Natural Product Communications
Volume 18(7): 1–22

DOI: 10.1177/1934578X231189143
journals.sagepub.com/home/npx
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Baeckea frutescens L.: A Review on Phytochemistry, Biosynthesis, Synthesis, and Pharmacology

Do Thi Lan Huong[1], Dau Xuan Duc[2] and Ninh The Son[3]

Abstract

Background: In traditional medicine of Southeast Asian countries, *Baeckea frutescens* L. (family Myrtaceae) has a long history of use. Numerous research projects have shown that this plant contains metabolites with remarkable medicinal value. No review document, to date, has given an insight into the role of *B frutescens* constituents in pharmacological development. **Objective:** The current review briefly offers crucial information on the phytochemistry, biosynthesis, synthesis, and pharmacology of *B frutescens*. **Methods:** *B frutescens* is the most meaningful keyword to search for literature data. It was used either on its own or in combination with other keywords. References have been gathered from various resources such as Google Scholar, SciFinder, and PubMed. More than 50 electronic references were collected from the 1960s. **Results:** Approximately 130 metabolites have been isolated and structurally determined from this medicinal plant. They included phloroglucinols, phloroglucinol-based meroterpenoids, sesquiterpenoids, triterpenoids, flavonoids, chromones, 5-membered ring compounds, and others. *B frutescens* fresh tissues were thought to be a rich resource of essential oils. Tasmanone is a precursor in the biosynthesis of various *B frutescens* compounds, while phloroglucinol derivatives can be seen as initial compounds in the synthetic procedures of various *B frutescens* molecules. *B frutescens* plant extracts and compounds isolated from them possess a variety of pharmacological properties, such as cytotoxic, antimicrobial, anti-inflammatory, antioxidant, antirheumatoid, skin protective, and mosquito larvicidal activities. **Conclusion:** More experimental reports on phytochemistry and pharmacology are required. In vivo pharmacological studies on the mechanisms of action of the active compounds are urgently required since most of the results obtained so far have been from in vitro assays.

Keywords

Baeckea frutescens, phytochemistry, biosynthesis, synthesis, pharmacology

Received: May 7th, 2023; Accepted: July 4th, 2023.

Introduction

Baeckea frutescens L. is a member of the family Myrtaceae and is indigenous to Australia, New Guinea, and eastern Southeast Asia.[1] It is a shrub with arched branches, linear leaves, and 7-13 stamens on each of its white flowers. *B frutescens*, also known as "Jungrahab," is an Indonesian folk medicine.[2] Its aerial parts are employed to treat influenza, malaria, fever, headache, dysentery, and abdominal pain.[2] The leaves of this plant are recommended as a remedy for headache, rheumatism, and fever.[3] The leaf decoction was used in Malaysia for diuretic and emmenagogue features.[4] In China, the leaves have been applied as a refreshing herbal tea to cure fever and sunstroke, and the dried leaves could be a febrifuge.[4] The roots of this plant, known as "Pu Lao Zhong," have good effects in treating rheumatism and snake bites.[5,6] *B frutescens* is used as a daily health tea with the well-known name of "Gang Song Cha."[7]

By chromatographic procedures and liquid chromatography-mass spectrometry (LC-MS) analysis, diverse classes of phytochemicals have been detected. Along with other classes, phloroglucinols, flavonoids, and chromones are likely to be the main types of *B frutescens* secondary metabolites.[5–14] *B frutescens* essential oils are dominated by terpenoids.[15,16] The plant extracts, fractions, and their isolates are now potential agents for drug development since they possess pivotal pharmacological properties, such as cytotoxic, antimicrobial, and anti-inflammatory activities.[13,17,18] As an example, frutescone O, at 0.2-0.8 μM, suppressed lipopolysaccharide (LPS)-stimulated RAW264.7 cells by blocking TLR4-mediated mitogen-activated protein kinase (MAPK)/

[1]Faculty of Biology and Agricultural Engineering, Hanoi Pedagogical University 2 (HPU2), Phucyen, Vinhphuc, Vietnam
[2]Department of Chemistry, College of Education, Vinh University, Vinh City, Nghean, Vietnam
[3]Institute of Chemistry, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam

Corresponding Author:
Ninh The Son, Institute of Chemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Caugiay, Hanoi 10000, Vietnam.
Email: ntson@ich.vast.vn; yamantson@gmail.com

Table 1. Chemical Constituents of *Baeckea frutescens*.

No.	Compounds	Plant part used	Methods	References
Phloroglucinols				
1	Baekeol (BF-3)	Leaf	CC	13,20
2	Baeckenone A	Leaf	CC	13
3	Baeckenone B	Leaf	CC	13
4	Baeckenone C	Leaf	CC	13
5	Baeckenone D	Leaf	CC	14
6	Baeckenone E	Leaf	CC	14
7	Baeckenone F	Leaf	CC	14
8	Baeckenone G	Leaf	CC	3
9	Baeckenone H	Leaf	CC	3
10	Baeckenone I	Leaf	CC	3
11	Baeckenone J	Leaf	CC	3
12	Baeckenone K	Leaf	CC	3
13	BF-1[a]	Leaf	CC	20
14	(8a*R*)-8,8a-Dihydro-8a-hydroxy-7-methoxy-3,3,6,8,8-pentamethyl-1,2-benzodioxin-5(3*H*)-one	Leaf and aerial part	CC	14,21
Phloroglucinol-based meroterpenoids				
15	Baefrutone A	Aerial part	CC	23
16	Baefrutone B	Aerial part	CC	23
17	Baefrutone C	Aerial part	CC	23
18	Baefrutone D	Aerial part	CC	23
19	Baefrutone E	Aerial part	CC	23
20	Baefrutone F	Aerial part	CC	23
21	Baeckfrutone A	Twig and leaf	CC	25
22	(±)-Baeckfrutone B	Twig and leaf	CC	25
23	(±)-Baeckfrutone C	Twig and leaf	CC	25
24	Baeckfrutone D	Twig and leaf	CC	25
25	Baeckfrutone E	Twig and leaf	CC	25
26	Baeckfrutone F	Twig and leaf	CC	25
27	Baeckfrutone G	Twig and leaf	CC	25
28	Baeckfrutone H	Twig and leaf	CC	25
29	(±)-Baeckfrutone I	Twig and leaf	CC	25
30	Baeckfrutone J	Twig and leaf	CC	25
31	Baeckfrutone K	Twig and leaf	CC	25
32	Baeckfrutone L	Twig and leaf	CC	25
33	Baeckfrutone M	Twig and leaf	CC	26
34	Baeckfrutone N	Twig and leaf	CC	26
35	Baeckfrutone O	Twig and leaf	CC	26
36	Baeckfrutone P	Twig and leaf	CC	26
37	Baeckfrutone Q	Twig and leaf	CC	26
38	Baeckfrutone R	Twig and leaf	CC	26
39	Baeckfrutone S	Twig and leaf	CC	26
40	BF-2[a]	Leaf	CC	20
41	Frutescone A	Aerial part	CC	17
42	Frutescone B	Aerial part	CC	17
43	Frutescone C	Aerial part	CC	17
44	Frutescone D	Aerial part	CC	17
45	Frutescone E	Aerial part	CC	17
46	Frutescone F	Aerial part	CC	17
47	(±)-Frutescone G	Aerial part	CC	17
48	Frutescone H	Aerial part	CC	22
49	Frutescone I	Aerial part	CC	22
50	Frutescone J	Aerial part	CC	22
51	Frutescone K	Aerial part	CC	22
52	Frutescone L	Aerial part	CC	22
53	Frutescone M	Aerial part	CC	22
54	(±)-Frutescone N	Aerial part	CC	22
55	Frutescone O	Aerial part	CC	22
56	Frutescone P	Aerial part	CC	22
57	(±)-Frutescone Q	Aerial part	CC	22
58	(±)-Frutescone R	Aerial part	CC	22
59	Frutescone S	Aerial part	CC	24
60	Frutescone T	Aerial part	CC	24
61	Frutescone U	Aerial part	CC	24
Sesquiterpenoids				
62	Caryophyllene-4β,5α-epoxide	Aerial part	CC	27
63	(−)-Clovane-2,9-diol	Aerial part	CC	27
64	Humulene	Leaf	CC	3
65	(±)-Humulene epoxide II	Aerial part	CC	27
Triterpenoids				
66	Betulinic acid	Whole plant	CC	12

(Continued)

Table 1. Continued

No.	Compounds	Plant part used	Methods	References
67	Oleanolic acid	Whole plant	CC	[12]
68	Ursolic acid	Leaf	CC	[3]
Flavonoids				
Flavones				
69	Baeckein A	Root and aerial part	CC LC-MS	[5,8,9]
70	Baeckein B	Root and aerial part	CC LC-MS	[5,8,9]
71	Baeckein C	Root and aerial part	CC LC-MS	[6,8,9]
72	Baeckein D	Root and aerial part	CC LC-MS	[6,8,9]
73	Baeckein E	Root and aerial part	CC LC-MS	[8,9]
74	Baeckein F	Root and aerial part	CC LC-MS	[7,9]
75	Baeckein G	Root and aerial part	CC LC-MS	[7,9]
76	Baeckein H	Root and aerial part	CC LC-MS	[7,9]
77	Baeckein I	Root and aerial part	CC LC-MS	[7,9]
78	Baeckein J	Root	CC	[10]
79	Baeckein K	Root	CC	[10]
80	Baeckein L	Root	CC	[11]
81	Baeckein M	Root	CC	[11]
82	Betmidin	Aerial part	CC	[32]
83	6,8-Di-*C*-methylkaempferol	Aerial part	CC	[32]
84	6,8-Di-*C*-methylkaempferol 3-*O*-α-L-rhamnopyranoside	Aerial part	CC LC-MS	[9,32]
85	6-*C*-Methylquercetin (pinoquercetin)	Aerial part and root	CC LC-MS	[8,9,28,29,32]
86	6-Methylquercetin 7-*O*-β-D-glucopyranoside	Aerial part	CC LC-MS	[28,29]
87	6-*C*-Methylquercetin 4′-*O*-β-D-glucopyranoside	Aerial part and root	CC LC-MS	[8,9,28,32]
88	6-*C*-Methylquercetin 3-*O*-α-L-rhamnopyranoside	Aerial part	CC LC-MS	[9,32]
89	Myricetin	Aerial part	LC-MS	[9,29]
90	Myricetin 3-*O*-(5″-*O*-galloyl)-α-L-arabinofuranoside	Aerial part	CC LC-MS	[28,29]
91	Myricitrin (myricetin 3-*O*-α-L-rhamnopyranoside)	Leaf and aerial part	CC LC-MS	[9,30,32]
92	Quercetin	Aerial part	CC LC-MS	[9,32]
93	Quercetin-3-*O*-α-L-rhamnoside	Aerial part	LC-MS	[9,29]
94	Quercetin 3-*O*-(5″-*O*-galloyl)-α-L-arabinofuranoside	Aerial part	CC	[28]
Flavanones				
95	BF-4[a]	Leaf	CC	[31]
96	BF-5[a]	Leaf	CC	[31]
97	BF-6[a]	Leaf	CC	[31]
98	2,3-Dihydro-5,7-dihydroxy-8-[1-(2-hydroxy-4-methoxy-3,3,5-trimethyl-6-oxo-1,4-cyclohexadien-1-yl)-2-methylpropyl]-6-methyl-2-phenyl-4*H*-1-benzopyran-4-one	Leaf and aerial part	CC	[13,21]
99	5,7-Dihydroxy-6,8-dimethylflavanone	Leaf and aerial part	CC LC-MS	[13,29]
100	(±)-5,7-Dihydroxy-8-isobutyryl-6-methyldihydroflavonol	Aerial part	CC	[24]
101	5-Hydroxy-6-methyl-7-methoxyflavanone	Whole plant and aerial part	CC LC-MS	[9,12]
102	5-Hydroxy-7-methoxy-8-methylflavanone	Whole plant and aerial part	CC LC-MS	[9,12]
Chromones				
103	2,5-Dihydroxy-7-methoxy-2-isopropylchromanone	Aerial part	CC	[34]
104	2,5-Dihydroxy-7-methoxy-2,6-dimethylchromanone	Aerial part	CC	[34]
105	2,5-Dihydro-7-methoxy-2,8-dimethylchromanone	Aerial part	CC	[34]
106	2,5-Dihydro-7-methoxy-2-isopropyl-6-methylchromanone	Aerial part	CC	[34]
107	2,5-Dihydro-7-methoxy-2-isopropyl-8-methylchromanone	Aerial part	CC	[34]
108	7-*O*-(4′,6′-Digalloyl)-β-D-glucopyranosyl-5-hydroxy-2-methylchromone	Aerial part	CC	[28]
109	5-Hydroxy-7-methoxy-2-isopropylchromone	Aerial part and whole plant	CC LC-MS	[9,12,34]

(Continued)

Table 1. Continued

No.	Compounds	Plant part used	Methods	References
110	5-Hydroxy-7-methoxy-2-isopropyl-6-methylchromone	Aerial part	CC LC-MS	[9,34]
111	5-Hydroxy-7-methoxy-2-isopropyl-8-methylchromone	Aerial part	CC LC-MS	[9,34]
112	5-Hydroxy-7-methoxy-2-methylchromone (eugenin)	Aerial part	CC LC-MS	[9,34]
113	5-Hydroxy-7-methoxy-2,8-dimethylchromone	Aerial part	LC-MS	[9]
114	6-β-*C*-Glucopyranosyl-5,7-dihydroxy-2-methylchromone	Leaf	CC	[30,33]
115	6-β-*C*-Glucopyranosyl-5,7-dihydroxy-2-isopropylchromone	Leaf	CC	[30,33]
116	6-β-*C*-(2′-Galloylglucopyranosyl)-5,7-dihydroxy-2-methylchromone (5)	Leaf	CC	[30]
117				

[a]No name.
Abbreviations: CC, column chromatography; LC-MS, liquid chromatography-mass spectrometry.

nuclear factor kappa B (NF-κB) signaling pathways and inhibiting MyD88 and iNOS expressions.[19]

Although there are plenty of experimental reports, no review article has been recorded until now. For the first time, we review several important aspects of this plant, including phytochemical separations, essential oil identifications, biosynthetic and synthetic pathways, and, especially, the applications of chemical constituents in biomedical examinations.

Phytochemistry

In this section, the outcomes of phytochemical investigations of *B frutescens* are based on the use of column chromatography (CC) to isolate purified compounds and LC-MS analysis to detect compounds in plant extracts. A list of isolates is summarized in Table 1 and Figures 1 to 3, including phloroglucinols **1-14**,[3,13,14,20,21] phloroglucinol-based meroterpenoids **15-61**,[17,20,22–26] sesquiterpenoids **62-65**,[3,27] triterpenoids **66-68**,[3,12] flavonoids **69-102**,[5–13,21,24,28–32] chromones **103-121**,[9,12,28,30,33,34] 5-membered ring compounds **122-126**,[2,21] *mono*-phenol **127**,[12] and phytosterol **128**.[12] In addition, the names of these isolates have been ordered in an alphabetic arrangement.

Phloroglucinols, Phloroglucinol-Based Meroterpenoids, Sesquiterpenoids, and Triterpenoids

Phloroglucinols **1-14** are the first chemical class found in this species (Table 1 and Figure 1).[3,13,14,20,21] From the EtOH leaf extract, Fujimoto et al[20] isolated a new phloroglucinol BF-1 (**13**) and a known analog, baekeol (**1**). Significantly, 11 new phloroglucinols, baeckenones A-K (**2-12**), were successfully separated from the $CHCl_3$ extracts of Indonesian *B frutescens*.[3,13,14] (8a*R*)-8,8a-Dihydro-8a-hydroxy-7-methoxy-3,3,6,8,8-pentamethyl-1,2-benzodioxin-5(3*H*)-one (**14**) was first isolated as a new racemic mixture from the aerial part and then was found in the leaf.[14,21] Compound **14**, containing an endoperoxide part, was an unusual metabolite. The successful isolation of this compound suggested a close chemotaxonomic relationship between Myrtaceae species since some analogs were also isolated from other Myrtaceae plants.[21]

The hybrid-type phloroglucinol-based meroterpenoids **15-61** were the second chemical class detectable in *B frutescens* (Table 1 and Figure 1)[17,20,22–26]; all of these isolates were new in nature. Six new meroterpenoids with rare phloroglucinol-monoterpene/sesquiterpene backbones, named baefrutones A-F (**15-20**), were isolated from the 95% EtOH aerial part extract under high-performance liquid chromatography (HPLC)-Q/TOF-MS^2 guidance.[23] In the same manner, 19 previously undescribed compounds, baeckfrutones A-S (**21-39**), were observed in the twig and leaf, in which compounds **22-23** and **29** were present in enantiomeric forms.[25,26] BF-2 (**40**) was among the new compounds found in the EtOH leaf extract.[20] The 95% EtOH extract of the Chinese *B frutescens* aerial part contained new secondary metabolites, frutescones A-U (**41-61**).[17,22,24] Compounds **47**, **54**, and **57-58** appeared as enantiomeric forms, whereas **41** and **44** were marked with an unprecedented oxa-spiro[5.8] tetradecadiene skeleton.

Four sesquiterpenoids **62-65** have been isolated from *B frutescens* to date.[3,27] Chromatographic procedures aided by HPLC of the CH_2Cl_2 aerial part extract afforded a new sesquiterpene, (−)-clovane-2,9-diol (**63**), along with 2 known analogs caryophyllene-4β,5α-epoxide (**62**) and (±)-humulene epoxide II (**65**).[27] Humulene (**64**), a well-known sesquiterpene, was 1 of the isolates from the leaf.[3] Two common triterpenoids, betulinic acid (**66**) and oleanolic acid (**67**), were detectable in the whole plant, while the other known agent ursolic acid (**68**) was only found in the leaf.[3,12]

Flavonoids

Flavonoids are low-molecular-weight phenolic compounds that are found in a variety of higher plants.[35–37] As shown in Table 1 and Figure 2, flavonoids derived from *B frutescens* can be divided into flavones **69-94**[5–11,28–30,32] and flavanones **95-102**.[9,12,13,21,24,29,31]

Regarding flavones, 13 new derivatives, baeckeins A-M (**69-81**), were isolated from the roots and structurally determined from spectroscopic and mass spectrometric evidence.[5–8,10,11]

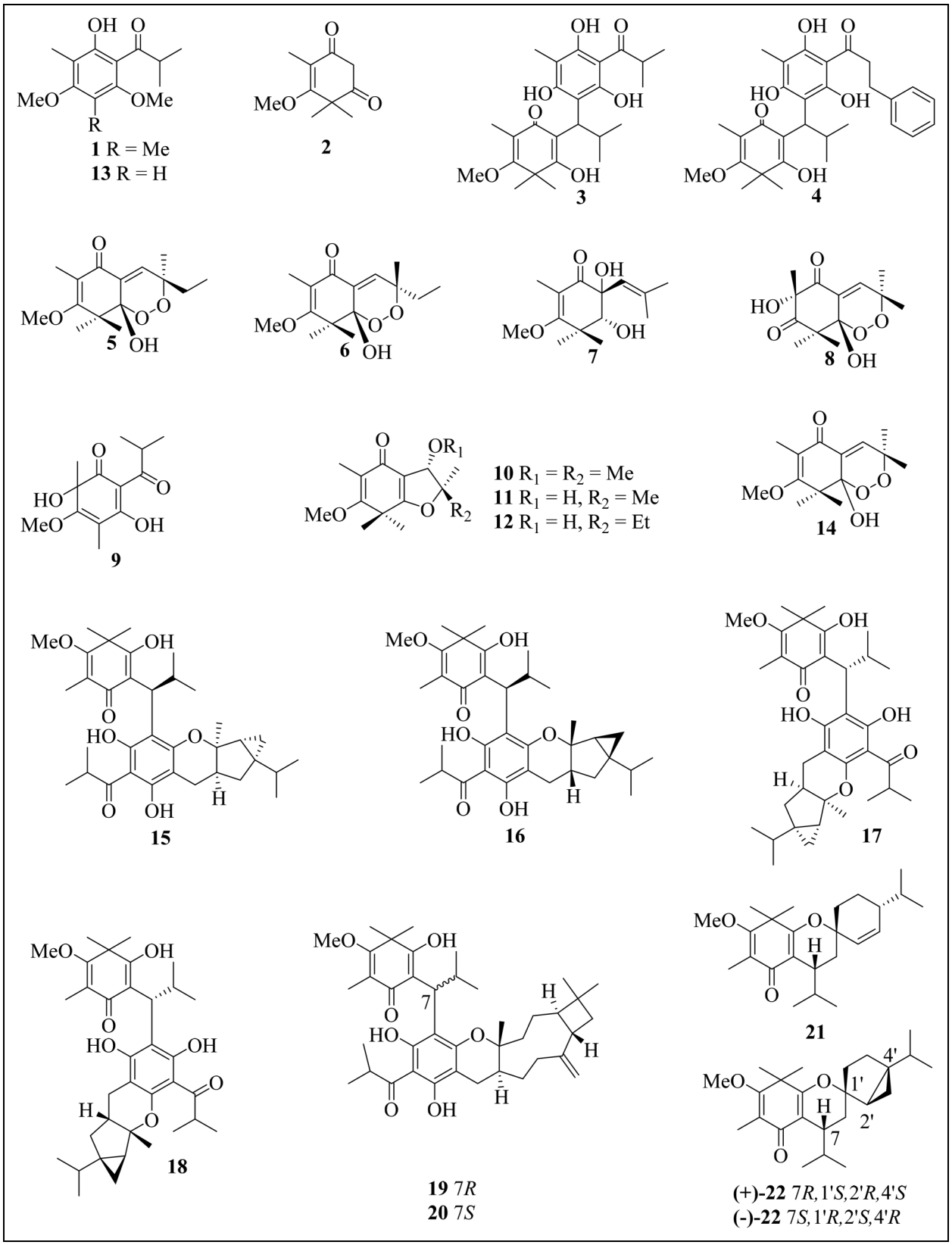

Figure 1. Phloroglucinols, phloroglucinol-based meroterpenoids, sesquiterpenes, and triterpenoids from *Baeckea frutescens*. (continued)

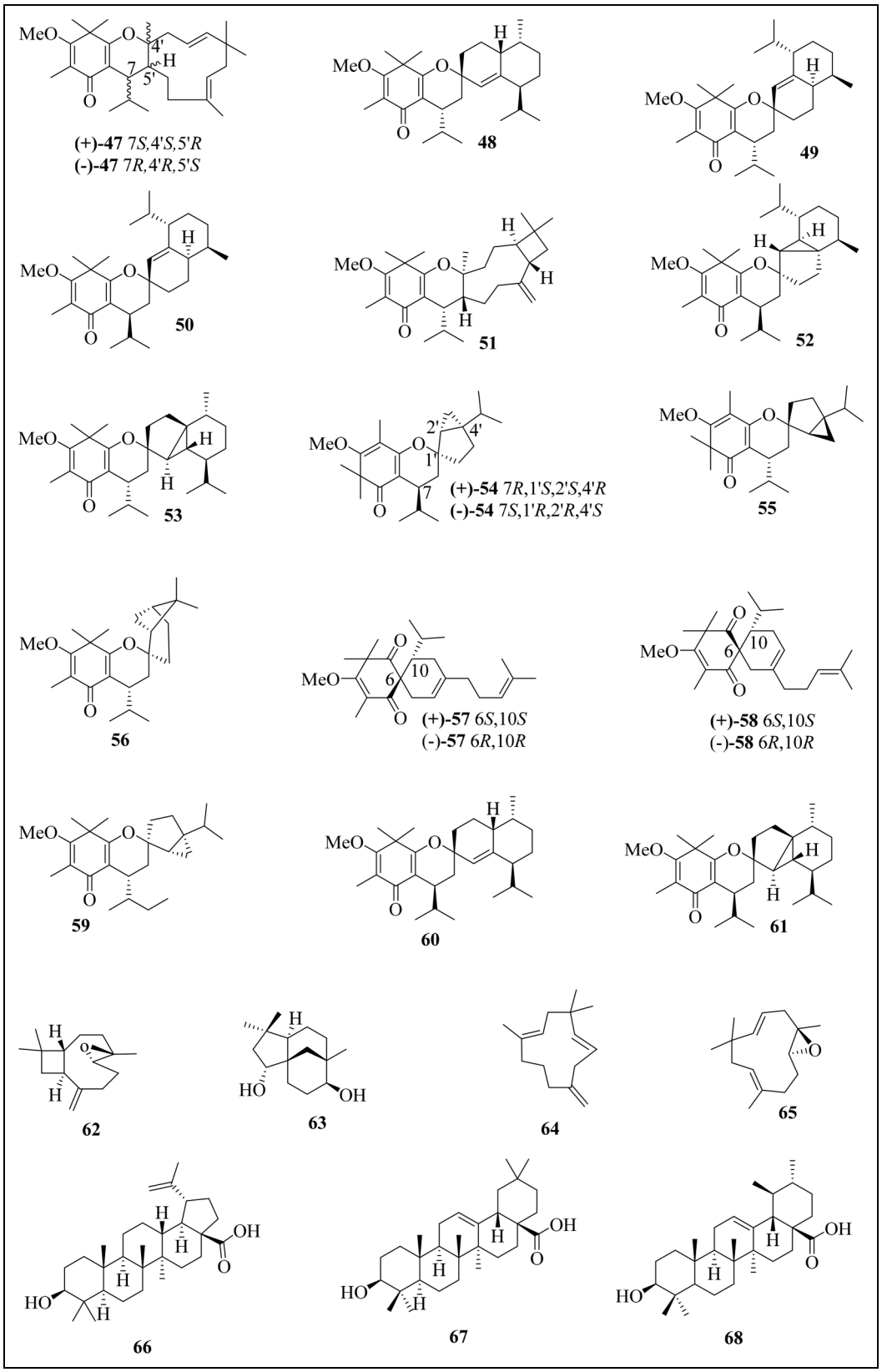

Figure 1. Continued.

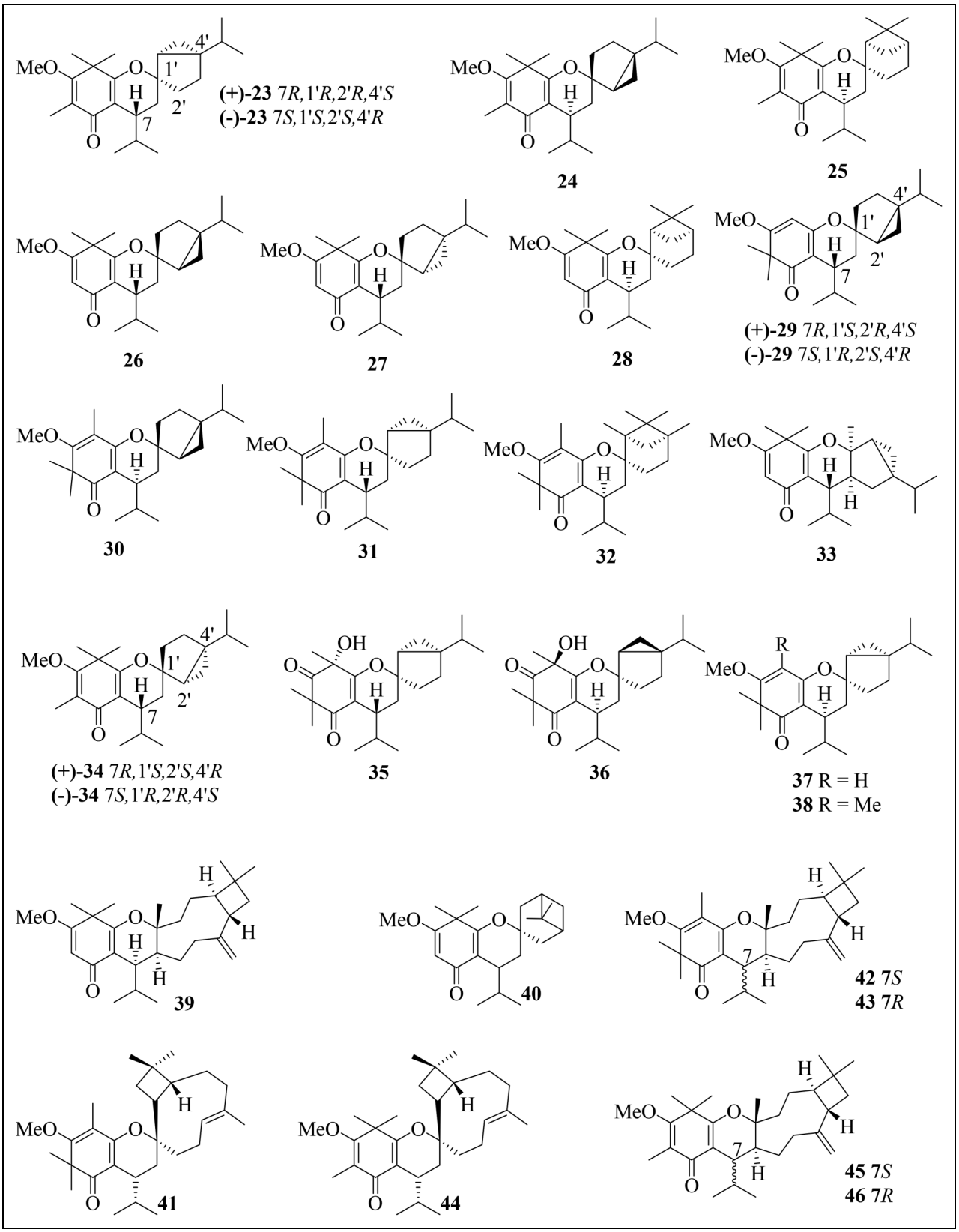

Figure 1. Continued.

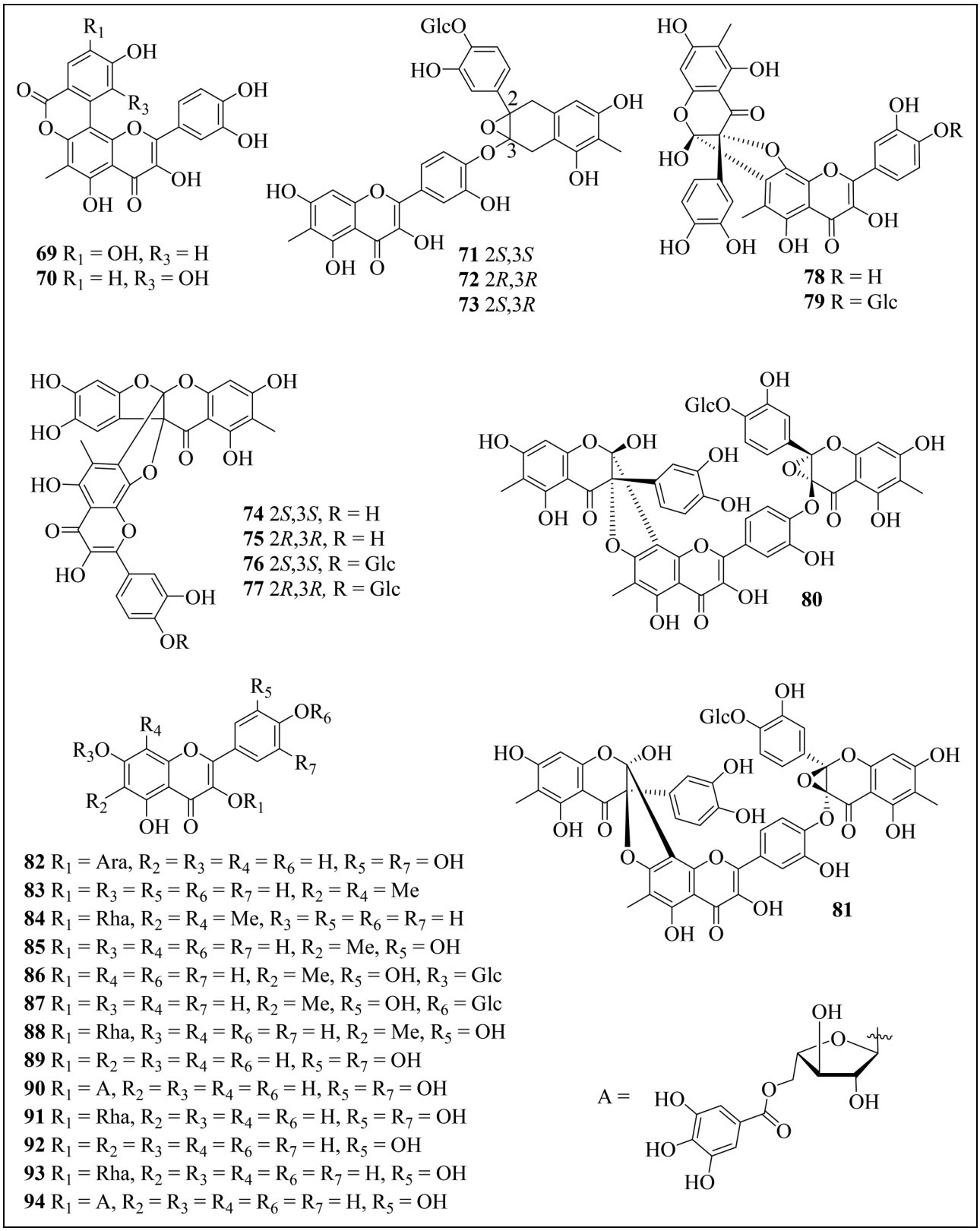

Figure 2. Flavonoids from *Baeckea frutescens.* (continued)

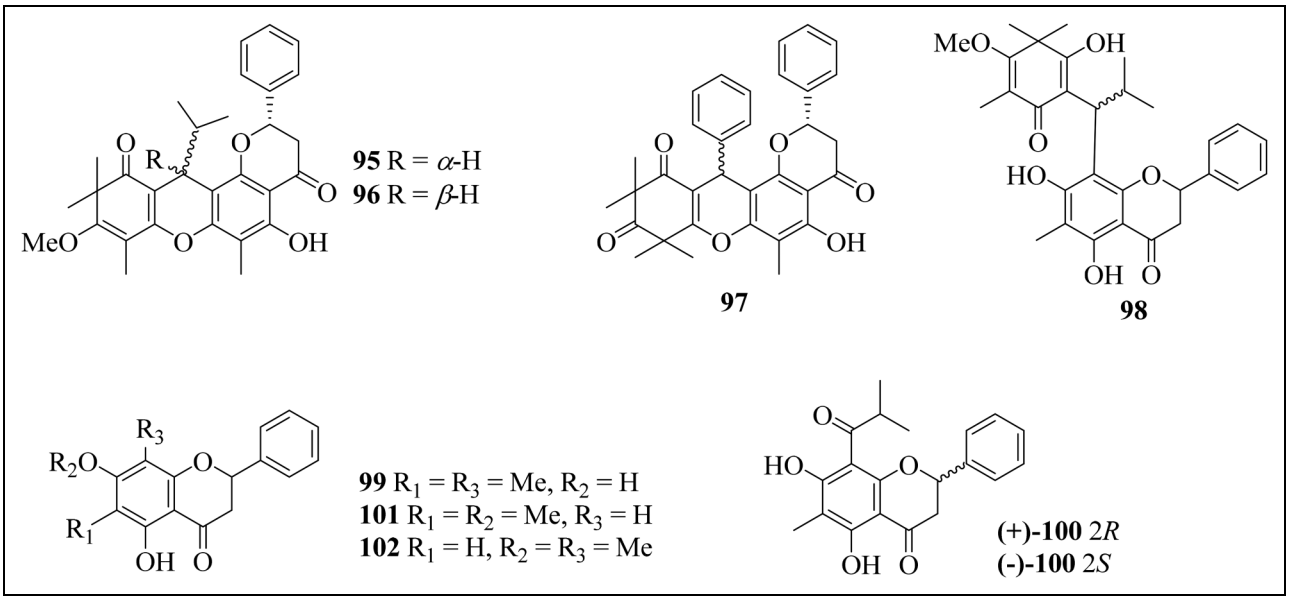

Figure 2. Continued.

From the EtOAc extract of the aerial part, a new flavone, 6,8-di-*C*-methylkaempferol (**83**), and 3 new glycoside derivatives, 6,8-di-*C*-methylkaempferol 3-*O*-α-L-rhamnopyranoside (**84**), 6-*C*-methylquercetin 4′-*O*-β-D-glucopyranoside (**87**), and 6-*C*-methylquercetin 3-*O*-α-L-rhamnopyranoside (**88**) were isolated.[32] 6-*C*-Methylquercetin (**85**) is a well-known compound,[8,9,28,29,32] but its 7-*O*-β-D-glucopyranoside (**86**) was a new flavone separated from the aerial part.[28] Likewise, myricetin (**89**)[9,29] and myricitrin (**91**)[9,30,32] are 2 well-known plant constituents, but myricetin 3-*O*-(5″-*O*-galloyl)-α-L-arabinofuranoside (**90**) was isolated by CC and then identified by LC-MS from the aerial part for the first time.[28,29] In the last case, by either CC or LC-MS procedures, quercetin (**92**), its 3-*O*-α-L-rhamnoside (**93**), and 3-*O*-(5″-*O*-galloyl)-α-L-arabinofuranoside (**94**) were confirmed to be present in the aerial part.[8,28,29,32]

In the search for bioactive compounds from natural resources, 3 new cytotoxic flavanones, BF-4 (**95**), BF-5 (**96**), and BF-6 (**97**), were separated from the EtOH leaf extract.[31] 2,3-Dihydro-5,7-dihydroxy-8-[1-(2-hydroxy-4-methoxy-3,3,5-trimethyl-6-oxo-1,4-cyclohexadien-1-yl)-2-methylpropyl]-6-methyl-2-phenyl-4*H*-1-benzopyran-4-one (**98**) was a new derivative found in the CH_2Cl_2 extract of the aerial part.[21] It was then isolated from the leaf.[13] The aerial part of *B frutescens* has been further recorded to contain another new enantiomeric flavanone, (±)-5,7-dihydroxy-8-isobutyryl-6-methyldihydroflavonol (**100**).[24] Two known flavanones, 5-hydroxy-6-methyl-7-methoxyflavanone (**101**) and 5-hydroxy-7-methoxy-8-methylflavanone (**102**), were also identified by both CC and LC-MS techniques.[9,12]

Chromones, 5-Membered Ring Compounds, and Others

Chromones, a subclass of flavonoids, are also present in *B frutescens*. A list of 19 metabolites (**103-121**) is compiled in Table 1.[9,12,28,30,33,34] Their structures were characterized as either free or glycosylated forms (Figure 3). Besides 6 known compounds (**103-107** and **112**), the CH_2Cl_2 extract of the aerial part contained 3 new chromones, 5-hydroxy-7-methoxy-2-isopropylchromone (**109**), 5-hydroxy-7-methoxy-2-isopropyl-6-methylchromone (**110**), and 5-hydroxy-7-methoxy-2-isopropyl-8-methylchromone (**111**).[34] Compound **108**, named 7-*O*-(4′,6′-digalloyl)-β-D-glucopyranosyl-5-hydroxy-2-methylchromone, was a new metabolite due to substitution of a digalloyl-glycopyranosyl unit at carbon C-7.[28] Glycosylated chromones **114-121** were secondary metabolites found in the leaf, in which 6-β-*C*-glucopyranosyl-5,7-dihydroxy-2-methylchromone (**114**), 6-β-*C*-glucopyranosyl-5,7-dihydroxy-2-isopropylchromone (**115**), 6-β-*C*-(2′-galloylglucopyranosyl)-5,7-dihydroxy-2-isopropylchromone (**117**), 8-β-*C*-glucopyranosyl-5,7-dihydroxy-2-isopropylchromone (**119**), and 8-β-*C*-(2′-galloylglucopyranosyl)-5,7-dihydroxy-2-isopropylchromone (**121**) were new in the literature.[30,33]

Phytochemical studies on *B frutescens* further identified the presence of 5-membered ring compounds **122-126** (Table 1 and Figure 3).[2,21] In addition to the known compound 4-hydroxy-2,2,5-trimethyl-4-cyclopentene-1,3-dione (**125**), 4 derivatives, frutescencenones A-C (**122-124**) and 5-(2-hydroxy-2-methylpropylidene)-3-methoxy-2,4,4-trimethyl-2-cyclopenten-1-one (**126**), were new metabolites detected in the leaf.[2] Compound **126** was also found in the aerial part.[21] Compounds **122-126** have also been isolated from the genus *Baeckea* for the first time. Two final compounds, **127-128**, can be classified as a *mono*-phenol and phytosterol, respectively. They originated from the 95% EtOH extract of the whole plant.[12]

Essential Oils

Essential oils are made up of lipophilic and extremely volatile secondary plant metabolites that are physically separable from

Table 2. The Main Compounds in *Baeckea frutescens* Essential Oils.

Part of use	Collection	Main compounds	References
Leaf	Hatinh, Vietnam	α-Humulene (19.2%), α-caryophyllene (17.3%), baeckeol (13.8%), α-thujene (8.8%), linalool (5.6%), and 1,8-cineole (5.4%)	[15]
Leaf	Danang, Vietnam	β-Pinene (19.0%), γ-terpinene (11.7%), α-pinene (11.1%), 1,8-cineole (10.1%), α-humulene (9.9%), and (*E*)-caryophyllene (7.1%)	[16]
Leaf and stem	Hue, Vietnam	*p*-Cymene (22.2%), α-thujene (12.3%), 1,8-cineole (10.9%), terpinen-4-ol (7.9%), linalool (6.0%), α-humulene (5.8%), and humulene 6,7-epoxide (5.4%)	[41]
Leaf and stem	Hanoi, Vietnam	β-Pinene (23.3%), 1,8-cineole (8.6%), α-pinene (8.2%), α-eudesmol (6.5%), β-eudesmol and γ-terpinene (6.3%), and α-humulene (5.3%)	[41]
Leaf and stem	Quangbinh, Vietnam	Tasmanone (24.3%), γ-terpinene (9.4%), β-pinene (9.0%), 1,8-cineole (6.6%), and *p*-cymene (5.0%)	[41]
Leaf	Sabah, Malaysia	β-Pinene (37.3%), α-pinene (18.2%), and borneol (8.9%)	[4]
Leaf	Kepong, Malaysia	α-Pinene (20.9%), β-pinene (19.0%), γ-terpinene (17.0%), α-humulene (6.1%), and α-terpineol (5.3%)	[4]
Leaf	Selangor, Malaysia	α-Pinene (48.2%), γ-terpinene (18.7%), linalool (8.6%), and 1,8-cineole (6.0%)	[4]
Leaf	Terengganu, Malaysia	γ-Terpinene (34.1%), α-humulene (10.6%), *p*-cymene (9.6%), β-caryophyllene (6.3%), linalool (7.1%), and α-pinene (5.1%)	[4]
Leaf	Guangxi, China	β-Caryophyllene (28.05%), α-caryophyllene (24.02%), δ-cadinene (6.29%), eucalyptol (5.46%), and β-pinene (5.21%)	[42]

other plant parts and have a mass below a molecular weight of 300.[38] Hydrodistillation extraction (HE) is likely to be the best extraction approach to obtain a high yield of essential oil.[39,40] The major compounds (≥5.0%) of the essential oil of *B frutescens*, analyzed by gas chromatography-mass spectrometry (GC-MS), are listed in Table 2.

The leaf oil, collected from Hatinh, Vietnam, was dominated by α-humulene (19.2%), α-caryophyllene (17.3%), baeckeol (13.8%), α-thujene (8.8%), linalool (5.6%), and 1,8-cineole (5.4%), whereas the sample from Danang, Vietnam, yielded β-pinene (19.0%), γ-terpinene (11.7%), α-pinene (11.1%), 1,8-cineole (10.1%), α-humulene (9.9%), and (*E*)-caryophyllene (7.1%).[15,16] In another report, the compounds present in the highest amount in the leaf and stem oils collected from Hue, Hanoi, and Quangbinh, Vietnam, were *p*-cymene (22.2%), β-pinene (23.3%), and tasmanone (24.3%), respectively.[41] By means of GC-MS analysis, 2 pinene isomers were the best representatives for the leaf oils of Sabah, Kepong, and Selangor, Malaysia, but the leaf oil obtained from Terengganu, Malaysia, contained γ-terpinene (34.1%) and others.[4] β-Caryophyllene (28.05%), α-caryophyllene (24.02%), δ-cadinene (6.29%), eucalyptol (5.46%), and β-pinene (5.21%) were characteristic compounds in the leaf oil of a Chinese sample (Table 2).

Biosynthesis and Synthesis

Biosynthesis

Information on the biosynthesis of *B frutescens* metabolites is now available in the literature and is focused on meroterpenoids. As shown in Figure 4, phloroglucinol-based meroterpenoids baeckfrutones A-L (**21-32**) could biosynthetically originate from tasmanone and its demethylated derivative by divergent hetero-Diels-Alder (HAD) reactions.[25] The reduction of tasmanone and its demethylated derivative and subsequent dehydration could generate intermediates **A1** and **A2**, which could undergo HAD reactions through pathways I and II with various monoterpenes, comprising α-phellandrene, sabinene, and β-pinene, to afford compounds **21-32** by region and stereoselective [4 + 2] cycloaddition reactions.[25]

Along with the isolation of frutescones A-G (**41-47**), Hou et al[17] suggested a plausible biosynthetic pathway of these compounds based on the key precursor, tasmanone (Figure 5). The key compound, tasmanone, β-caryophyllene, and α-humulene appeared as the major constituents of *B frutescens* essential oil. Selective reduction and dehydration of tasmanone provided the intermediate **A3**. Then, this intermediate could undergo HAD reactions with either β-caryophyllene or α-humulene to achieve compounds **41-47** in regio- and stereoselective manners.

Synthesis

The synthetic procedure for baeckenone B (**3**) has been outlined in Figure 6.[43] Friedel–Craft acylation of phloroglucinol gave isobutyrylphloroglucinol **A** in 91% yield. Trimethylated **B** was formed from isobutyrylphloroglucinol in 67% yield by treatment with MeI. Methylation of **B** generated tasmanone, which then underwent a reduction–carbonylation reaction with diisobutylaluminum hydride (DIBAL-H) to provide the Michael reaction acceptor **C**. The Michael addition reaction between **C** and **D** (which was also prepared from phloroglucinol through a sequence of Vilsmeier–Haack formylation, reduction with sodium cyanoborohydride, and isobutyrylation) furnished compound **3** in 83% yield.

In 2003, Gray et al[44] demonstrated synthetic steps of 5-hydroxy-7-methoxy-2-isopropylchromone (**109**) and 5-hydroxy-7-methoxy-2-methylchromone (**112**) (Figure 7). The procedure started with 2,4,6-trihydroxyacetophenone. Treatment of this compound with dimethyl sulfate and

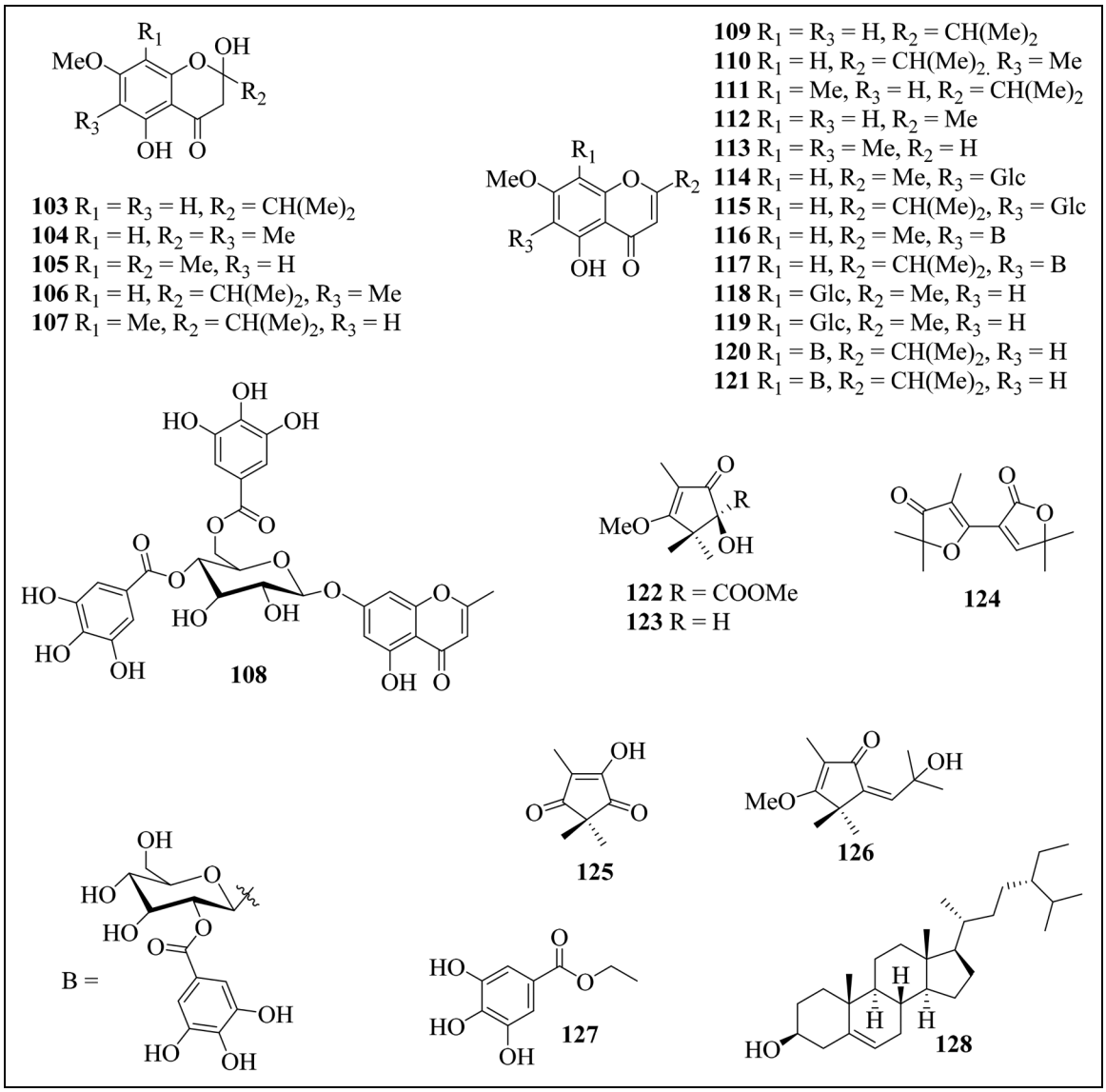

Figure 3. Chromones, 5-membered ring compounds, and others from *Baeckea frutescens*.

anhydrous K_2CO_3 in acetone under reflux provided **E** in 90% yield. The resulting dimethylated compound was treated with NaOEt in EtOH, and then ethyl carboxylate esters [RCOOEt; R = $(CH_3)_2CH$, CH_3] afforded mixtures of condensation products in enol tautomer form **F** and their cyclized derivatives **G**. Treatment of these mixtures with HOAc and H_2SO_4 generated 5,7-dimethoxychromone derivative **H**, which was converted to **109** and **112** by heating with Ac_2O and hydriodic acid.

Pharmacology

Cytotoxicity

BF-1 (**13**), BF-2 (**40**), and BF-6 (**96**) have cytotoxic effects on L-1210 cancer cells, with respective half maximal inhibitory concentration (IC_{50}) values of 50, 5, and 10 μg/mL. In particular, compounds BF-4 (**94**) and BF-5 (**95**) were very active with the same IC_{50} value of 0.25 μg/mL.[20,31] New phloroglucinol-based meroterpenoids frutescones A-G (**41-47**) suppressed the proliferation of Caco-2 and A549 cancer cells with IC_{50} values of 7.96-41.33 μM, but they failed to control HepG2 liver cancer cells ($IC_{50} > 50$ μM).[17] The difference in results between compounds **42** and **43**, as well as between **45** and **46**, may be due to the stereochemistry at carbon C-7.

Baeckenone F (**7**) moderately restricted the growth of A549, PSN-1, and MDA-MB-231 cancer cells with IC_{50} values of 33.3-39.3 μM when 5-fluorouracil was used as a positive control (IC_{50} 1.8-4.0 μM).[14] Baeckenones J-K (**11-12**) strongly inhibited A549 and PSN-1 cancer cells, with IC_{50} values of 11.8-19.2 μM, but baeckenone I (**10**) showed either weak activity

Table 3. Pharmacological Activities of Isolated Compounds and Plant Extracts from *Baeckea frutescens*.

Compounds	Models	Effect	References
Cytotoxicity			
5	In vitro	IC_{50} = 60 μM/A549	14
7	In vitro	IC_{50} = 34 μM/A549	14
		IC_{50} = 33.3 μM/PSN-1	
		IC_{50} = 39.3 μM/MDA-MB-231	
10	In vitro	IC_{50} = 91.7 μM/A549	3
11	In vitro	IC_{50} = 19.2 μM/A549	3
		IC_{50} = 11.8 μM/PSN-1	
12	In vitro	IC_{50} = 17.8 μM/A549	3
		IC_{50} = 15.8 μM/PSN-1	
13	In vitro	IC_{50} = 50 μg/mL/L-1210	20
14	In vitro	IC_{50} = 74.1 μM/A549	14
(+)-22	In vitro	IC_{50} = 79.45 μM/DU145	25
(−)-22	In vitro	IC_{50} = 1.33 μM/DU145	25
(+)-23	In vitro	IC_{50} = 62.64 μM/HCT116	25
		IC_{50} = 85.79 μM/HeLa	
		IC_{50} = 17.65 μM/DU145	
		IC_{50} = 86.68 μM/A549	
(−)-23	In vitro	IC_{50} = 49.09 μM/HCT116	25
		IC_{50} = 91.22 μM/HeLa	
		IC_{50} = 15.85 μM/DU145	
		IC_{50} = 86.62 μM/A549	
24	In vitro	IC_{50} = 38.32 μM/HCT116	25
		IC_{50} = 83.85 μM/HeLa	
		IC_{50} = 6.46 μM/DU145	
		IC_{50} = 76.47 μM/A549	
26	In vitro	IC_{50} = 39.5 μM/HCT116	25
		IC_{50} = 80.72 μM/DU145	
		IC_{50} = 15.61 μM/A549	
27	In vitro	IC_{50} = 49.76 μM/HCT116	25
		IC_{50} = 31.87 μM/HeLa	
		IC_{50} = 17.40 μM/DU145	
		IC_{50} = 62.64 μM/A549	
28	In vitro	IC_{50} = 19.50 μM/HCT116	25
		IC_{50} = 30.44 μM/HeLa	
		IC_{50} = 15.14 μM/DU145	
		IC_{50} = 82.75 μM/A549	
(+)-29	In vitro	IC_{50} = 19.5 μM/HCT116	25
		IC_{50} = 53.71 μM/HeLa	
		IC_{50} = 26.11 μM/DU145	
		IC_{50} = 84.13 μM/A549	
30	In vitro	IC_{50} = 52.93 μM/HCT116	25
		IC_{50} = 4.04 μM/DU145	
		IC_{50} = 79.45 μM/A549	
31	In vitro	IC_{50} = 12.89 μM/HCT116	25
		IC_{50} = 77.06 μM/DU145	
		IC_{50} = 80.11 μM/A549	
32	In vitro	IC_{50} = 16.48 μM/HCT116	25
		IC_{50} = 19.81 μM/HeLa	
		IC_{50} = 10.0 μM/DU145	
		IC_{50} = 88.81 μM/A549	
40	In vitro	IC_{50} = 5 μg/mL/L-1210	20
41	In vitro	IC_{50} = 8.08 μM/Caco-2	17
		IC_{50} = 20.07 μM/A549	
42	In vitro	IC_{50} = 23.25 μM/Caco-2	17
		IC_{50} = 41.33 μM/A549	
43	In vitro	IC_{50} = 14.83 μM/Caco-2	17
		IC_{50} = 27.74 μM/A549	

(Continued)

Table 3. Continued

Compounds	Models	Effect	References
44	In vitro	IC_{50} = 10.2 μM/Caco-2 IC_{50} = 26.25 μM/A549	17
45	In vitro	IC_{50} = 7.96 μM/Caco-2 IC_{50} = 12.14 μM/A549	17
46	In vitro	IC_{50} = 16.51 μM/Caco-2 IC_{50} = 39.02 μM/A549	17
47	In vitro	IC_{50} = 14.31 μM/Caco-2 IC_{50} = 25.71 μM/A549	17
94 and **95**	In vitro	IC_{50} = 0.25 μg/mL/L-1210	31
96	In vitro	IC_{50} = 10 μg/mL/L-1210	31
122	In vitro	IC_{50} = 36.3 μM/A549 IC_{50} = 29.3 μM/PSN-1 IC_{50} = 38.2 μM/MDA-MB-231	2
123	In vitro	IC_{50} = 83.9 μM/A549 IC_{50} = 76.0 μM/PSN-1	2
124	In vitro	IC_{50} = 88.0 μM/A549 IC_{50} = 20.1 μM/PSN-1	2
126	In vitro	IC_{50} = 80.3 μM/MDA-MB-231	2
The 50% EtOH leaf extract	In vitro	IC_{50} = 108 μg/mL/MCF-7	45
The 70% EtOH leaf extract	In vitro	IC_{50} = 124 μg/mL/MCF-7	45
The 90% EtOH leaf extract	In vitro	IC_{50} = 84 μg/mL/MCF-7	45
The water leaf extract	In vitro	IC_{50} = 115 μg/mL/MCF-7	45
The *n*-hexane leaf extract	In vitro	IC_{50} = 56.24 μg/mL/A549 IC_{50} = 26.7 μg/mL/NCI-H1299 IC_{50} = 10 μg/mL/MCF-7 IC_{50} = 80 μg/mL/MDA-MB-231	45,46
The rich flavonoid fraction	In vitro	IC_{50} = 110.8 μg/mL and apoptosis rate 27.54%/ SiHa	47
Antimicrobial activity			
3	In vivo	MIC = 40 μM/*Bacillus subtilis* MIC = 3.125 μg/mL/*Salmonella paratyphi*	13,43
15-18 and **44-46**	In vivo	MIC = 25 μg/mL/*S paratyphi*	43
41	In vivo	MIC = 6.25 μg/mL/*S paratyphi*	43
The EtOH and water leaf extracts	In vitro	MIC < 50 μg/mL/*Escherichia coli* and *Salmonella thypi*	48
The EtOH leaf extract (50 mg/mL)	In vitro	IZ = 11.5 mm/MRSA ST/0903-24 IZ = 8.5 mm/MRSA ST/0904-25 IZ = 11.5 mm/MRSA ST/0904-28 IZ = 8.5 mm/MRSA ST/0904-30	49
The EtOH leaf extract (100 mg/mL)	In vitro	IZ = 14.0 mm/MRSA ST/0903-24 IZ = 12.0 mm/MRSA ST/0904-25 IZ = 14.5 mm/MRSA ST/0904-28 IZ = 12.0 mm/MRSA ST/0904-30	49
The MeOH leaf extract (10 mg/mL)	In vitro	IZ = 13 mm/*Streptococcus mutans*	50
The MeOH leaf extract (20 mg/mL)	In vitro	IZ = 14 mm/*S mutans*	50
The leaf oil	In vitro	MIC = 5.11 μg/mL/*Pseudopestalotiopsis camelliae* MIC = 4.79 μg/mL/*Colletotrichum gloeosporioides* MIC = 64 μg/mL/*Enterococcus faecalis* MIC = 16 μg/mL/*Candida albicans*	16,42
The HE and ES-UME leaf oils	In vitro	MIC = 1.25%/*C albicans* MIC = 0.625%/*Staphylococcus aureus*, *E coli*, and *B subtilis* MIC = 0.3125%/*Pseudomonas aeruginosa*, *Fecal bacterial*, and *Propionibacterium acnes*	51
Mosquito larvicidal activity			
The leaf oil	In vitro	24-h LC_{50} = 23 μg/mL/*Aedes aegypti* 24-h LC_{90} = 40.05 μg/mL/*Ae aegypti* 24-h LC_{50} = 25.73 μg/mL/*Aedes albopictus* 24-h LC_{90} = 37.01 μg/mL/*Ae albopictus*	16

(Continued)

Table 3. Continued

Compounds	Models	Effect	References
		24-h LC_{50} = 81.72 μg/mL/*Culex quinquefasciatus* 24-h LC_{90} = 112.7 μg/mL/*Cx quinquefasciatus* 48-h LC_{50} = 15.31 μg/mL/*Ae aegypti* 48-h LC_{90} = 34.69 μg/mL/*Ae aegypti* 48-h LC_{50} = 23.98 μg/mL/*Ae albopictus* 48-h LC_{90} = 37.63 μg/mL/*Ae albopictus* 48-h LC_{50} = 64.06 μg/mL/*Cx quinquefasciatus* 48-h LC_{90} = 116.6 μg/mL/*Cx quinquefasciatus*	
Anti-inflammatory activity			
15	In vitro	IC_{50} = 9.15 μM/NO production	23
16	In vitro	IC_{50} = 17.73 μM/NO production	23
17	In vitro	IC_{50} = 11.62 μM/NO production	23
18	In vitro	IC_{50} = 18.04 μM/NO production	23
26 (50 μM)	In vitro	76.64% inhibition/NO production	25
27 (50 μM)	In vitro	75.37% inhibition/NO production	25
(+)-29 (50 μM)	In vitro	55.13% inhibition/NO production	25
30 (50 μM)	In vitro	75.01% inhibition/NO production	25
34	In vitro	IC_{50} = 20.86 μM/NO production	26
39	In vitro	IC_{50} = 36.21 μM/NO production	26
40 (0.4-1.6 μM)	In vitro	To inhibit NLRP3 inflammasome in J774A.1 macrophages via inhibiting MAPK/NF-κB signaling pathways	18
40 (50 mg/kg)	In vivo	To inhibit NLRP3 inflammasome in mice via inhibiting MAPK/NF-κB signaling pathways	18
49	In vitro	IC_{50} = 18.75 μM/NO production	22
52	In vitro	IC_{50} = 30.54 μM/NO production	22
53	In vitro	IC_{50} = 15.17 μM/NO production	22
54	In vitro	IC_{50} = 1.80 μM/NO production	22
55	In vitro	IC_{50} = 0.36 μM/NO production	22
55 (0.2-0.8 μM)	In vitro	To suppress LPS-stimulated RAW264.7 cells by inhibiting MAPK/NF-κB and MyD88 and iNOS expressions	19
56	In vitro	IC_{50} = 3.7 μM/NO production	22
57	In vitro	IC_{50} = 2.07 μM/NO production	22
58	In vitro	IC_{50} = 6.50 μM/NO production	22
59	In vitro	IC_{50} = 0.81 μM/NO production	24
74	In vitro	IC_{50} = 54.7 μM/NO production	7
75	In vitro	IC_{50} = 25.4 μM/NO production	7
76	In vitro	IC_{50} = 43.8 μM/NO production	7
77	In vitro	IC_{50} = 15.2 μM/NO production	7
85	In vitro	IC_{50} = 5.54 μM/COX-1 IC_{50} = 2.14 μM/COX-2	28
86	In vitro	IC_{50} = 4.53 μM/COX-1 IC_{50} = 1.89 μM/COX-2	28
87	In vitro	IC_{50} = 4.15 μM/COX-1 IC_{50} = 1.63 μM/COX-2	28
90	In vitro	IC_{50} = 1.95 μM/COX-1 IC_{50} = 1.01 μM/COX-2	28
94	In vitro	IC_{50} = 5.42 μM/COX-1 IC_{50} = 1.61 μM/COX-2	28
98 (100 μg/mL)	In vitro	To show anti-inflammatory effect in MALP-2-stimulated RAW264.7 cells via inhibition of MyD88 and NF-κB	52
100	In vitro	IC_{50} = 9.73 μM/NO production	24
108	In vitro	IC_{50} = 4.17 μM/COX-1 IC_{50} = 2.27 μM/COX-2	28
Antioxidative activity			
69	In vitro	IC_{50} = 12.0 μM/DPPH radical scavenging	8

(Continued)

Table 3. Continued

Compounds	Models	Effect	References
70	In vitro	IC_{50} = 12.1 μM/DPPH radical scavenging	8
71	In vitro	IC_{50} = 15.1 μM/DPPH radical scavenging 34.8% inhibition/H_2O_2-stimulated PC12 cells	8
72	In vitro	IC_{50} = 15.0 μM/DPPH radical scavenging 36.0% inhibition/H_2O_2-stimulated PC12 cells	8
73	In vitro	IC_{50} = 16.1 μM/DPPH radical scavenging 31.8% inhibition/H_2O_2-stimulated PC12 cells	8
78	In vitro	54.8% inhibition/H_2O_2-stimulated PC12 cells	10
79	In vitro	60.2% inhibition/H_2O_2-stimulated PC12 cells	10
83	In vitro	IC_{50} = 120.6 μM/DPPH radical scavenging	32
84	In vitro	IC_{50} = 125.9 μM/DPPH radical scavenging	32
85	In vitro	IC_{50} = 11.8 μM/DPPH radical scavenging 43.0% inhibition/H_2O_2-stimulated PC12 cells	8
87	In vitro	IC_{50} = 13.5 μM/DPPH radical scavenging 44.7% inhibition/H_2O_2-stimulated PC12 cells	8,32
88	In vitro	IC_{50} = 12.1 μM/DPPH radical scavenging	32
91	In vitro	IC_{50} = 3.39 μM/copper-induced LDL oxidation	30
116	In vitro	IC_{50} = 3.35 μM/copper-induced LDL oxidation	30
117	In vitro	IC_{50} = 3.90 μM/copper-induced LDL oxidation	30
120	In vitro	IC_{50} = 3.98 μM/copper-induced LDL oxidation	30
121	In vitro	IC_{50} = 3.91 μM/copper-induced LDL oxidation	30
The EtOH leaf extract	In vitro	IC_{50} = 41.96 μg/mL/DPPH radical scavenging	48
The water leaf extract	In vitro	IC_{50} = 93.3 μg/mL/DPPH radical scavenging	48
The *n*-hexane leaf extract	In vitro	EC_{50} = 0.347 mg/mL/DPPH EC_{50} = 0.162 mg/mL/ferric reducing power EC_{50} = 0.047 mg/mL/metal chelating	46
The EtOAc leaf extract	In vitro	EC_{50} = 0.084 mg/mL/DPPH EC_{50} = 0.033 mg/mL/ferric reducing power EC_{50} = 0.158 mg/mL/metal chelating	46
The MeOH leaf extract	In vitro	EC_{50} = 0.101 mg/mL/DPPH EC_{50} = 0.041 mg/mL/ferric reducing power EC_{50} = 0.067 mg/mL/metal chelating	46
The water leaf extract	In vitro	EC_{50} = 0.110 mg/mL/DPPH EC_{50} = 0.026 mg/mL/ferric reducing power EC_{50} = 0.039 mg/mL/metal chelating	46
The HE leaf oil	In vitro	IC_{50} = 15.929 μg/mL/DPPH radical scavenging	51
The ES-UME leaf oil	In vitro	IC_{50} = 14.012 μg/mL/DPPH radical scavenging	51
The leaf oil	In vitro	EC_{50} = 1.39 μg/mL/ferric reducing power EC_{50} = 0.44 μg/mL/metal chelating EC_{50} = 0.29 μg/mL/β-carotene bleaching	53
Antirheumatoid arthritis			
25-100 mg/kg	In vivo	To inhibit toe swelling of mice and relieve the degradation of articular cartilage matrix and inflammatory cell infiltration	54
Skin protective activity			
The EtOH leaf extract	In vitro	14% proliferation/HaCaT cells at 6.25 μg/mL 24% proliferation/HaCaT cells at 3.125 μg/mL 36% proliferation/BJ cells at 25 μg/mL 51% proliferation/BJ cells at 12.5 μg/mL	29

A549, lung cancer cells; Caco-2 and HCT116, colon cancer cells; COX, cyclooxygenase; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DU145, prostate cancer cells; EC_{50}, half maximal effective concentration; ES-UME, enzymatic surfactant-ultrasonic microwave extraction; HE, hydrodistillation extraction; IZ, inhibitory zone; LC_{50}, half lethal concentration; LC_{90}, 90% lethal concentration; LPS, lipopolysaccharide; L-1210, leukemia cells; LDL, low-density lipoprotein; MCF-7 and MDA-MB-231, breast cancer cells; MAPK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MALP-2, macrophage-activating lipopeptide-2; NO, nitric oxide; NF-κB, nuclear factor kappa B; PSN-1, pancreatic cancer cells; SiHa, cervical cancer cells.

(IC_{50} = 91.7 μM/A549) or was inactive (IC_{50} > 100 μM/PSN-1).[3] This result can be explained by functional groups at carbons C-7 and C-8. Five isolated compounds (**122-126**) showed cytotoxicity at different levels (Table 3); frutescencenone

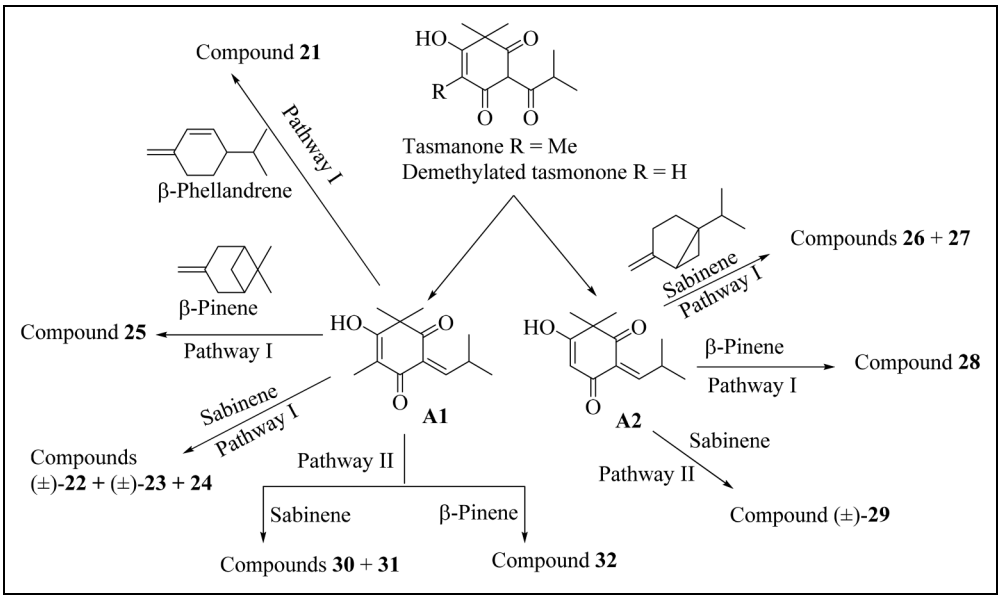

Figure 4. Biosynthetic pathway of baeckfrutones A-L (**21-32**).

A (**122**) was remarkably active against A549, PSN-1, and MDA-MB-231 cancer cells, with IC_{50} values of 36.3, 29.3, and 38.2 μM.[2] Frutescencenone C (**124**) showed selective activity against PSN-1 cancer cells, with an IC_{50} value of 20.1 μM, but 4-hydroxy-2,2,5-trimethyl-4-cyclopentene-1,3-dione (**125**) was inactive toward these 3 cancer cells ($IC_{50} > 100$ μM).[2]

Baeckfrutones B-L (**22-32**) inhibited the growth of HCT116, HeLa, DU145, and A549 cancer cells at different levels, especially (−)-**22**, **26**, and **31**, which were remarkably cytotoxic to DU145, A549, and HCT116 cells, with IC_{50} values of 1.33, 15.61, and 12.89 μM, respectively.[25]

Cytotoxicity of the *n*-hexane leaf extract against A549 and NCI-H1299 cancer cells was associated with IC_{50} values of 56.24 and 26.7 μg/mL, respectively, but the EtOAc, MeOH, and water extracts were either weak or inactive ($IC_{50} > 100$ μg/mL).[46] From Table 3, *n*-hexane, EtOH, and water extracts of the leaf exhibited cytotoxicity against MCF-7 cancer cells (IC_{50} 10-124 μg/mL), but only the *n*-hexane extract showed activity against MDA-MB-231 (IC_{50} 80 μg/mL).[45] The rich flavonoid fraction remarkably controlled the proliferation of SiHa cancer cells (IC_{50} 110.8 μg/mL, 27.54% apoptosis rate).[47]

Antimicrobial and Mosquito Larvicidal Activities

Baeckenone B (**3**) moderately controlled the bacterium *Bacillus subtilis* with a MIC value of 40 μM.[13] Baefrutones A-D (**15-18**) and frutescones D-F (**44-46**) suppressed *Salmonella paratyphi* with the same MIC value of 25 μg/mL, as compared with that of baeckenone B (**3**, MIC 3.125 μg/mL), frutescone A (**41**, MIC 6.25 μg/mL), and the standard fluconazole (MIC 3.125 μg/mL).[43]

The EtOH and water extracts of *B frutescens* leaf were active against both *Escherichia coli* and *Salmonella thypi* with MIC values of less than 50 μg/mL.[48] At 50 and 100 mg/mL, the EtOH leaf extract also suppressed methicillin-resistant *Staphylococcus aureus* (MRSA) with inhibitory zone (IZ) values of 8.5-14.5 mm (Table 3).[49] Similarly, at 10 and 20 mg/mL, the MeOH leaf extract was responsible for the inhibition of *Streptococcus mutans* with IZ values of 13 and 14 mm, respectively.[50]

B frutescens leaf oil controlled the growth of *Pseudopestalotiopsis camelliae*, *Colletotrichum gloeosporioides*, *Enterococcus faecalis*, and *Candida albicans*, with MIC values of 5.11, 4.79, 64, and 16 μg/mL, respectively.[16,42] In another approach, the leaf oils extracted by HE and enzymatic surfactant-ultrasonic microwave extraction (ES-UME) exhibited the same antimicrobial activity against *C albicans* (MIC 1.25%), *S aureus*, *E coli*, and *B subtilis* (MIC 0.625%), *Pseudomonas aeruginosa*, and *Propionibacterium acnes* (MIC 0.3125%).[51]

Besides antimicrobial activity, *B frutescens* leaf oil showed 24- and 48-h LC_{50} values of 15.31-81.72 μg/mL and LC_{90} values of 34.69-116.6 μg/mL against *Aedes aegypti*, *Aedes albopictus*, and *Culex quinquefasciatus*.[16]

Anti-inflammatory Activity

Compound BF2 (**40**), at 0.4-1.6 μM, showed in vitro NLRP3 inflammasome activation inhibition by suppressing cell proptosis and interleukin-1β (IL-1β) secretion in J774A.1 macrophages.[18] In an in vivo model, this compound (50 mg/kg, gastric injection) inhibited NLRP3 inflammasome activation in mice by inhibiting the MAPK/NF-κB signaling pathway and mitochondrial damage-mediated oxidative stress.[18] Frutescone O (**55**), at 0.2-0.8 μM, suppressed LPS-stimulated RAW264.7 cells by blocking TLR4-mediated MAPK/NF-κB signaling pathways and inhibiting MyD88 and iNOS expressions.[19] At 100 μg/mL, compound **98** also showed an anti-

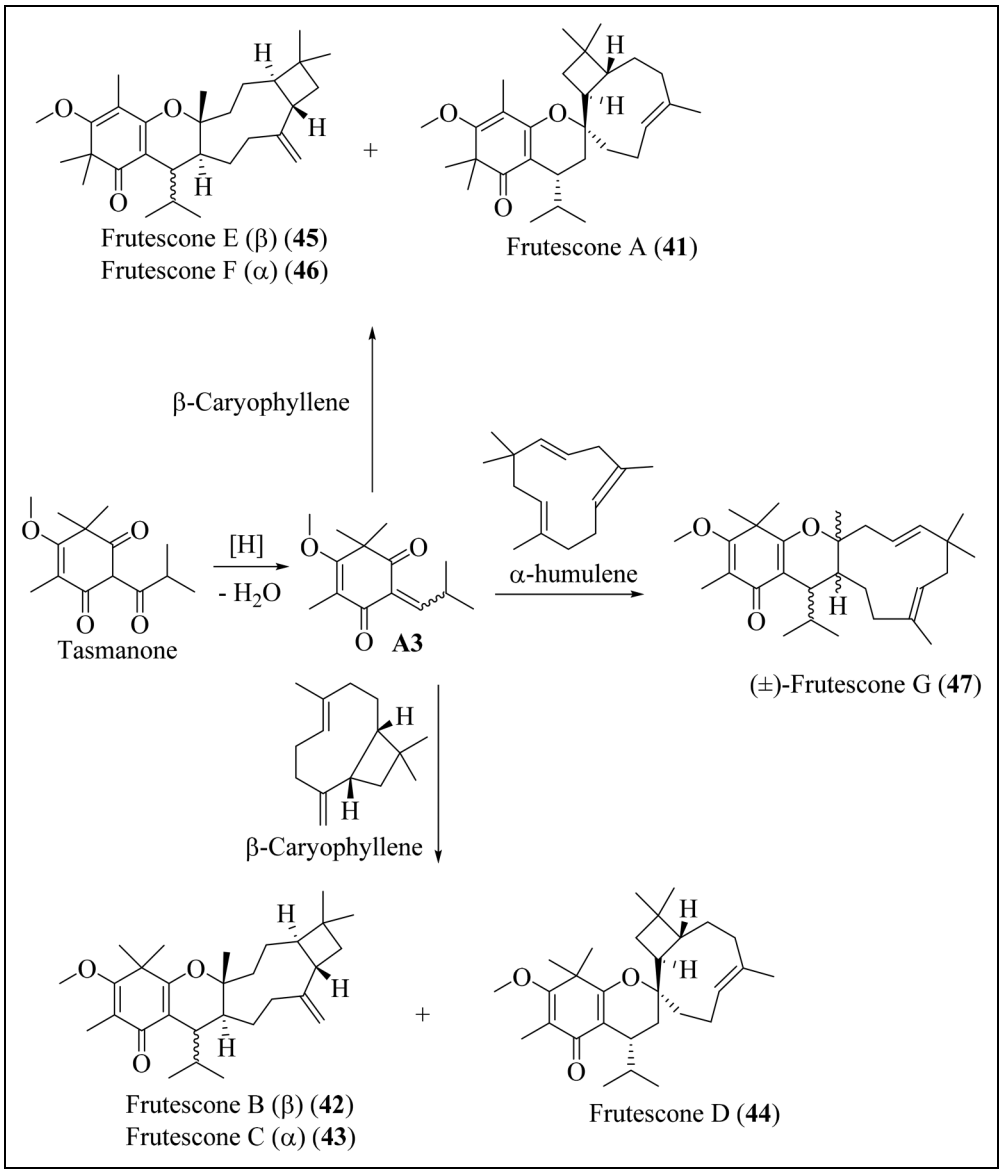

Figure 5. Biosynthetic pathway of frutescones A-G (**41-47**).

inflammatory effect in macrophage-activating lipopeptide-2 (MALP-2)-stimulated RAW264.7 cells by inhibition of MyD88 and NF-κB (Figure 8).[52]

In an anti-inflammatory assay against nitric oxide (NO) production in LPS-stimulated RAW264.7 cells, the IC_{50} values of baefrutones A-D, N, and S (**15-18**, **34**, and **39**), frutescones I and L-S (**49** and **52-59**), and 5,7-dihydroxy-8-isobutyryl-6-methyldihydroflavonol (**100**), ranging from 0.36 to 36.21 μM, were comparable with that of the standard N-monomethyl-L-arginine (L-NMMA) (IC_{50} 30.92 μM), but baefrutones E-F (**19-20**) and frutescones H, J-K, and T-U (**48**, **50-51**, and **60-61**) did not show activity (IC_{50} > 50 μM).[22–24,26] Furthermore, the anti-inflammatory activity of compound **55** was involved in the suppression of NF-κB p65 and the decrease of IL-6 and tumor nuclear factor-α (TNF-α).[22]

The flavones baeckeins F-I (**74-77**) were also active against NO production with IC_{50} values of 54.7, 25.4, 43.8, and 15.2 μM, respectively, as compared with that of the standard indomethacin (IC_{50} 13.8 μM).[7] This difference can be explained by the stereochemistry at carbons C-2 and C-3 and functional groups at phenyl carbon C-4. At 50 μM, compounds **26**, **27**, (+)-**29**, and **30** inhibited NO production by up to 74.64%, 75.37%, 55.13%, and 75.01%, respectively.[25]

As shown in Table 3, flavones **85-87**, **90**, and **94** and chromone **108** had greater anti-inflammatory activity against cyclooxygenase (COX)-2 (IC_{50} 1.95-5.54 μM) than COX-1 (IC_{50} 1.01-2.27 μM).[28]

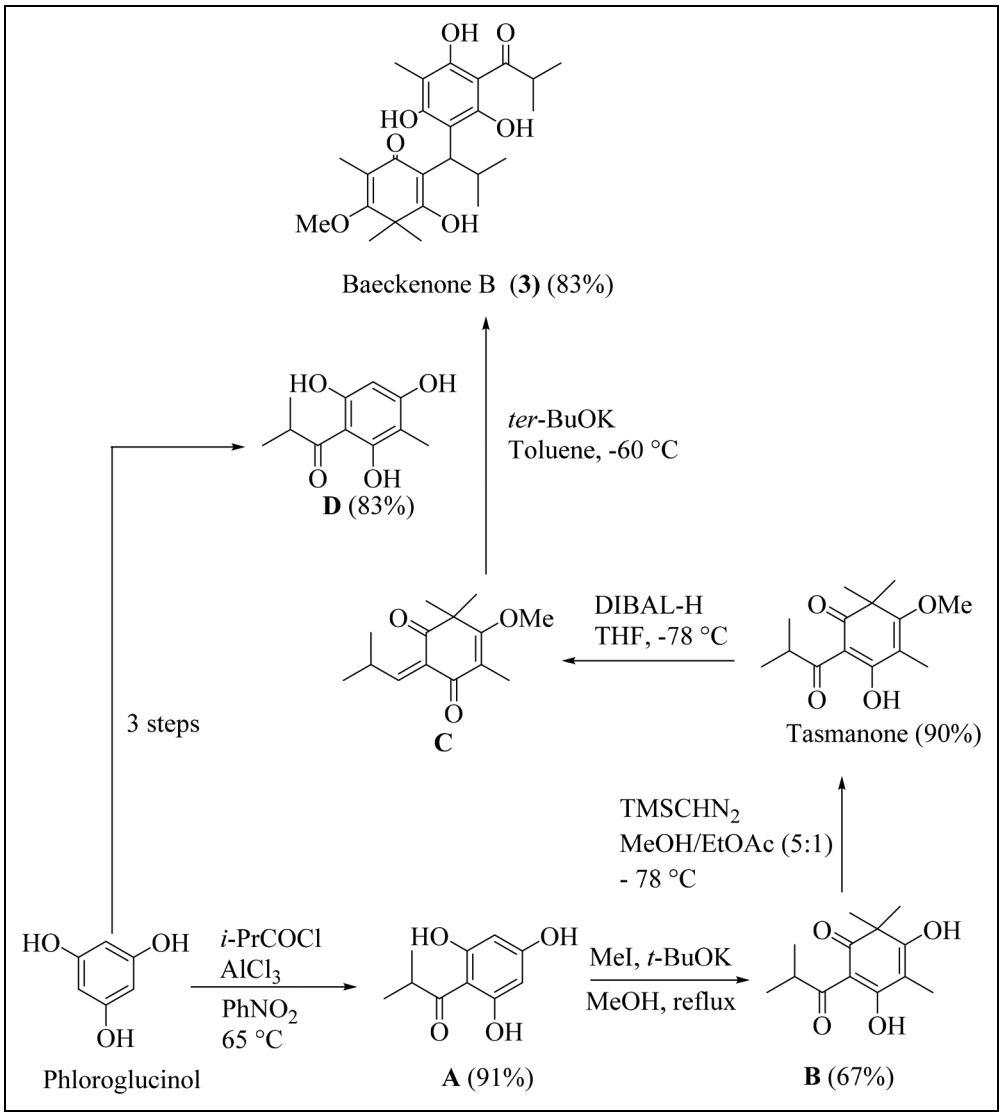

Figure 6. Synthetic pathway of phloroglucinol **3**.

Antioxidant Activity

Baeckeins J (**78**) and K (**79**), on the one hand, have no cytotoxicity to PC12 cells (IC_{50} > 100 μM) but, on the other hand, at a dose of 10 μM, inhibited H_2O_2-stimulated PC12 cells by up to 54.8% and 60.2%, respectively.[10] Similarly, the inhibitory rates of baeckeins C-E (**71-73**), 6-*C*-methylquercetin (**85**), and 6-*C*-methylquercetin 4′-*O*-β-D-glucopyranoside (**87**) were 31.8%-44.7%.[8] Flavone **91** and chromones **116-117** and **120-121**, containing 1 pyrogallolyl unit, inhibited copper-induced low-density lipoprotein (LDL) oxidation with IC_{50} values of 3.35-3.91 μM, but chromones **114-115** and **118-119**, which had no pyrogallolyl unit, did not show activity.[30]

Flavones baeckeins A-E (**69-73**) and 6-*C*-methylquercetin (**85**), with IC_{50} values of 11.8-16.1 μM, were also superior to the standard compound quercetin (IC_{50} 18.2 μM) in scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals.[8] The difference among compounds **71-73** is due to the stereochemistry at carbons C-2 and C-3.

Two new flavones **87-88** showed strong antioxidative activity to scavenge DPPH radicals, with IC_{50} values of 12.1-13.5 μM, but their new derivatives **83-84** exerted only weak activity, with IC_{50} values of 120.6-125.9 μM.[32] Thereby, it can be concluded that the quercetin skeleton seems better than the kaempferol skeleton, and the glycosyl parts did not show a significant role in the activity.

The EtOH and water extracts of *B frutescens* leaf were also the subjects of a DPPH assay, producing respective IC_{50} values of 41.96 and 93.30 μg/mL, in comparison with that of the standard gallic acid (IC_{50} 3.81 μg/mL).[48] The *n*-hexane, MeOH, EtOAc, and water extracts of *B frutescens* leaf showed antioxidative activity in the DPPH radical scavenging, ferric reducing power, and metal chelating models (Table 3).[46] In particular, the water extract (EC_{50} 0.039 mg/

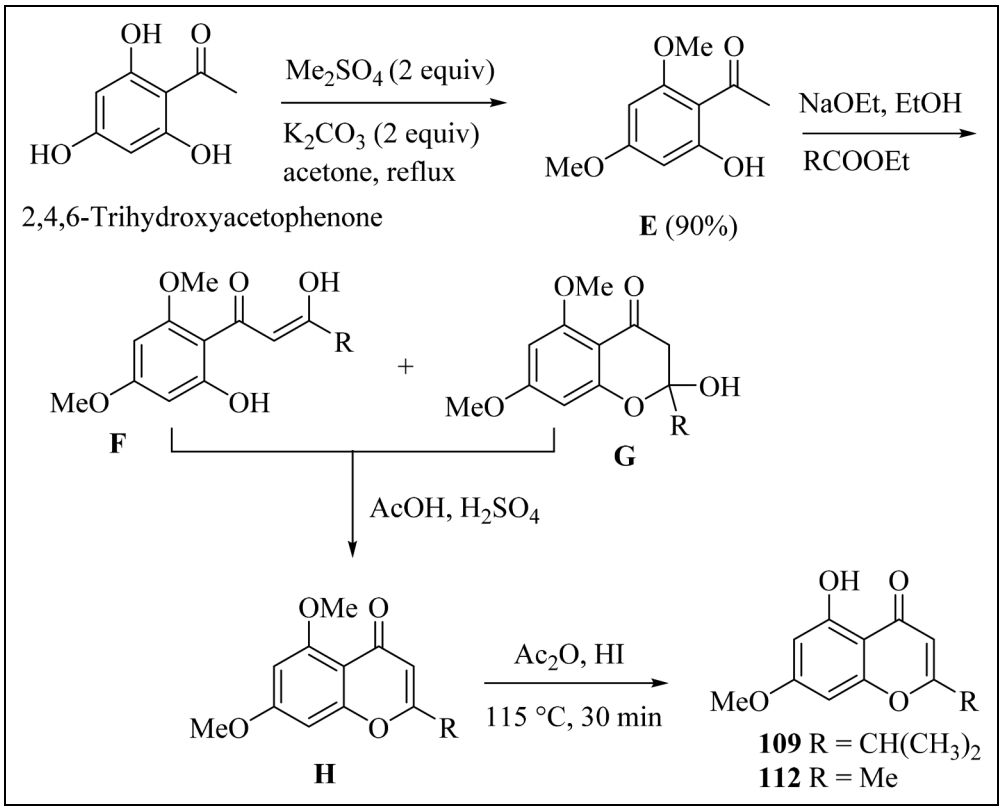

Figure 7. Synthetic pathway of chromones **109** and **112**.

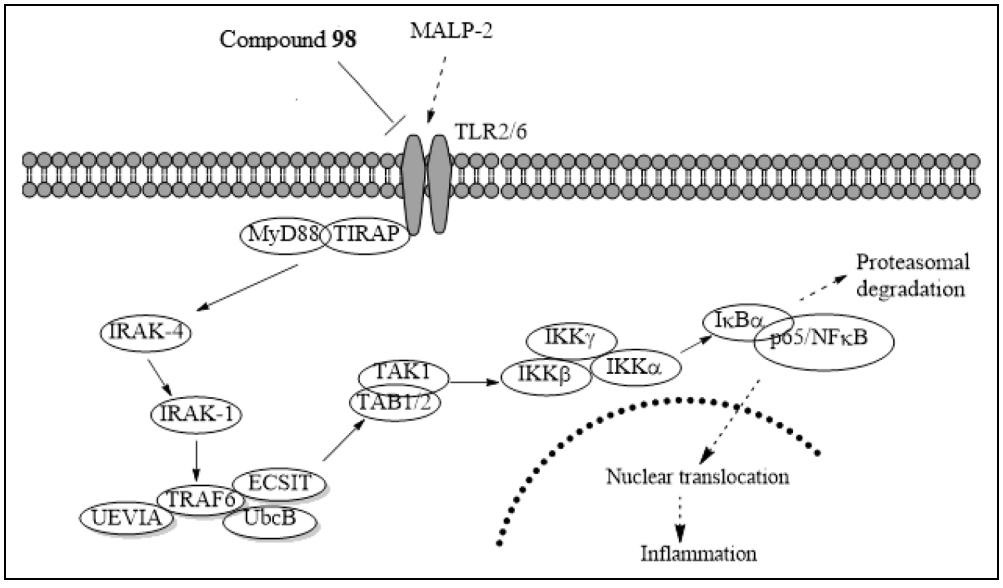

Figure 8. Anti-inflammatory mechanism of compound **98**.

mL) was better than the standard EDTA (EC_{50} 0.042 mg/mL) in the metal chelating assay.[46]

Besides antimicrobial activity, the HE and ES-UME leaf oils generated IC_{50} values of 15.9 and 14.0 μg/mL, respectively, in a DPPH antioxidative assay when α-tocopherol was used as a positive control (IC_{50} 0.12 μg/mL).[51] *B frutescens* leaf oil was also demonstrated as a potential agent in other antioxidative models, in which it possessed ferric reducing power, metal chelating, and β-carotene bleaching, with EC_{50} values of 0.29-1.39 μg/mL.[53]

Antirheumatoid Arthritis and Skin Protective Activities

BF-2 (**40**) acted as a prostaglandin E2 receptor 4 (EP4) antagonist, which has potential antirheumatoid arthritis activity. At a dose of 25-100 mg/kg, it could inhibit toe swelling of mice and relieve the degradation of articular cartilage matrix and inflammatory cell infiltration.[54]

The EtOH leaf extract increased the proliferation and migration of keratinocytes and fibroblast BJ cells. In detail, HaCaT's proliferation was increased by 14% and 24% at 6.25 and 3.125 μg/mL, respectively, after 48 h treatment, and BJ's proliferation was increased by 36% and 51% at 25 and 12.5 μg/mL, respectively, after 24 h treatment.[29]

Conclusion and Perspective

For the first time, the current review provides full information on the phytochemistry, biosynthesis, synthesis, and pharmacology of *B frutescens* constituents. Phytochemical studies of *B frutescens* tissues have led to the isolation and structural determination of 128 secondary metabolites, including 14 phloroglucinols, 47 phloroglucinol-based meroterpenoids, 4 sesquiterpenoids, 3 triterpenoids, 34 flavonoids, 19 chromones, 5 5-membered ring compounds, 1 *mono*-phenol, and 1 phytosterol. *B frutescens* is also rich in essential oils, in which monoterpenes, monoterpenoids, sesquiterpenes, and sesquiterpenoids were the main chemical classes. Generally, tasmanone acted as a precursor in biosynthesis, whereas the previous reports dealt with the use of phloroglucinol derivatives in the synthetic procedures of *B frutescens* molecules. Crude plant extracts, fractions, and the isolates of *B frutescens* possess a variety of pharmacological activities, such as cytotoxic, antimicrobial, anti-inflammatory, antioxidative, antirheumatoid, skin protective, and mosquito larvicidal activities.

However, further chemical examination is necessary. Some compounds contain stereogenic centers pending the assignment of the absolute configuration, and a good number of compounds have been described as racemic mixtures, which is not common in the biogenesis of natural products. Hence, structural elucidation studies are welcome. There is also a lack of in vitro and in vivo studies of the pharmacological mechanisms of action since most of the data obtained so far have been the result of initial screenings. Many isolated metabolites, especially the major potential compounds, have not yet received attention in pharmacological examinations. Last but not least, structure–activity relationship studies are required, as well as virtual docking calculations.

Authors' Contributions

DTLH: formal analysis and revision; DXD: collection and formal analysis; and NTS: designated and wrote the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Ninh The Son https://orcid.org/0000-0002-7374-5914
Dau Xuan Duc https://orcid.org/0000-0002-3538-8565

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