*S. racemosa*	[11]
7	3*β*,22*α*-dihydroxy-12-oleanen-29-oic acid	trunks	*S. setchuensis*	[10]
8	9*β*,25-cyclo-3*β*-*O*-(*β*-D-glucopyranosyl)-echynocystic acid	barks	S. *paniculata*	[12]
9	2*α*,3*β*,19*α*,23-tetrahydroxyoean-12-en-28-oic acid	roots	*S. laurina*	[13]
10	2*α*,3*β*,23-trihydroxyolean-12-en-28-oic acid	roots	*S. laurina*	[13]
11	naucleaorine	leaves	*S.anomala*	[14]
12	2*α*,3*β*,19*α*,23-tetrahydroxy-12-oleanen-28-oic acid 28-*β*-D-glucopyranosyl ester	roots	*S. caudata*	[15]
13	2*α*,3*β*,19*α*,23,24-pentahydroxy-12-oleanen-28-oic acid 28-*β*-D-glucopyranosyl ester	roots	*S. caudata*	[15]
14	19*α*-hydroxyarjunolic acid 3,28-*O*-bis-*β*-D-glucoside	barks	*S. spicata*	[16]
15	3-*O*-[*β*-D-glucopyranosyl]-28-*O*-[*α*-L-rhamnopyranosyl-(1⟶2)-*β*-D-glucopyranosyl]maslinic acid	leaves	*S. lancifolia*	[17]
16	3-*O*-[*β*-D-glucopyranosyl]-28-*O*-[*α*-L-rhamnopyranosyl-(1⟶2)-*β*-D-glucopyranosyl]arjunolic acid	leaves	*S. lancifolia*	[17]
17	19*α*-hydroxy-4-oxo-3,24-dinor-2,4-secoolean-12-en-2,28-dioic acid	roots	*S. laurina*	[13]
18	symplocososide A	roots	*S. chinensis*	[18]
19	symplocososide B	roots	*S. chinensis*	[18]
20	symplocososide C	roots	*S. chinensis*	[18]
21	symplocososide D	roots	*S. chinensis*	[18]
22	symplocososide E	roots	*S. chinensis*	[18]
23	symplocososide F	roots	*S. chinensis*	[18]
24	symplocososide Q	roots	*S. chinensis*	[5]
25	symplocososideG	trunks	*S. chinensis*	[19]
26	symplocososide H	trunks	*S. chinensis*	[19]
27	symplocososide J	trunks	*S. chinensis*	[19]
28	symplocososide L	roots	*S. chinensis*	[5]

29	symplocososide M	roots	*S. chinensis*	[5]
30	symplocososide O	roots	*S. chinensis*	[5]
31	symplocososideP	roots	*S. chinensis*	[5]
32	symplocososide I	barks	*S. chinensis*	[19]
33	symplocososide K	barks	*S. chinensis*	[19]
34	symplocososide N	roots	*S. chinensis*	[5]
35	symplocososideR	roots	*S. chinensis*	[5]
36	symplocososide S	roots	*S. chinensis*	[5]
37	symplocosin J	leaves	*S. cochinchinensis*	[20]
38	symplocosin K	leaves	*S. cochinchinensis*	[20]
39	symplocosin P	leaves	*S. cochinchinensis*	[20]
40	symplocosin L	leaves	*S. cochinchinensis*	[20]
41	symplocosin N	leaves	*S. cochinchinensis*	[20]
42	symplocosin M	leaves	*S. cochinchinensis*	[20]
43	symplocosin O	leaves	*S. cochinchinensis*	[20]
44	symplocosin I	leaves	*S. cochinchinensis*	[20]
45	21-*β*-*O*-cinnamoyl-22*α*-*O*-(2-methylbutanoyl)-15*α*,16*α*,28-trihydroxyolean-12-ene-3*β*-*O*-[*β*-D-glucopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→4)-*β*-D-glucuronopyranoside	roots	*S. chinensis*	[21]
46	21-*β*-*O*-cinnamoyl-22*α*-*O*-(2-ethylbutanoyl)-15*α*,16*α*,28-rihydroxyolean-12-ene-3*β*-*O*-(3-*O*-acetyl)-[*β*-D-glucopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→4)-*β*-D-glucuronopyranoside	roots	*S. chinensis*	[21]
47	3*β*-*O*-[*β*-D-xylopyranosyl(1→4)-[2-*O*-acetyl]-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl]-morolicacid	barks	*S. glomerata*	[22]
48	3-*O*-[*α*-L-arabinopyranosyl-(1→4)-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl]-oleanolicacid	barks	*S. glomerata*	[22]
49	3-*O*-[*α*-L-arabinopyranosyl-(1→4)-[2-*O*-acetyl]-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl]-oleanolicacid	barks	*S. glomerata*	[22]
50	salsoloside C	barks	*S. glomerata*	[22]
51	3′-*O*-acetylsalsoloside C	barks	*S. glomerata*	[22]
52	2′-*O*- acetylsalsoloside C	barks	*S. glomerata*	[22]
53	2′,3′-*O*-diacetylsalsoloside C	barks	*S. glomerata*	[22]
54	copteroside E	barks	*S. glomerata*	[22]
55	3-*O*-{[*β*-D-xylopyranosyl-(1→2)]-[*β*-D-xylopyranosyl-(1→4)]-[3-*O*-acetyl]-*β*-D-glucuronopyranosyl}-28-*O*-[*β*-D-glucopyranosyl]-oleanolic acid	barks	*S. glomerata*	[22]
56	3-*O*-{[*β*-D-glucopyranosyl-(1→2)]-[*β*-D-xylopyranosyl-(1→4)]-[3-*O*-acetyl]-*β*-D-glucuronopyranosyl}-28-*O*-[*β*-D-glucopyranosyl]-oleanolic acid	barks	*S. glomerata*	[22]
57	3-*O*-{[*β*-D-glucopyranosyl-(1→2)]-[*α*-L-arabinofuranosyl-(1→4)]-[3-*O*-acetyl]-*β*-D-glucuronopyranosyl}-28O-[*β*-D-glucopyranosyl]-oleanolic acid	barks	*S. glomerata*	[22]
58	3*β*,17*β*-dihydroxy-28-nor-12-oleanen-16-one 3-*O*-*β*-D-galactopyranosyl-(1⟶2)-{*α*-L-arabinopyranosyl-(1⟶3)-[*α*-L-arabinofuranosyl-(1⟶4)-*β*-D-glucuronopyranoside]}	roots	*S. caudata*	[15]

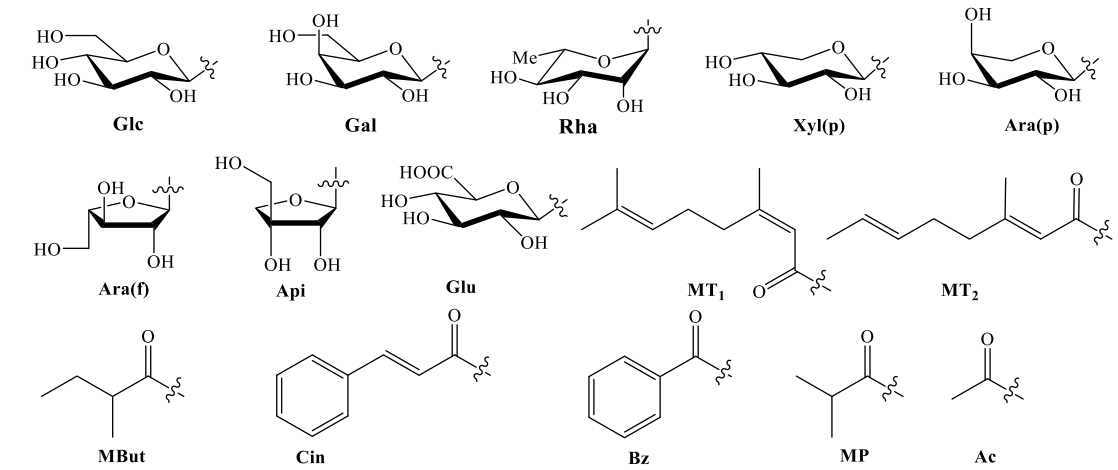
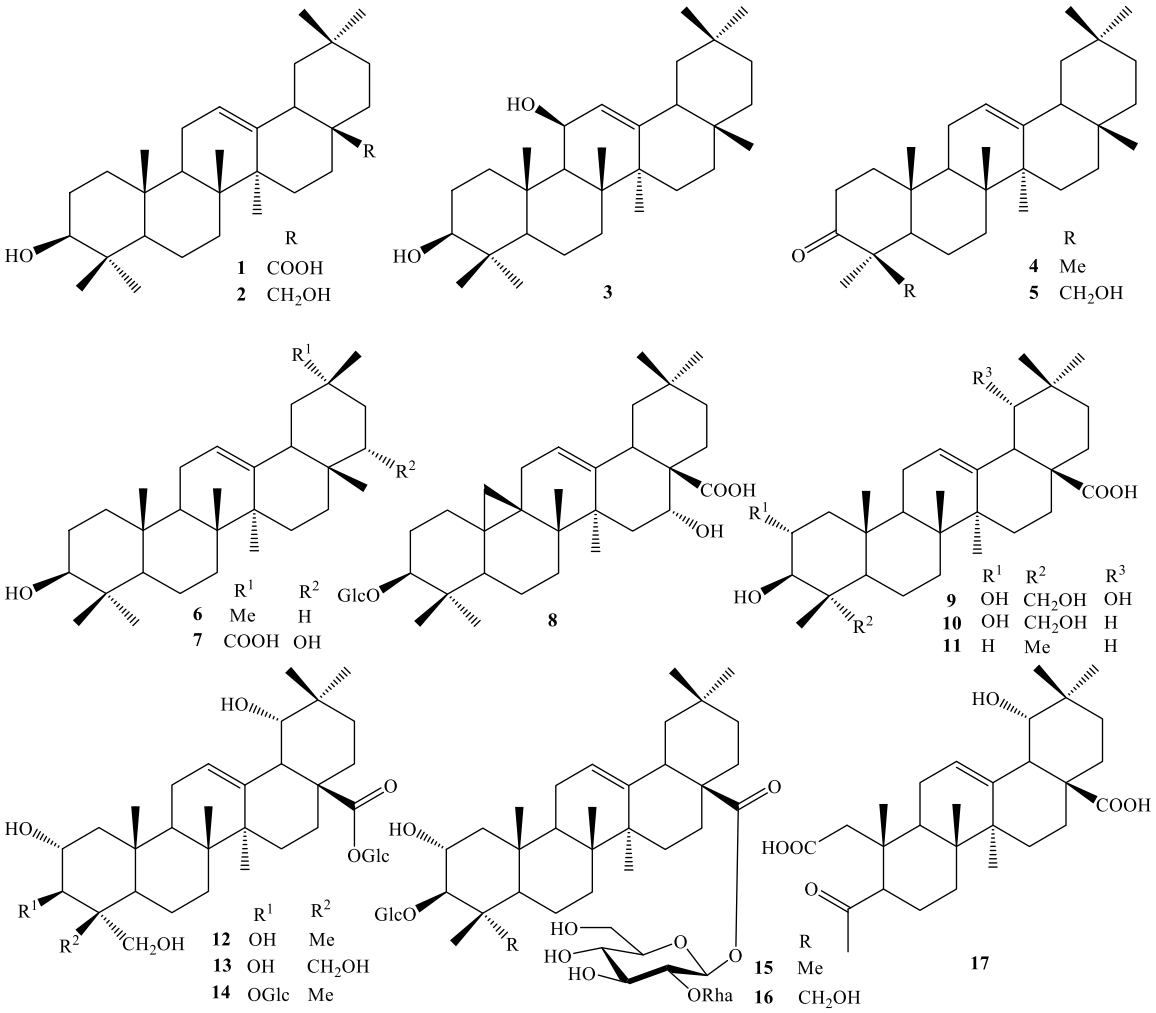
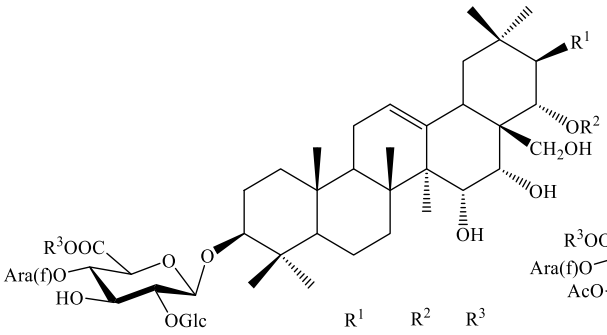
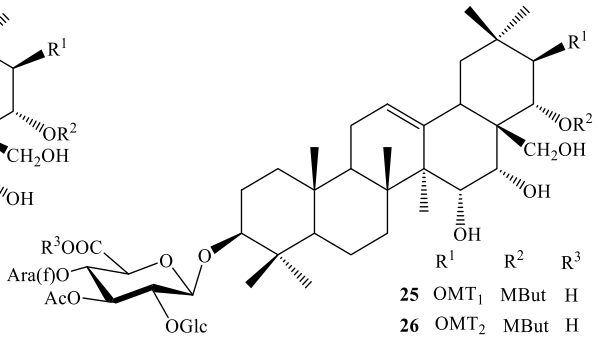


Figure 6. Structures of typical groups.

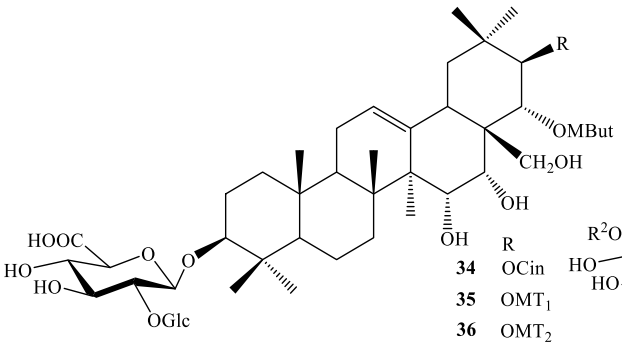




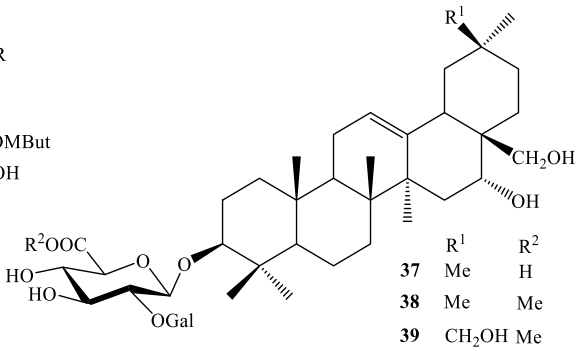
	R^1	R^2	R^3
18	OMT_1	MBut	Me
19	OMT_2	MBut	Me
20	OMT_1	MBut	n-But
21	OMT_2	MBut	n-But
22	OCin	MBut	n-But
23	H	MT_1	n-But
24	OMT_1	MBut	Et



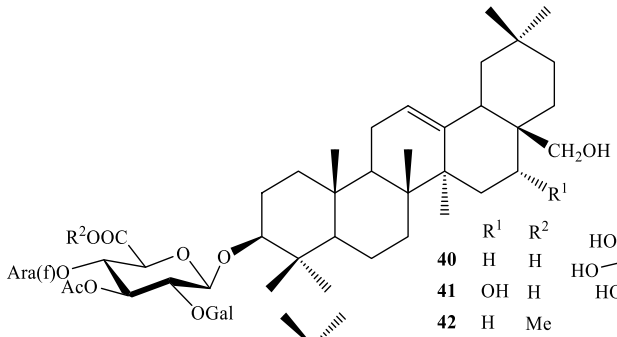
	R^1	R^2	R^3
25	OMT_1	MBut	H
26	OMT_2	MBut	H
27	OMT_1	Bz	H
28	OMT_1	MP	H
29	OMT_2	MP	H
30	H	MT_1	H
31	OBz	MBut	H
32	OMT_1	MBut	Me
33	OMT_1	Bz	Me



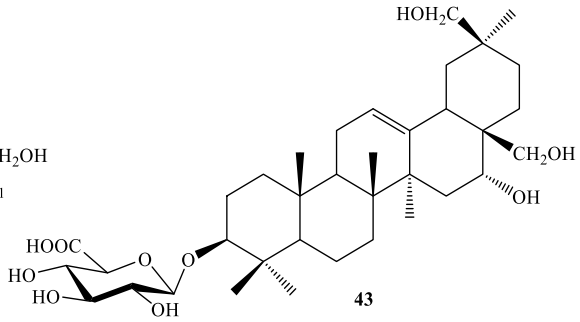
	R
34	OCin
35	OMT_1
36	OMT_2



	R^1	R^2
37	Me	H
38	Me	Me
39	CH_2OH	Me



	R^1	R^2
40	H	H
41	OH	H
42	H	Me



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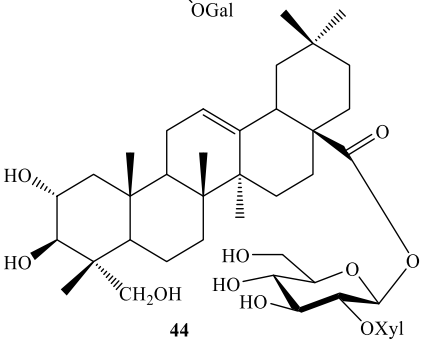

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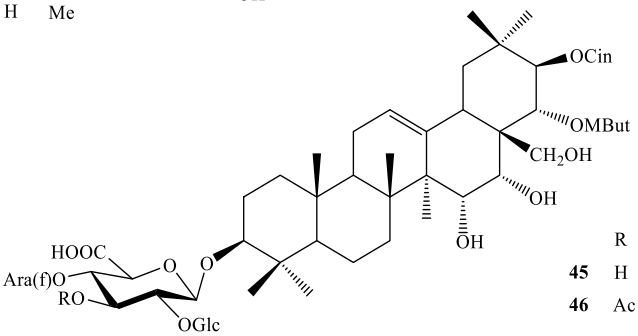


	R
45	H
46	Ac

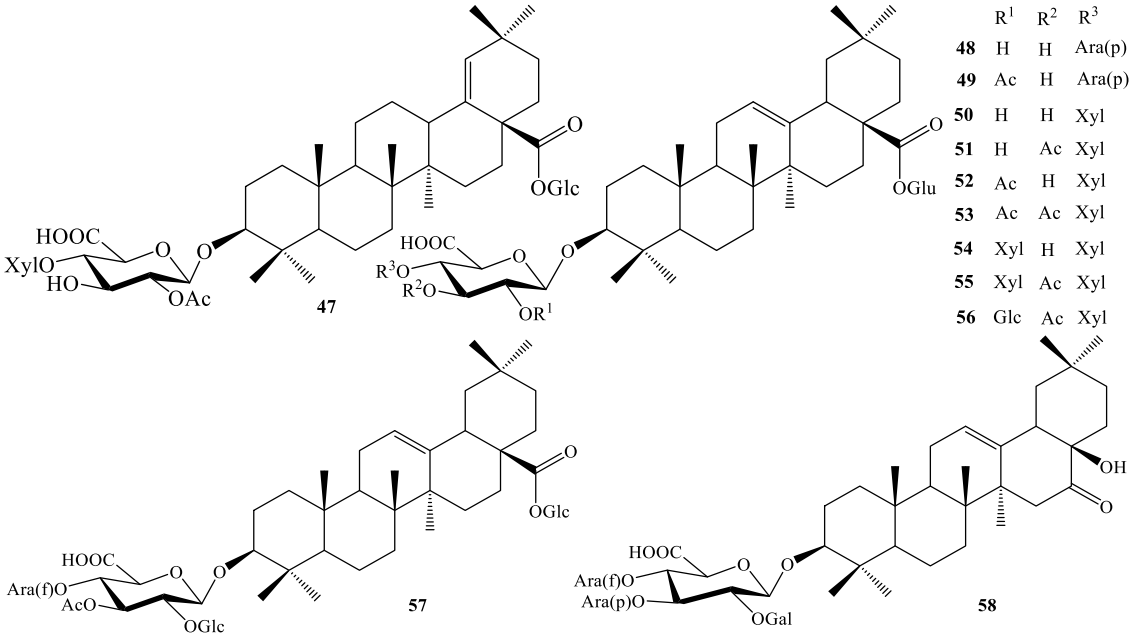
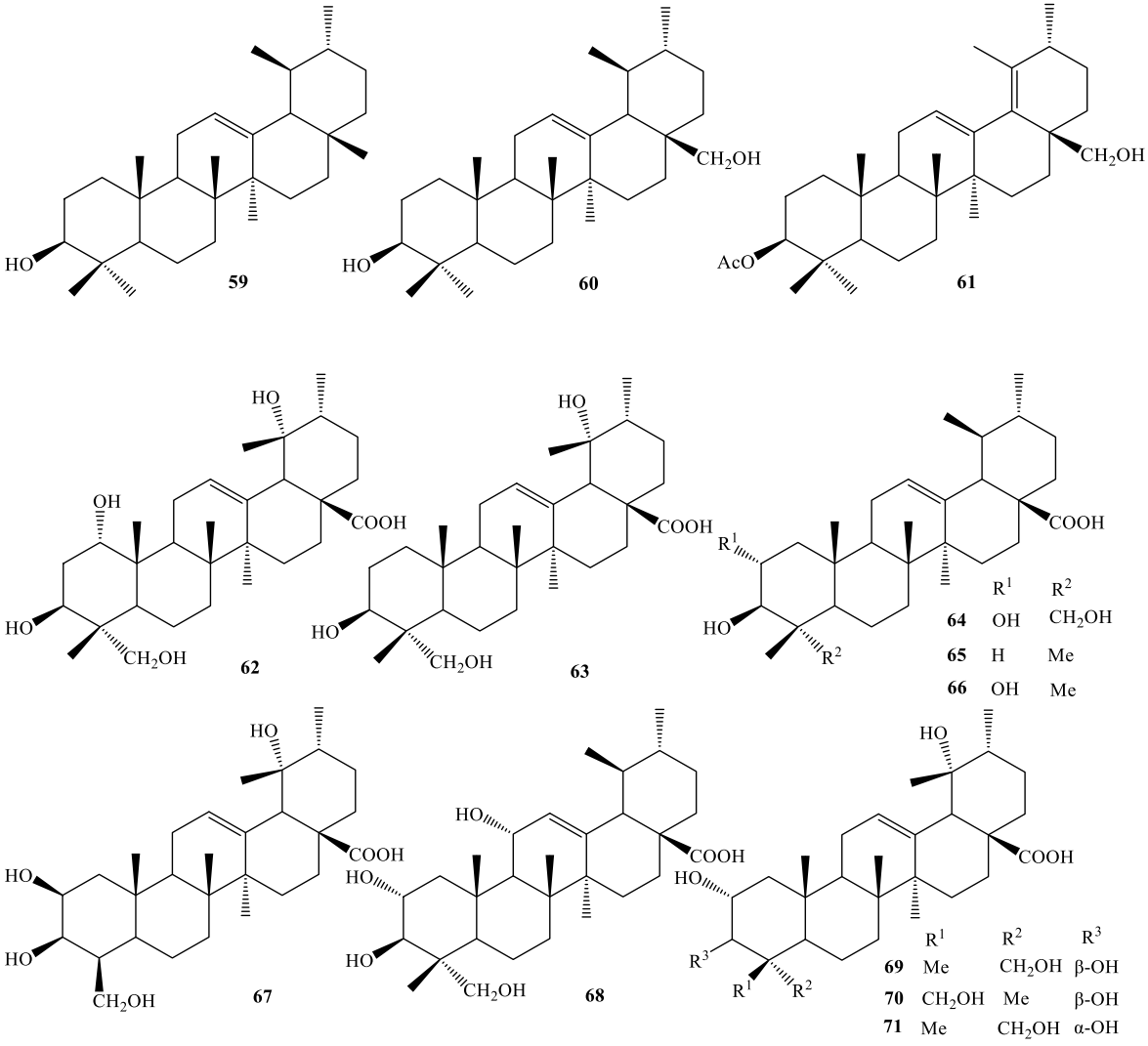


Figure 7. Chemical structures of oleananes from *Symplocos* genus.

Table 7. Ursanes from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
59	*α*-amyrin	trunks	*S. setchuensis*	[10]
60	3*β*,28-dihydroxy-urs-12-ene	trunks	*S. setchuensis*	[10]
61	28-hydroxy-20*α*-urs-12,18(19)-dien-3*β*-yl acetate	barks	*S. racemosa*	[9]
62	1*α*,3*β*,19*α*,23-tetrahydroxyurs-12-en-28-oic acid	roots	*S. laurina*	[13]
63	3*β*,19*α*,23-trihydroxyurs-12-en-28-oic acid	roots	*S. laurina*	[13]
64	asiatic acid	trunks leaves barks leaves, stems	*S. setchuensis* *S. anomala* *S. fasculata* *S. paniculata*	[10] [14] [10, 14, 23, 24] [24]
65	ursolic acid	leaves, trunks	*S. paniculata*	[10, 24]
66	corosolic acid	leaves, stems	*S. paniculata*	[24]
67	2*β*,3*β*,19*α*,24-tetrahydroxy-23-norurs-12-en-28-oic acid	roots	*S. chinensis*	[25]
68	11*α*-hydroxyasiatic acid	leaves	*S. lancifolia*	[17]
69	nigaichigoside F1	trunks, leaves	*S. cochinchinensis*	[26]
70	trachelosperoside A1	trunks, leaves	*S. cochinchinensis*	[26]
71	2*α*,3*α*,19*α*,23-tetrahydroxyurs-12-en-28-oic acid	roots	*S. chinensis*	[25]
72	2-oxo-3*β*,19*α*,23-trihydroxyurs-12-en-28-oic acid	roots	*S. laurina*	[13]
73	3-oxo-urs-12,18(19)-dien-28-oic acid	barks	*S. racemosa*	[9]
74	3-oxo-19*α*,23,24-trihydroxyurs-12-en-28-oic acid	roots	*S. chinensis*	[25]
75	quadranoside IV	leaves	*S. cochinchinensis*	[20]
76	niga-ichigoside F2	leaves	*S. cochinchinensis*	[20]
77	niga-ichigoside F1	leaves	*S. cochinchinensis*	[20]
78	4-epi-niga-ichigoside F1	leaves	*S. cochinchinensis*	[20]
79	2*α*,3*β*,19*α*,23,24-pentahydroxyurs-12-en-28-oic	roots	*S. caudata*	[15]

	acid 28-β-D-glucopyranosyl ester			
80	19α-hydroxyasiatic acid 3,28-*O*-bis-β-D-glucoside	trunks	*S. spicata*	[16]
81	symplocoside A	leaves	*S. cochinchinensis*	[27]
82	symplocosin C	leaves	*S. cochinchinensis*	[20]
83	symplocosin D	leaves	*S. cochinchinensis*	[20]
84	symplocosin F	leaves	*S. cochinchinensis*	[20]
85	symplocosin E	leaves	*S. cochinchinensis*	[20]
86	symplocoside B	leaves	*S. cochinchinensis*	[27]
87	symplocosin G	leaves	*S. cochinchinensis*	[20]
88	symplocosin H	leaves	*S. cochinchinensis*	[20]
89	3-*O*-[β-D-glucopyranosyl]-28-*O*-[*R*-L-rhamnopyranosyl-(1⟶2)-β-D-lucopyranosyl]asiatic acid	leaves	*S. lancifolia*	[17]
90	jacoumaric acid	leaves	*S. anomala*	[14]



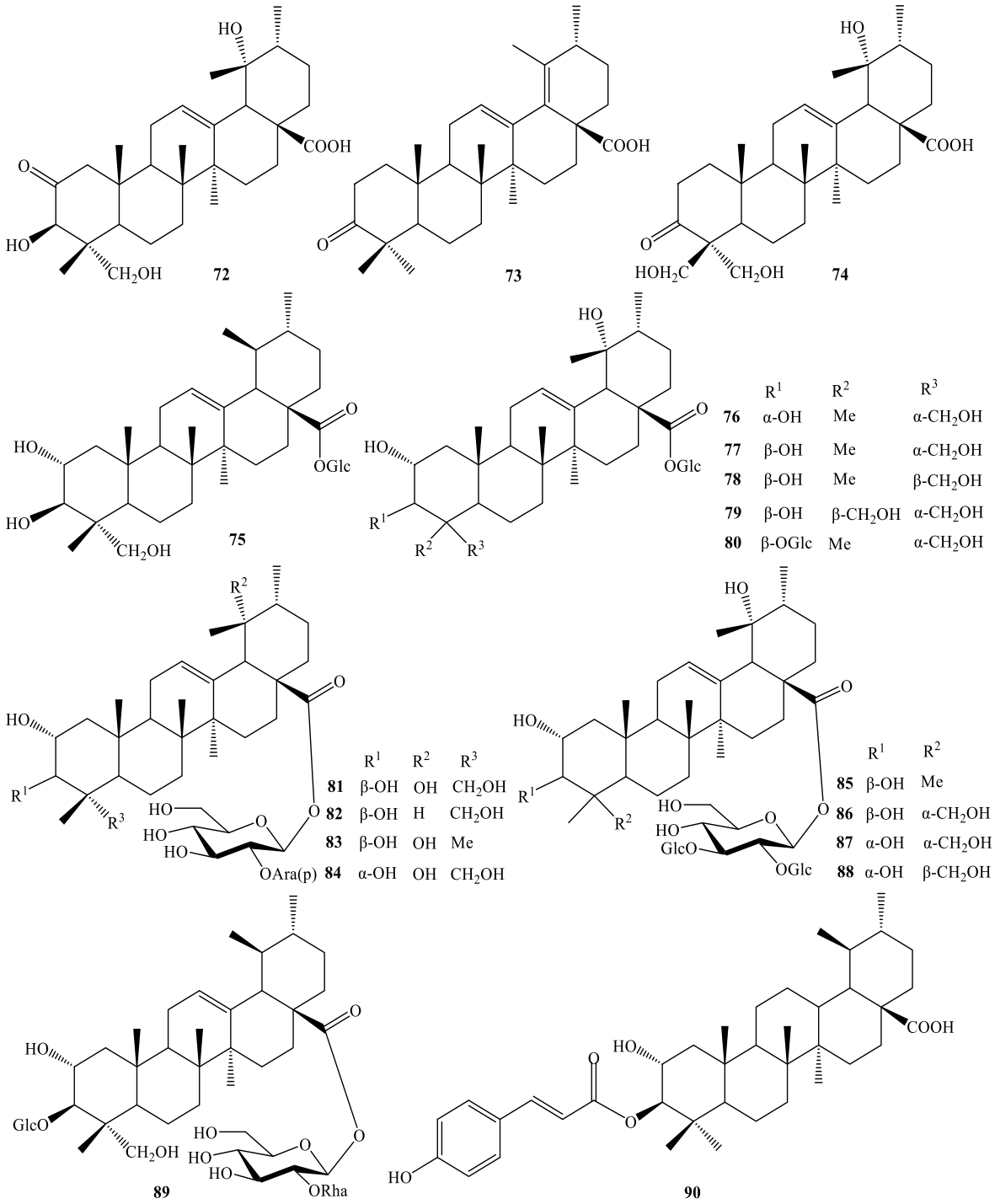


Figure 8. Chemical structures of ursanes from *Symplocos* genus.

Lupane and hopane framework compounds

Table 8. Lupanes and hopanes from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
91	lupeol	leaves	*S. paniculata*	[28]
92	30-ethyl 2*α*,16*α*-dihydroxy 3*β*-*O*-(*β*-D-glucopyranosyl) hopan-24-oic acid	barks	*S. paniculata*	[12]
93	32,33,34-trimethyl-bacteriohopan-16-ene-3-*O*-*β*-D-glucopyranosid	barks	*S. paniculata*	[12]

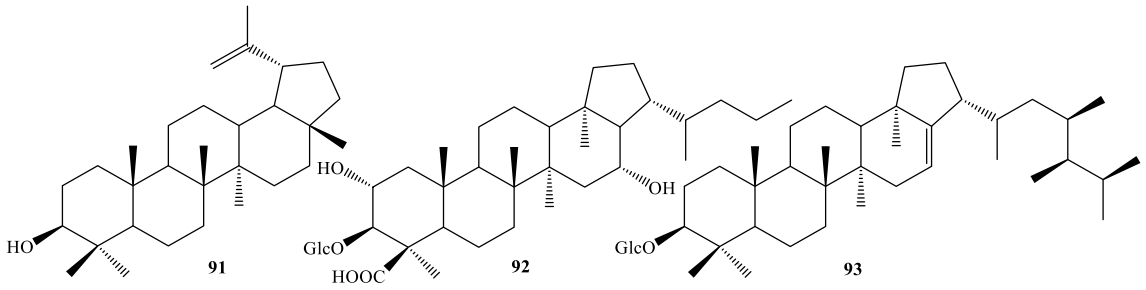


Figure 9. Chemical structures of lupanes and hopanes from *Symplocos* genus.

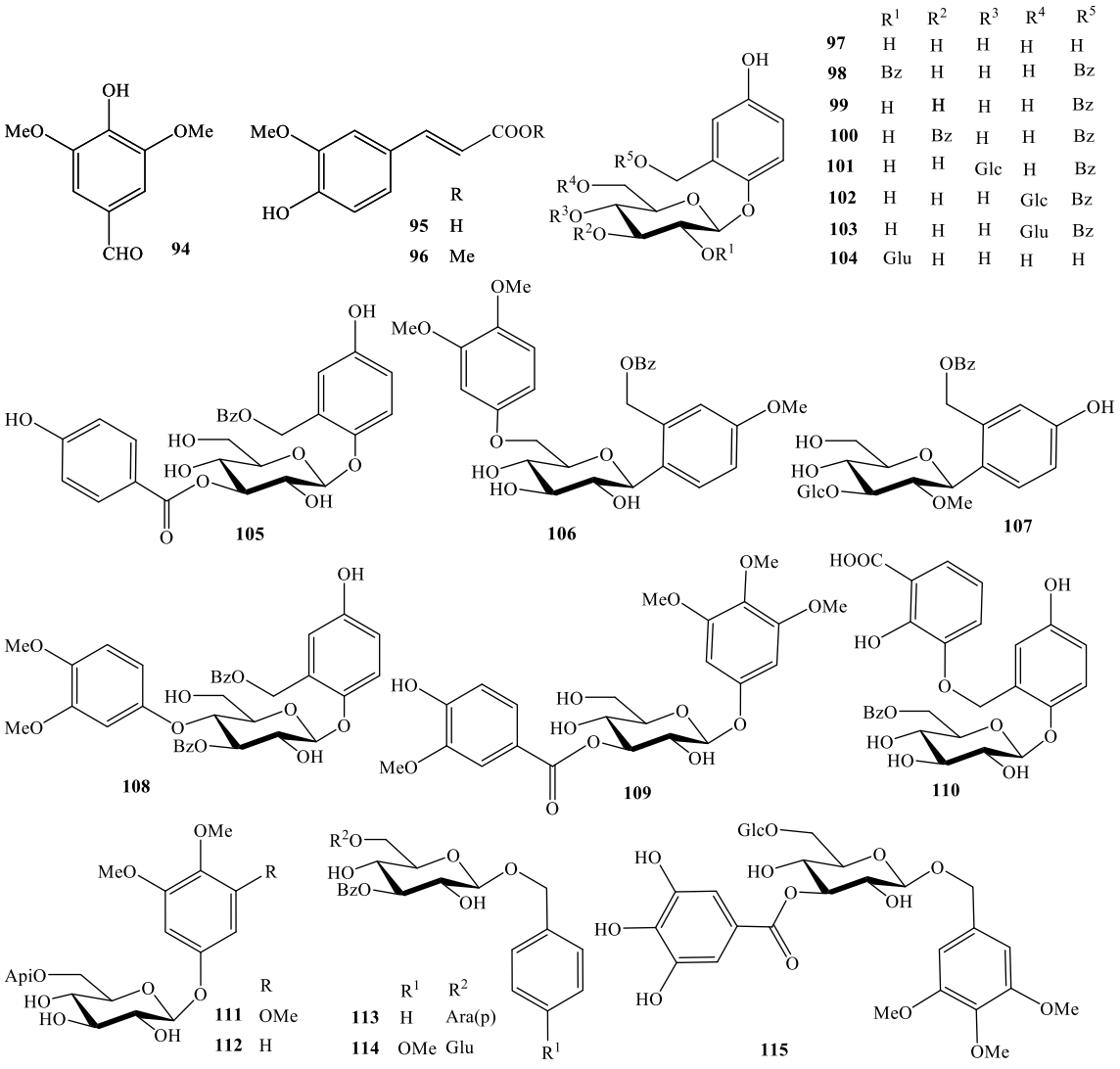
3.2.2. Phenolics

According to published papers, 32 phenolic compounds (**94-125**) have been isolated (*Table 9* and *Figure 10*).

Table 10. Phenolics from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
94	syringaldehyde	leaves	*S. anomala*	[14]
95	*trans*-ferulic acid	leaves	*S. anomala*	[14]
96	*trans*-methyl ferulate	leaves	*S. anomala*	[14]
97	salirepin	leaves	*S. paniculata*	[28]
98	symponoside	barks	*S. racemora*	[29]
99	salireposide	barks	*S. racemora*	[11, 30]
100	benzoylsalireposide	barks	*S. racemora*	[11, 30]
101	symconoside B	barks	*S. racemosa*	[31]
102	symconoside A	barks	*S. racemosa*	[31]
103	symplocuronic acid	barks	*S. racemora*	[4]
104	sympocemoside	barks	*S. racemora*	[4]
105	symplososide	barks	*S. racemora*	[29]
106	symploveroside	barks	*S. racemora*	[29]
107	symplomoside	trees	*S. racemosa*	[30]
108	symploracemoside	trees	*S. racemosa*	[30]
109	1-*O*-(3,4,5-trimethoxyphenyl)-3-vanilyl-*β*-D-glucopyranosid	barks	*S. racemosa*	[32]
110	symplocomoside	barks	*S. racemora*	[29]
111	kelampayoside A	roots	*S. caudata*	[33]
112	3,4-dimethoxyphenol-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside	roots	*S. caudata*	[33]
113	locoracemoside A	barks	*S. racemora*	[34]
114	locoracemoside B	barks	*S. racemora*	[34]

115	locoracemoside C	barks	*S. racemora*	[34]
116	4' -*O*-*β*-D-glucopyranosylphloretin	leaves	*S. microcalyx*	[35]
117	phlorizin	leaves	*S. microcalyx*	[35]
118	vacciniifolin	leaves	*S. vacciniifolia*	[36]
119	trilobatin	leaves	*S. vacciniifolia*	[36]
120	sieboldin	leaves	*S. vacciniifolia*	[36]
121	confusoside	leaves	*S. vacciniifolia*	[36, 37]
		leaves	*S. confusa*	[36, 37]
122	(1*S*,2*R*)-1-(4' -*O*-*β*-D-glucopyranosyl-3' -methoxyphenyl)-2-(4' ' -hydroxy-3' ' -methoxyphenyl)-1,3-propanediol	roots	*S. caudata*	[33]
123	1-*O*-[*β*-D-xylopyranosyl-(1→6)-*O*-*β*-D-glucopyranosyl]-2,6-dimethoxy-4-propenyl-phenol	roots	*S. caudata*	[38]
123	salidroside	leaves	*S. anomala*	[14]
125	2-[4-(3-hydroxypropyl)-2-methoxyphenoxy] -1,3-propanediol1-*O*-glucoside	roots	*S. caudata*	[33, 38]



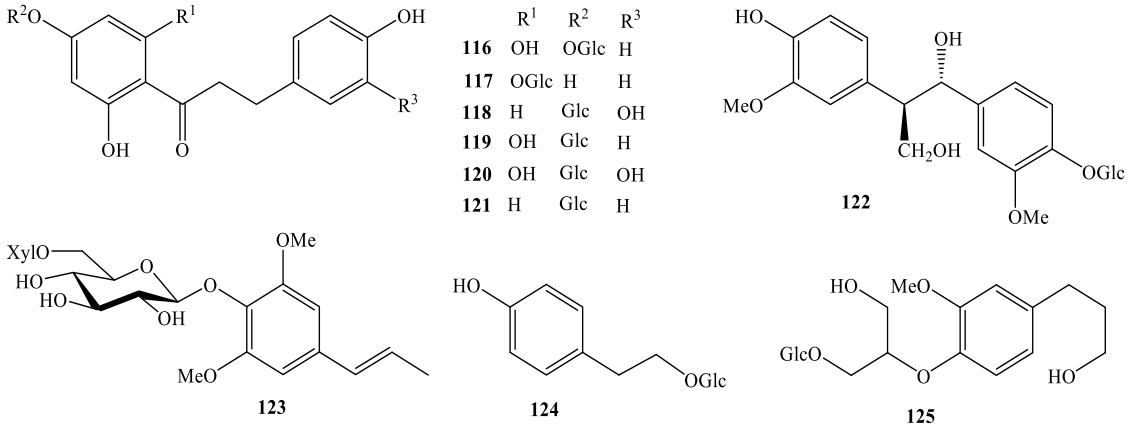


Figure 11. Chemical structures of phenolics from *Symplocos* genus.

3.2.3. Lignans and neolignans

Compiling research on chemical components, there are 21 lignans and neolignans (**126-146**) which have been isolated from the *Symplocos* genus (*Table 11* and *Figure 12*).

Table 12. Lignans and neolignans from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
126	arctigenin	trunks	*S. setchuensis*	[6]
		leaves	*S. sumuntia*	[6, 39]
127	matairesinol	leaves	*S. sumuntia*	[39]
128	matairesinoside	barks	*S. setchuensis*	[6, 38]
		roots	*S. caudata*	[38]
129	8*R*,8'*R*-matairesinol-4-*O*-*β*-D-xylopyranosyl-(1→ 2)-*O*-*β*-D-glucopyranoside	roots	*S. caudata*	[38]
130	(+)-lariciresinol	leaves	*S. anomala*	[14]
131	(+)-lariciresinol 9-*O*-*β*-D-glucopyranoside	leaves	*S. anomala*	[14]
132	(+)-sesamin	leaves	*S. anomala*	[14]
133	(+)-pinoresinol	trunks	*S. sumuntia*	[39]
134	(+)-pinoresinol-*β*-D-glucoside	trunks	*S. setchuensis*	[6]
135	monomethylpinoresinol	barks	*S. glomerata*	[22, 39]
		trunks	*S. sumuntia*	[39]
136	(+)-syringaresinol	leaves	*S. anomala*	[14]
137	(+)-1-acetoxypinoresinol-4''-*O*-methyl ether	leaves	*S. anomala*	[14]
138	(7*S*,8*S*)-*threo*-7,9,9'-trihydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan-4-*O*-*β*-D-glucopyranoside	roots	*S. caudata*	[38]
139	(7*R*,8*R*)-*threo*-7,9,9'-trihydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan-4-*O*-*β*-D-glucopyranoside	roots	*S. caudata*	[38]
140	(7*R*,8*S*)-*erythro*-7,9,9'-trihydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan-4-*O*-*β*-D-glucopyranoside	roots	*S. caudata*	[38]
141	(7*S*,8*R*)-*erythro*-7,9,9'-trihydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan-4-*O*-*β*-D-glucopyranoside	roots	*S. caudata*	[38]
142	(7*R*,8*S*)-*erythro*-7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-*O*-	roots	*S. caudata*	[3]

	4'-neolignan-4-*O*-D-glucopyranoside			
143	symplocosneolignan	leaves	*S. cochinchinensis*	[27]
144	(+)-isolariciresinol	trunks	*S. setchuensis*	[6]
145	symplolignanoside A	roots	*S. caudata*	[33]
146	Dihydrodehydrodiconiferylalcohol 4'-*O*-*β*-D-glucoside	roots	*S. caudata*	[33]

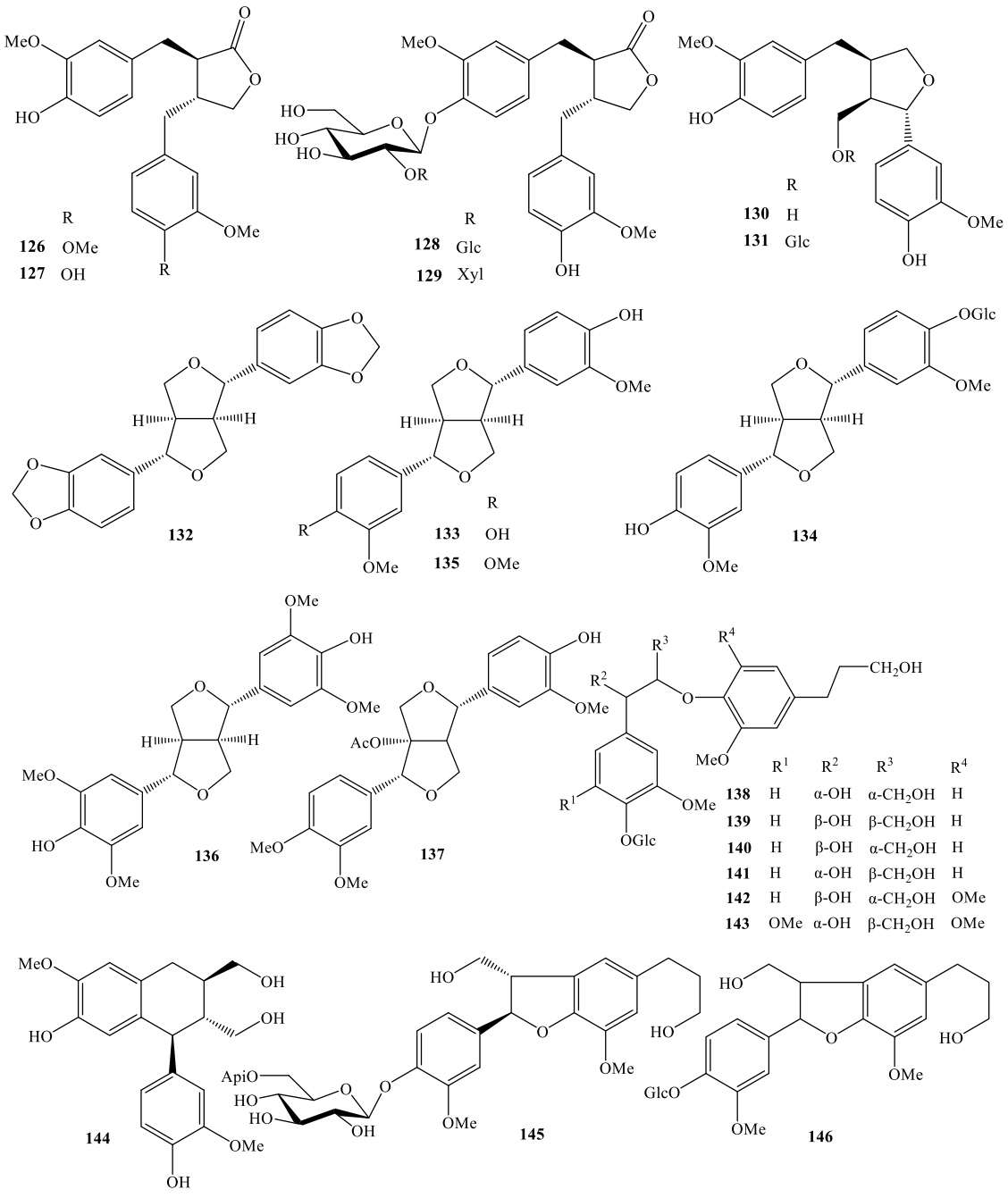


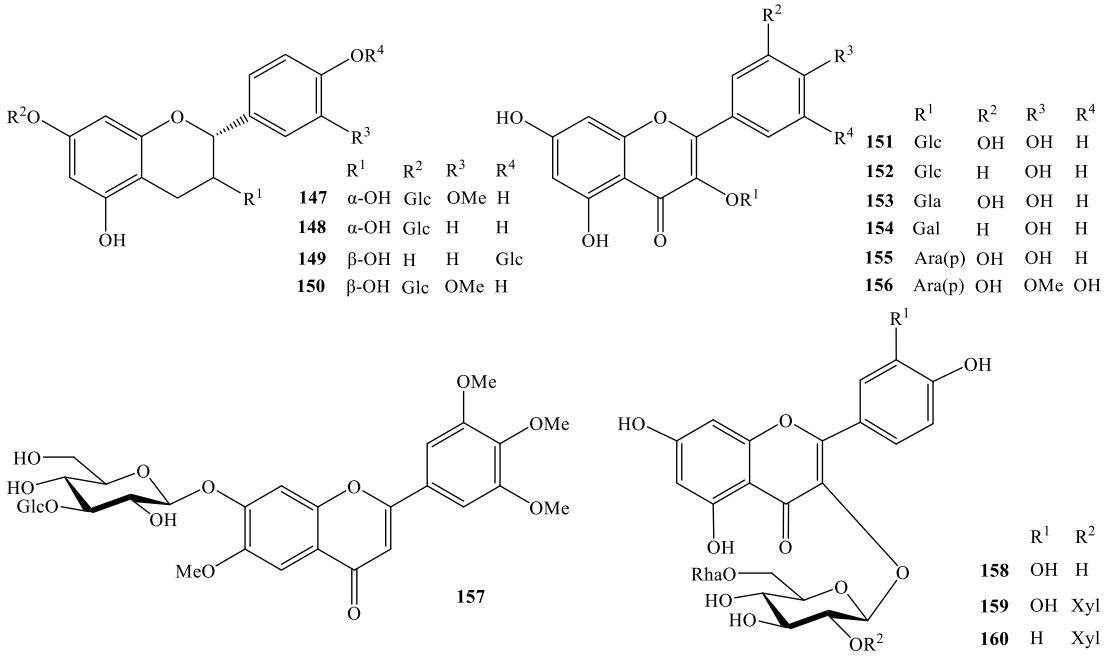
Figure 13. Chemical structures of lignans and neolignans from *Symplocos* genus.

3.2.4. Flavonoids

17 flavonoids (**147-163**) have been isolated from the *Symplocos* genus, such as *S. racemosa, S. paniculata, and S. unijlora* (*Table 13* and *Figure 14*).

Table 14. Flavonoids from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
147	symplocoside	barks	*S. unijlora*	[40]
148	(-)-epiafzelechin-7-*O*-*β*-D-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
149	afzelechin-4'-*O*-*β*-D-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
150	3'-*O*-methycatechin-7-*O*-*β*-D-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
151	quercetin-3-*O*-*β*-D-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
152	kaempferol-3-*O*-*β*-D-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
153	quercetin-3-*O*-*β*-D-galactopyranoside	trunks, leaves	*S. racemosa*	[41]
154	kaempferol-3-*O*-*β*-D-galactopyranoside	trunks, leaves	*S. racemosa*	[41]
155	quercetin-3-*O*-*α*-L-rhamnopyranoside	trunks, leaves	*S. racemosa*	[41]
156	mearnsetin-3-*O*-*α*-L-rhamnopyranoside	trunks, leaves	*S. racemosa*	[41]
157	3',4',5',6-tetramethoxyflavone-7-*O*-*β*-D-glucopyranosyl (1→3)-*β*-D-glucopyranoside	barks	*S. paniculata*	[12]
158	quercetin-3-*O*-rutinoside	trunks, leaves	*S. racemosa*	[41]
159	quercetin-3-*O*-(2''-*β*-D-xylopyranosylrutinoside)	trunks, leaves	*S. racemosa*	[41]
160	kaempferol-3-*O*-(2''-*β*-D-xylopyranosylrutinoside	trunks, leaves	*S. racemosa*	[41]
161	quercetin-3-*O*-*β*-D-(6''-*O*-galloyl)-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
162	kaempferol-3-*O*-*β*-D-(6''-*O*-galloyl)-glucopyranoside	trunks, leaves	*S. racemosa*	[41]
163	sympracemoside	trunks, leaves	*S. racemosa*	[41]



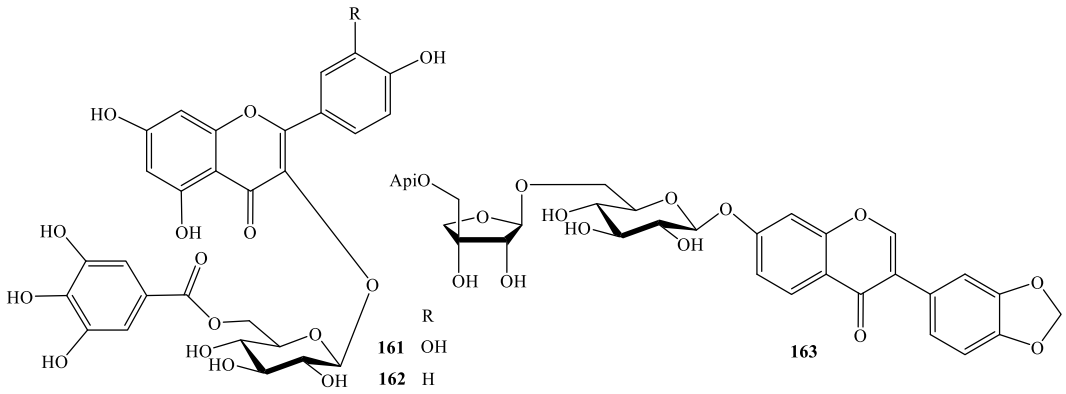


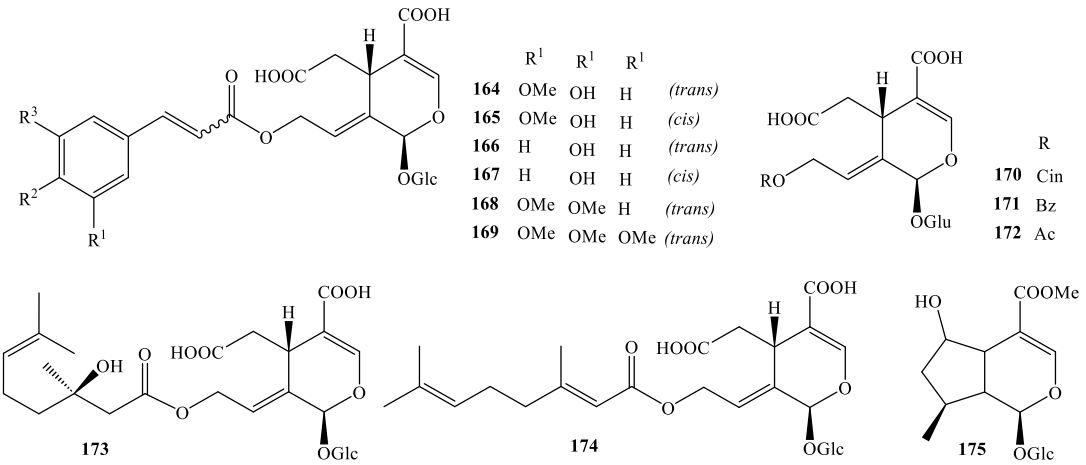
Figure 15. Chemical structures of flavonoids from *Symplocos* genus.

3.2.5. Iridoids

There are 13 iridoid compounds isolated from the *Symplocos* genus (**164-177**) (*Table 15* and *Figure 16*).

Table 16. Iridoids from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
164	symplocochinside A	trunks, leaves	*S. cochinchinensis*	[26]
165	symplocochinside B	trunks, leaves	*S. cochinchinensis*	[26]
166	symplocochinside C	trunks, leaves	*S. cochinchinensis*	[26]
167	symplocochinside D	trunks, leaves	*S. cochinchinensis*	[26]
168	symplocochinside E	trunks, leaves	*S. cochinchinensis*	[26]
169	symplocochinside F	trunks, leaves	*S. cochinchinensis*	[26]
170	10-cinnamoyloxyoleoside	trunks, leaves	*S. cochinchinensis*	[26]
171	symplocochinside G	trunks, leaves	*S. cochinchinensis*	[26]
172	symplocochinside H	trunks, leaves	*S. cochinchinensis*	[26]
173	symplocochinside I	trunks, leaves	*S. cochinchinensis*	[26]
174	symplocochinside J	trunks, leaves	*S. cochinchinensis*	[26]
175	6-dihydroverbenalin	fruits	*S. glauca*	[42]
176	symplolucidin A	fruits	*S. lucida*	[43]
177	symplolucidin B	fruits	*S. lucida*	[43]



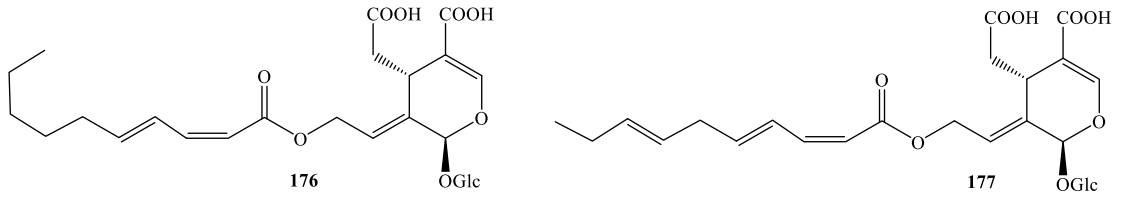


Figure 17. Chemical structures of iridoids from *Symplocos* genus.

3.2.6. Steroids

According to published papers, 9 steroids (**178-184**) have been isolated (*Table 17* and *Figure 18*).

Table 18. Steroids from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
178	(22*E*,24*R*)-ergosta-7,22-diene-3*β*-ol	trees	*S. setchuensis*	[10]
179	*β*-sitosterol	trees	*S. setchuensis*	[10, 11]
		trees	*S. racemosa*	[11]
180	*β*-sitosterol glycoside	trees	*S. racemosa*	[11]
181	stigmasterol	leaves	*S. paniculata*	[6, 28]
182	9*β*,19-cyclo-24-methylcholan-5,22-diene 3*β*-*O*-{*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside}	barks	*S. paniculata*	[12]
183	*α*-spinasterol	leaves	*S. anomala*	[14]
184	androst-5(6)-ene-17-one-3*β*-*O*-(*β*-D-glucopyranoside)	barks	*S. paniculata*	[12]

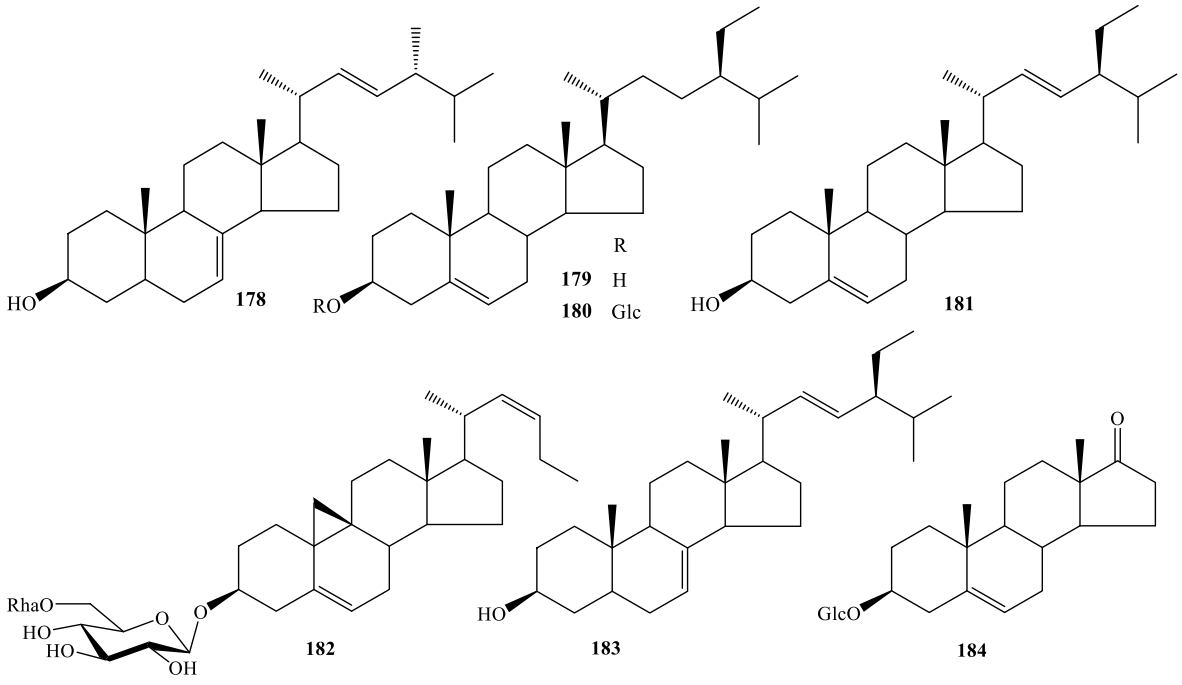


Figure 19. Chemical structures of steroids from *Symplocos* genus.

3.2.7. Athraquinones

Only 7 athraquinones have been isolated from *S. racemosa* (**185-191**) (*Table 19* and *Figure 20*).

Table 20. Athraquinones from *Symplocosracemosa*.

No.	Compound name	Part	Source	Ref.
185	1,4-dihydroxy-6-(ethoxymethyl)-8-propylanthracene-9,10-dione	trees	S. *racemosa*	[44]
186	1,4-dihydroxy-6-(hydroxymethyl)-8-butylanthracene-9,10-dione	trees	S. *racemosa*	[44]
187	symploquinone A	trees	S. *racemosa*	[45]
188	1,4-dihydroxy-6-(hydroxymethyl)-8-propyl anthracene-9,10-dione	trees	S. *racemosa*	[44]
189	symploquinone B	trees	S. *racemosa*	[45]
190	symploquinone C	trees	S. *racemosa*	[45]
191	physcione	trees	S. *racemosa*	[10]

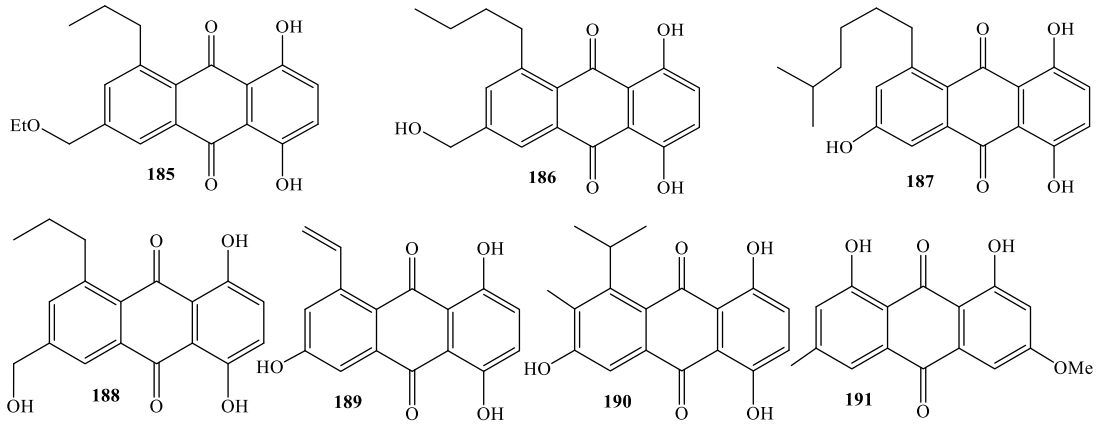


Figure 21. Chemical structures of athraquinones from *Symplocos* genus.

3.2.8. Other compounds

In addition to the substances mentioned above, scientists have isolated a number of other compounds (**192-202**) from the *Symplocos* genus such as alkaloids, megastigmanes, etc. (*Table 21* and *Figure 22*).

Table 22. Other compounds from *Symplocos* genus.

No.	Compound name	Part	Source	Ref.
192	(+)-3-oxo-*α*-ionone	leaves	*S. anomala*	[14]
193	symplocosionoside A	leaves	*S. cochinchinensis*	[27]
194	symplocosionoside B	leaves	*S. cochinchinensis*	[27]
195	symplocosionoside C	leaves	*S. cochinchinensis*	[27]
196	linarionoside B	leaves	*S. anomala*	[14]
197	(8*R*,9*S*)-8,9-dihydromegastigmane-4,6-diene-3-one	trunks, leaves	*S. cochinchinensis*	[26]
198	blumenol B	leaves	*S. anomala*	[14]
199	harman	trunks	*S. setchuensis*	[6]

200	vincoside lactam	leaves	*S. anomala*	[14]
201	symploate	trees	*S. racemosa*	[46]
202	5-hydroxymethylfurfural	trees	*S. chinensis*	[47]

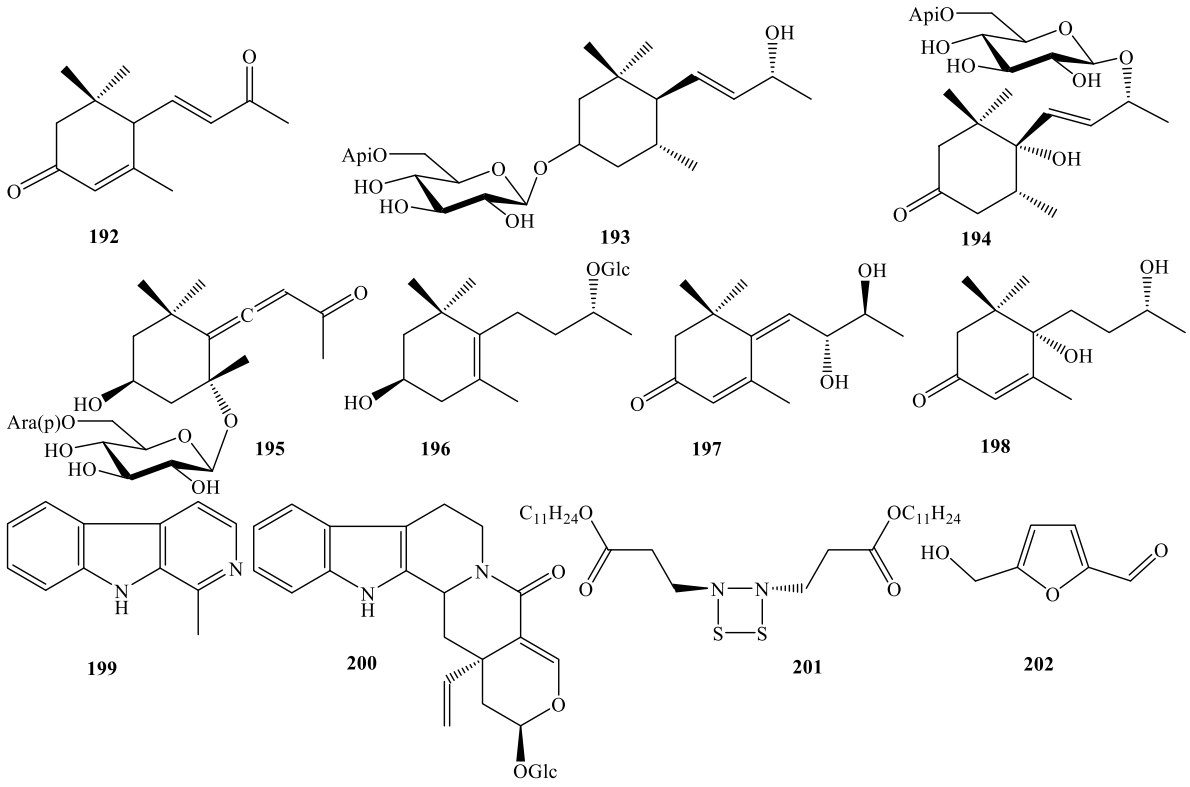


Figure 23. Chemical structures of other compounds from *Symplocos* genus.

3.3. Biological activities

The traditional uses and bioactive compounds from the *Symplocos* genus have attracted researchers' interest in studying their pharmacological activities and verifying the potential uses of the genus. The following discussion provides the biological effects of the extracts and compounds from the *Symplocos* genus. Species of the *Symplocos* genus possess a wide range of biological effects such as anti-cancer, antioxidant, anti-inflammatory, antibacterial, hypoglycemic, and other activities. Below is a summary of the important biological activities of the *Symplocos* species.

3.3.1. Cytotoxic and antitumor activities

The results of a worldwide research overview show that many species of the *Symplocos* genus are potentially toxic to cancer cell lines. The ethyl acetate and chloroform extracts of *S. racemosa* barks showed their toxicity to Hep3B cancer cells *in vitro* with IC_{50} values of 63.45 and 75.55 µg/mL, respectively, compared with the drug doxorubicin (IC_{50} 55.63 µg/mL) [48]. According to Fu, the symplocososides G-K (**25, 26, 32, 27, 33**) isolated from the roots of *S. chinensis* collected in Guangxi, China, showed significant and moderate cytotoxicity on cancer cell lines KB, HCT-8, A549, BEL-7402, and BGC-823 with IC_{50} values ranging from 0.82 to

5.09 μM. Compound **32** did not show cytotoxic effects on all tested cancer cell lines; compound **33** did not show cytotoxic effects on the BGC-823 cancer cell line, compared with positive control, adriamycin (IC_{50} values of 0.21-0.67 μM) [19]. In another study, Fu isolated eight symplocososides L, M, O, P, R, N, S, and Q (**28, 29, 30, 31, 35, 34, 36,** and **24**) from the ethanol extract of *S. chinensis* roots. These compounds were evaluated on the A2780 cancer cell line. Compounds **24, 35,** and **36** showed significant cytotoxic activity on the A2780 cancer cell line, with IC_{50} values ranging from 1.9 to 3.3 μM. Compounds **28, 29, 30,** and **34** were potentially toxic to cancer cell lines HCT-8 and Bel-7402 (IC_{50} in the range of 1.7 - 3.8 μM) when compared to positive control, adriamycin (IC_{50} 0.8 and 1.0 μM, respectively) [5]. From the extract of the roots of *S. chinensis*, Tang isolated six new triterpenoids, of which three compounds showed *in vitro* cancer cytotoxic activity using the MTT method: symplocososide A (**18**) has cytotoxic potential against cancer cell lines A549, KB, HCT-8, and HELF with IC_{50} in the range of 0.67 - 4.62 μg/mL. Symplocososide C (**20**) and symplocososide F (**23**) showed significant cytotoxic activity on the HCT-8 cancer cell line with IC_{50} in the range of 2.86 and 4.04 μg/mL [18]. According to Li, the3-oxo-19*α*,23,24-trihydroxyurs-12-en-28-oic acid (**74**) isolated from the roots of *S. chinensis* showed significant cytotoxic activity against cancer cell lines BGC-823 and B16 (IC_{50} values of 0.025 and 0.068 μM, respectively) and significant cytotoxic activity against cancer cell lines B16-BL6 and Ketr-3 (IC_{50} values of 0.25 and 0.35 μM, respectively) by the MTT method [25]. Among 18 compounds isolated from the leaves of *S. cochinchinensis*, Ohyama found symplocosin K (**38**) exhibited *in vitro* cytotoxic activity against A549 cancer cells with an IC_{50} value of 73.8 ± 2.31 μM [20].

3.3.2. Antioxidant activity

In 2017, Kar reported the antioxidant activity of methanol extract from the barks, leaves, and roots of *S. racemosa* using the ABTS method. The results showed free radical scavenging activity with IC_{50} values of 30.91 - 41.35 μg/mL [49]. According to Maitra' s research, the methanol extract of *S. racemose* was evaluated for its antioxidant activity using the DPPH method. At a concentration of 100 μg/mL of this extract, the free radical scavenging ability of the extract was 87.60 % [50]. The methanol extract of *S. cochinchinensis* was evaluated by Sunli for its *in vitro* antioxidant activity using the DPPH method. The methanol extract from its leaves and barks had moderate free radical scavenging activity with the IC_{50} values of 620.30 and 820.34 μg/mL, respectively, compared to positive control, ascorbic acid (IC_{50} 290.32 μg/mL) [51]. Antu analyzed the antioxidant activity of *S. cochinchinensis* barks using the ABTS method. Trolox was used as a positive control (IC_{50} value of 5.00 ± 0.51 mg/mL). The ethanol extract showed moderate antioxidant activity with an IC_{50} value of 54.95 ± 1.12 μg/mL [52].

3.3.3. Antimicrobial activity

The aqueous extract from the bark of *S. racemosa* showed broad-spectrum antibacterial activity, inhibiting 11 out of 13 bacterial strains tested, and showed a moderate inhibitory zone of 12-17 mm [53]. Studying the antibacterial activity of the bark of *S. racemosa*, Sood' s research results showed that the ethyl acetate extract contains flavonoids with significant and broad-spectrum antibacterial activity with a moderate inhibitory zone ranging from 14.6 to 28.3 mm. The antibacterial activity against *S. epidermidis* is equivalent to gentamicin (26.5 mm) and chloramphenicol (28.5 mm) against *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, similar to positive control, chloramphenicol (25.0-28.5 mm) [54]. According to Semwal' s research, the methanol extract of *S. paniculata* bark has inhibitory activity against bacterial strains *S. aureus, B. subtilis, P. autogiros*, and *E. coli*, with the MIC values of 250 and 500 μg/mL. From further analysis, 9*β*,25-cyclo-3*β*-*O*-(*β*-D-glucopyranosyl)-echynocystic acid (**8**) and 30-ethyl 2*α*,16*α*-

dihydroxy 3*β*-*O*-(*β*-D-glucopyranosyl) hopan-24-oic acid (**92**) show inhibitory activity against all four bacterial strains above with the MIC values of 25, 50, and 100 μg/mL [12]. The triterpenoids oleanolic acid (**1**), asiatic acid (**64**), ursolic acid (**65**), and corosolic acid (**66**) isolated from the leaves of *S. lancifolia* show antibacterial activity against *E. faecalis* and *S. aureus* strains with the MIC values in the range of 16-128 μg/mL [17]. The results of evaluating the antibacterial activity of symploquinones A-C (**187, 189, 190**) isolated from *S. racemosa* species showed that the MIC values for compounds **187** and **190** were found in the concentration range of 160 to 83 μg/mL, equal to or lower than the MIC value of gentamicin (125 μg/mL). The MIC values of compounds **187** and **190** for *P. mirabilis* were more than 160 μg/mL [45].

3.3.4. Hypoglycemic effect

Over the world, there have been many studies on the blood sugar-lowering ability of species of the genus *Symplocos*. According to Antu' s research, the ethanol extract of *S. cochinchinesis* has the ability to inhibit *α*-glucosidase enzyme well (the IC_{50} value of 82.07±2.10 mg/mL), demonstrated through insulin-dependent glucose uptake (3-fold increase), pancreatic beta cell regeneration (3.5-fold increase), reduced triglyceride accumulation (22 % decrease), and hypoglycemia (59.57 % decrease) [52]. The results of studying the ability to treat type 2 diabetes *in vivo* by the *n*-hexane extract from *S. cochinchinensis* leaves showed that after 28 days of treatment at doses of 250 and 500 mg/kg, the plasma glucose level was reduced by 17.04 % and 42.10 %, respectively. Plasma insulin, total cholesterol in plasma and liver, triglycerides, and free fatty acids decreased, while glycogen content in the liver increased [55]. Methanol extract from *S. cochinchinensis* bark was administered at doses of 250 and 500 mg/kg to diabetic mice. After 28 days of treatment, sugar content, plasma insulin content, and liver glycogen returned to normal levels, comparable to a glibenclamide dose of 600 mg/kg [56]. Antu *et al*. studied the effects of ethanol extract from *S. cochinchinensis* on mice with type 2 diabetes.Their results showed that after 21 days of testing at a dose of 500 mg/kg, the blood sugar was lowered by 46.28 %, homeostasis-insulin resistance was reduced by 2.47%, and glycogen content in the liver was remarkably increased. The activity of the ethanol extract is equivalent to metformin at a dose of 100 mg/kg [57]. From *S. racemosa*, Abbasi isolated symploate (**201**) that has the ability to inhibit *α*-glucosidase with an IC_{50} value of 691.1 ± 3.29 μM [46]. In medicine, inhibiting the PTP1B enzyme is used to treat type 2 diabetes and obesity. From the methanol extract of the leaves and stems of *S. paniculata*, ursolic acid (**65**) and corosolic acid (**66**) with *in vitro* inhibitory activity against PTP1B enzyme with IC_{50} values of 3.8 ± 0.5 μM and 7.2 ± 0.8 μM have been isolated [24].

3.3.5. Anti-inflammatory and analgesic activity

Krishna *et al*. investigated the *in vivo* anti-ulcer activity of *S. racemosa* bark and found that ethanol and water extracts at a concentration of 500 mg/kg exhibited 68.51 % and 70.41 % protective capacity, respectively, comparable to lansoprazole (at a dose of 8 mg/kg, with a protective capacity of 74.51 %) [58]. From *S. racemosa*, Mehjabeen and colleagues investigated the anti-inflammatory and analgesic activities *in vivo* using methanol extracts at doses of 300 and 500 mg/kg administered orally. The results indicated that the methanol extract exhibited potent anti-inflammatory and analgesic effects, equivalent to aspirin at 300 mg/kg [59]. Janani's research group studied the anti-inflammatory activity through a protein denaturation assay. Their findings showed that the *S. racemosa* extract demonstrated excellent anti-inflammatory activity, inhibiting protein denaturation by 76 %, comparable to diclofenac sodium (86 %) [60]. In a study on anti-inflammatory activity, Trieu' s group found that the residue extracted from the leaves of *S. cochinchinensis* had anti-inflammatory activity through protein denaturation and the

ability to inhibit heat-induced hemolysis and hypotonicity better than diclofenac sodium [61]. From the barks of *S. racemosa*, Rashid isolated three new phenolic compounds, namely locoracemosides A-C (**113-115**). A study on anti-inflammatory properties showed that compounds **114** and **115** had strong anti-inflammatory activity with the IC_{50} of 11.95 ± 1.85 and 6.04 ± 0.31 μM, equivalent to *α*-chymotrypsin (the IC_{50} value of 7.21 ± 2.31 μM) [34]. From the stem bark of *S. paniculata*, Semwal tested the *in vivo* analgesic activity of the ethanol extract at a dose of 500 mg/kg, and determined its protective capacity to be 48.77 %. Further analysis identified two of the seven isolated compounds as having the most potent analgesic activity, namely 9*β*,25-cyclo-3*β*-O-(*β*-D-glucopyranosyl)-echynocystic acid (**8**) and 32,33,34-trimethyl-bacteriohopan-16-ene-3-O-*β*-D-glucopyranoside (**93**), giving protective capacities of 72.00 and 64.95 %, respectively, at a dose of 300 mg/kg, comparable to paracetamol (protective capacity of 80.12 % at a dose of 100 mg/kg,). The anti-inflammatory ability of the ethanol extract and compounds **8, 93** were tested orally at a dose of 300 mg/kg, giving protective capacities of 40.98-50.00 %, which are equivalent to the drug phenylbutazone (protective capacity of 49.18 % at a dose of 100 mg/kg) [12].

3.3.6. Other activities

In addition to the *Symplocos* genus's cytotoxic activity and anti-inflammatory, analgesic, antimicrobial, antioxidant, blood sugar-lowering effects, its extracts and compounds also demonstrate hepatoprotective activity, lipid-lowering, anti-asthmatic effects, anti-coagulant properties, snake venom phosphodiesterase I inhibition, etc. When researching the bark of *S. racemora*, Ahmad isolated and tested the snake venom phosphodiesterase I inhibitory activity of the compounds obtained, namely benzoylsalireposide (**100**) and symconoside A (**102**), which showed strong activity with IC_{50} values in the range of 158 - 171 μM. Salireposide (**99**) and symploracemoside (**108**) showed moderate activity with the IC_{50} values ranging from 544 to 590 μM. Symplomoside (**107**) and symconoside B (**101**) showed weak activity with IC_{50} values ranging from 900 to 998 μM, compared with positive controls, cysteine (the IC_{50} of 748 μM) and EDTA (the IC_{50} of 274 μM) [11, 30, 31]. In another study by Abbasi and colleagues, from the bark of *S. racemora*, six phenolics were isolated: **99**, **100**, symponoside (**98**), symplososide (**105**), symplocomoside (**110**), and symploveroside (**106**). The test results showed that they all had inhibitory activity against phosphodiesterase I in snake venom, in which compounds **100**, **110** had strong activity with the IC_{50} value ranging from 122 to 171 μM, compounds **99**, **98**, **105**, **106** had weak to moderate activity with the IC_{50} values in the range of 504 - 909 μM, compared with positive controls cysteine (the IC_{50} of 748 μM) and EDTA (the IC_{50} of 274 μM) [29]. When studying the bark of *S. glomerata*, the saponins from the methanol extract, at a concentration of 370 mg/mL, exhibited hemolytic activity and caused 50 % hemolysis in a 10 % sheep red blood cell suspension [62]. The ethanol extract of *S. racemosa* leaves was found to have strong *in vitro* anti-acne activity. At concentrations of 25, 50, and 100 μg/mL, the inhibition zone was 8-13 nm, compared to the clindamycin positive control (concentrations of 10-30 μg/mL, inhibition zone of 8-11 nm). [63]. In 2010, Vijayabaskaran tested the *in vivo* antipyretic ability of ethanol extract from the bark of *S. racemosa*. The antipyretic effect at a dose of 100 mg/kg taken orally was equivalent to that of paracetamol at the same dose [32]. In a study of the formation and development of ovarian follicles in immature female mice, the aqueous extract of *S. racemosa* was administered orally. The results demonstrated a significant increase in the formation of ovarian follicles and the appearance of mature follicles, attributed to the elevated concentrations of FSH and LH in the serum [64]. The ethanol and *n*-hexane extracts from *S. racemosa* leaves were tested by Manure for their immunomodulatory activity on mice. The results showed increased phagocytic activity at oral doses of 200 and 400 mg/kg [65]. Wakchaure evaluated the

hepatoprotective effect of ethanol extract from the bark of *S. racemosa*. At doses of 200 and 400 mg/kg taken orally, the ethanol extract showed similar liver protection effects as silymarin [66]. In 2001, Ishida studied the anti-HIV activity of *S. setchuensis* and found that its ethanol extract showed potent activity with an EC_{50} value less than 20 µg/mL. Biologically oriented isolation of ethanol extracts identified matairesinol (**127**) and harman (**199**) as showing anti-HIV properties with EC_{50} values of 2.0 and 10.7 µM [6].

4. CONCLUSIONS

All the research above has shown that *Symplocos* is an important genus in the Symplocaceae family. However, chemical and biological studies are still limited, representing an opportunity to find new bioactive substances. The chemical constituent features of triterpenoids, phenolics, lignans, and neolignans have made them considered as the markers of the genus. However, the pre-clinical pharmacological studies in this review exhibited low methodological quality, hindering the unambiguous interpretation of the results. It is still noteworthy that several gaps need to be addressed to apply the genus *Symplocos* better. This review provides the medicinal potential and basic understanding of the genus *Symplocos* for further research on the application of medicinal plants. The review compiles information about the *Symplocos* genus that cytotoxic assays should investigate to develop new drugs for treating cancer diseases and symptoms.

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