Naturally Occurring Phenylethanoid Glycosides: Potential Leads for New Therapeutics

G. M. Fu, H. H. Pang, Y. H. Wong*

Department of Biochemistry, Molecular Neuroscience Center, and Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China

*Correspondence should be addressed to:

Prof. Yung H. Wong, Department of Biochemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China

Phone: 852-2358-7328

Fax: 852-2358-1552

Email: boyung@ust.hk

ABSTRACT

Natural products have long been regarded as excellent sources for drug discovery given their structure diversity and wide variety of biological activities. Phenylethanoid glycosides are naturally occurring compounds of plant origin and are structurally characterized with a hydroxyphenylethyl moiety to which a glucopyranose is linked through a glycosidic bond. To date several hundred compounds of this type have been isolated from medicinal plants and further pharmacological studies *in vitro* or *in vivo* have shown that these compounds possess a broad array of biological activities including antibacterial, antitumor, antiviral, anti-inflammatory, neuro-protective, antioxidant, hepatoprotective, immunomodulatory, and tyrosinase inhibitory actions. Given their extensive activity profile, structure-activity relationships analyses of these compounds have been performed in a number of studies to reveal potential leads for future drug design. This article will summarize the major developments in phenylethanoid glycosides-based research in the past decade. The progresses made in phytochemistry and biological activity studies of these compounds will be reviewed. Particular attention will be given to the novel structures identified to date and the prominent therapeutic values associated with these molecules.

Keywords: Phenylethanoid glycosides, herbal medicine, natural product.

1. INTRODUCTION

The naturally occurring phenylethanoid glycosides (PhGs) have long been a subject of interest to medicinal chemists given their great potentials in pharmaceutical and industrial applications. As their name suggests, the core structures of PhGs are characterized by a hydroxyphenylethyl moiety attached to a β -glucopyranose through glycosidic linkage. The core structures are often inundated with substituents such as aromatic acids (e.g., cinnamic acid, ferulic acid, and isoferulic acid) and various sugars (e.g., rhamnose, xylose, apiose, and arabinose) attached to the glucose residue through ester or glycosidic linkages, respectively. In fact some of the PhGs are also known as phenylpropanoid glycosides due to the presence of one or more phenylpropyl moieties contributed by the ester-forming aromatic acids such as cinnamic acid, caffeic acid, and ferulic acid.

PhGs are water-soluble and widely distributed in the plant kingdom. These compounds are not specific to any plant organ and have been isolated from plant roots, barks, leaves, aerial parts, and also from callus and suspension cultures. The majority of the PhGs reported to date are found in the Scrophulariaceae, Oleaceae, Plantaginaceae, Lamiaceae, and Orobanchaceae family. For example, acteoside (also known as verbascoside), has been isolated from a number of genera within the Lamiaceae family, including *Stachys*, *Eremostachys*, *Faradaya*, *Lamium*, *Leonurus*, *Marrubium*, *Phlomis*, *Prostanthera*, *Oxera*, *Scutellaria*, and *Sideritis* [1].

There have been a number of reviews on PhGs in the 90's in respect of their isolation and purification, structure elucidation, phytotherapeutic effects, and pharmacological activities [2-4]. The growing interest in PhGs in the past decade has generated a large

volume of information on these compounds. Novel structures with variations in the PhG skeleton or positions and types of substituents have been identified. Promising biological activities associated with some of the PhGs have been discovered and their pharmacological potentials warrant further evaluation. Here, we aim to provide an overview on the advances made on PhGs during the past decade. Emphasis will be given to new PhGs isolated from natural sources in the last decade and the major biological and pharmacological activities identified for PhGs.

2. NEW PhGs ISOLATED IN THE LAST DECADE

Owing to the rapid improvement of various isolation, purification, and structure elucidation technologies, nearly 200 new PhGs have been identified in the past ten years (Tables I to III and Figs. (1) to (5)). The compounds are categorized based on the number, type, and position of the sugars in the molecule or the variations in their core structures. References where the specific PhGs were first reported as a new compound are given. Moreover, the plant source and biological activities reported for the specific PhGs are also included.

PhGs with α -L-rhamnose at C-3' of the glucose are listed in Table I. In general, most of the PhGs found to date have less than four sugar moieties in the molecule. Substitution at C-3' is a common feature of PhGs with α -L-rhamnose being the most popular substituent at this position. All of the listed compounds are glucopyranosides, with caffeic, ferulic, coumaric, and gallic acids being the most frequently occurring aromatic acids that form esters with the glucose. Additional aromatic acids include vanillic, *cis*-caffeic, *cis*-ferulic,

cis-coumaric, isoferulic, syringic, and sinapic acids. Interestingly, teucrioside-3'''-*O*-methylether (**40**) and teucrioside-3''',4'''-*O*-dimethylether (**41**) from *Teucrium chamaedrys* are the only lyxose-containing PhGs [31] while newbouldioside B (**15**) exists in salt form [11].

PhGs that have no substituents or have sugars other than α -L-rhamnose at C-3' are summarized in Table II. Caffeic, ferulic, and cinnamic acids are often found forming an ester at C-4' of the glucose while xylose, apiose, arabinose, and rhamnose frequently occur at C-2' and C-6'. Although most of the PhGs reported hitherto are disaccharides or trisaccharides with non-linear sugar chains, exceptions have been noted. Turrilliosides B (**103**) [76] has a linear glc-rha-glc chain, while newbouldioside C (**114**) represents the first PhG with a linear glc-rha-api chain and a sinapoyl moiety [11].

Compounds (**173**) from *Coriandrum sativum* [123] and (**175**) from *Forsythia suspense* [125] are examples of PhGs with substituents at C-7 of the phenylethyl moiety (Table III). Substituents reported to date include hydroxyl and various alkoxy groups such as methoxyl, ethoxyl, and butoxyl group.

PhGs with 1,4-dioxane formed through condensation between C-7, 8 of aglycone and C-1', 2' of glucose are rare in nature (Fig. (1)). Examples include cuneatasides A (**176**) and cuneatasides B (**177**) that are isomers with configuration difference at C-7 [85]. Some PhGs are found to contain a secoiridoid moiety (Fig. (2)). Except for safghanoside E (**182**) [129], in which secoiridoid is connected directly to the aglycone, the other compounds all have secoiridoid attached to glucose. All these compounds are isolated from Oleaceae family and have cyclic hemiketal in their iridoid moiety. Compounds (**187**) to (**189**) have

Table I. PhGs with α -L-rhamnose at C-3' of glucose

No.	Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	Source	Biological Activity	Ref.
1	Acetyl forsythoside B	Ac	Caff	Api	H	H	H	OH	OH	<i>Callicarpa japonica</i>	Antioxidant and radical scavenging	5
2	Salsasides D	Ac	Caff	H	H	H	H	H	OH	<i>Cistanche salsa</i>	—	6
3	Salsasides E	Ac	Caff	H	H	H	H	OCH ₃	OH	<i>Cistanche salsa</i>	—	6
4	Salsasides F	Ac	H	Coum	H	H	H	OH	OH	<i>Cistanche salsa</i>	—	6
5	2'',3''-Diacetyl- <i>O</i> -betonyoside	H	Feru	Api	Ac	Ac	H	OH	OCH ₃	<i>Phlomis umbrosa</i>	—	7
6	3'',4''-Diacetyl- <i>O</i> -betonyoside	H	Feru	Api	H	Ac	Ac	OH	OCH ₃	<i>Phlomis umbrosa</i>	—	7
7	Cistantubulosides A	H	Caff	Glc	H	H	H	H	OH	<i>Cistanche tubulosa</i>	—	8
8	Cistantubulosides B1/B2	H	<i>Trans/Cis-Coum</i>	Glc	H	H	H	OH	OH	<i>Cistanche tubulosa</i>	—	8
9	Dolichandroside	Api	Feru	H	H	H	H	OH	OH	<i>Dolichandrone serrulata</i>	—	9
10	Lamiusides A	H	Caff	H	Gal	H	H	OH	OH	<i>Lamium purpureum</i>	Radical scavenging activity	10
11	Lamiusides B	H	Feru	H	Gal	H	H	OH	OH	<i>Lamium purpureum</i>	Radical scavenging activity	10
12	Lamiusides C	H	H	Caff	Gal	H	H	OH	OH	<i>Lamium purpureum</i>	Radical scavenging activity	10
13	Lamiusides E	H	<i>Cis-Feru</i>	Glc	H	H	H	OH	OCH ₃	<i>Lamium purpureum</i>	—	10
14	Newbouldioside A	5- <i>O</i> -Syringoyl Api	H	H	H	H	H	OH	OH	<i>Newbouldia laevis</i>	—	11
15	Newbouldioside B	5- <i>O</i> -Syringoyl Api	H	Feru	H	H	H	OH	OH	<i>Newbouldia laevis</i>	—	11
16	Kankanosides F	H	H	Glc	H	H	H	OH	OH	<i>Cistanche tubulosa</i>	Vasorelaxant activity	12
17	Kankanosides G	H	H	Caff	H	H	H	H	OH	<i>Cistanche tubulosa</i>	—	12
18	Trichotomoside	H	Feru	Feru	Ac	Ac	H	OH	OCH ₃	<i>Clerodendron trichotomum</i>	Antioxidative activity	13
19	Picfeosides A	H	Caff	H	H	H	Api	H	H	<i>Picria felterrae</i>	—	14

20	Picfeosides B	H	H	Caff	H	H	Api	H	H	<i>Picria felterrae</i>	—	14
21	Picfeosides C	H	H	H	H	H	Api	H	H	<i>Picria felterrae</i>	—	14
22	Phlinoside F	H	Feru	H	Xyl	H	H	OH	OCH ₃	<i>Phlomis angustissima</i>	—	15
23	Z-tubuloside E	Ac	<i>Cis</i> -Coum	H	H	H	H	OH	OH	<i>Callicarpa dichotoma</i>	Neuroprotective activity	16, 17
24	Myricoside-3'''-O-methylether	H	Feru	H	H	Api	H	OH	OH	<i>Phlomis oppositiflora</i>	—	18
25	Buddleoside A	H	Caff	Ara	Feru	H	H	OH	OH	<i>Buddleia lindleyana</i>	Neuroprotective activity	19
26	Velutinoside III	H	Feru	Glc	Ara	H	H	OH	OCH ₃	<i>Marrubium velutinum</i>	—	20
27	Velutinoside IV	H	Feru	H	Ara	H	H	OCH ₃	OH	<i>Marrubium velutinum</i>	—	20
28	2-(3-Methoxy-4-hydroxyphenyl)ethyl- <i>O</i> -2'',3''-diacetyl- α -L-rhamnopyranosyl (1 $\rightarrow$ 3)-4- <i>O</i> -(<i>E</i>)-feruloyl- β -D-glucopyranoside	H	Feru	H	Ac	Ac	H	OCH ₃	OH	<i>Clerodendrum inerme</i>	—	21
29	4- <i>O</i> - α -L-Rhamnopyranosyl-cistanoside E	H	H	H	H	H	H	OH	<i>O</i> -Rha	<i>Acanthus ilicifolius</i>	—	22
30	Lunariifolioside	H	Caff	Api	H	H	Api	OH	OH	<i>Phlomis lunariifolia</i>	—	23
31	Globusintenoside	H	Caff	H	H	H	6- <i>O</i> -Feru loyl-Glc	OH	OH	<i>Globularia sintenisii</i>	—	24
32	2'',3'''-Diacetyl acteoside	Ac	Caff	H	H	Ac	H	OH	OH	<i>Aeginetia indica</i>	—	25
33	Caerulescenoside	H	Caff	H	H	Glc	H	OH	OH	<i>Orobanchae caerulescens</i>	Antioxidative activity	26
34	Isocistanoside C	H	H	Feru	H	H	H	OCH ₃	OH	<i>Cistanchis Herba</i>	—	27
35	Epimeridinoside A	H	H	Feru	H	H	H	OCH ₃	OH	<i>Epimeredi indica</i>	—	28
36	Velutinosides I	H	Caff	Glc	Ara	H	H	OH	OH	<i>Marrubium velutinum</i>	—	29
37	Velutinosides II	H	Isofreu	Glc	Ara	H	H	OH	OH	<i>Marrubium velutinum</i>	—	29
38	Ligurobustosides M	H	H	H	H	H	Rha	OH	OH	<i>Ligustrum robustum,</i>	—	30
39	Ligurobustosides N	H	Caff	H	H	H	Rha	OH	OH	<i>Ligustrum robustum,</i>	Antioxidative activity	30

40	Teucrioside-3'''-O-methylether	H	Feru	H	Lyx	H	H	OH	OH	<i>Teucrium chamaedrys</i>	—	31
41	Teucrioside-3'''',4'''-O- dimethylether	H	DMC	H	Lyx	H	H	OH	OH	<i>Teucrium chamaedrys</i>	—	31
42	6'-O-Acetylacteoside	H	Caff	Ac	H	H	H	OH	OH	<i>Harpagophytum procumbens</i>	Inhibited human leukocyte elastase	32, 33
43	2'-O, 6'-O-Diacetylacteoside	Ac	Caff	Ac	H	H	H	OH	OH	<i>Harpagophytum procumbens</i>	—	32
44	Integrifoliosides A	H	Feru	H	H	H	Api	OH	OH	<i>Phlomis integrifolia</i>	—	34
45	Integrifoliosides B	H	Feru	H	H	H	Api	OH	OCH ₃	<i>Phlomis integrifolia</i>	—	34
46	Physocalycoside	H	Feru	Glc	Rha	H	H	OH	OCH ₃	<i>Phlomis physocalyx</i>	Radical scavenging activity	35
47	Wiedemannioside B	H	Feru	Ac	Ac	Ac	H	OH	OCH ₃	<i>Verbascum wiedemannianum</i>	—	36
48	Wiedemannioside C	H	Feru	Glc	H	H	H	OH	OH	<i>Verbascum wiedemannianum</i>	—	36
49	Wiedemannioside D	Ac	Feru	Rha	H	H	H	OH	OH	<i>Verbascum wiedemannianum</i>	—	36
50	Wiedemannioside E	Ac	Feru	Rha	Ac	H	H	OH	OH	<i>Verbascum wiedemannianum</i>	—	36
51	Verpectoside A	Rha	Feru	H	H	H	H	OH	OH	<i>Veronica pectinata</i> var. <i>glandulosa</i>	Radical scavenging	37
52	Verpectoside B	Glc	Caf	H	H	H	H	OH	OH	<i>Veronica pectinata</i> var. <i>glandulosa</i>	Radical scavenging	37
53	Verpectoside C	Glc	Feru	H	H	H	H	OH	OH	<i>Veronica pectinata</i> var. <i>glandulosa</i>	Radical scavenging	37
54	6''-O-Acetylverbascoside	H	Caff	Ac	H	H	H	OH	OH	<i>Barnettia kerrii</i>	—	38
55	4'''-O-Acetylverbascoside	H	Caff	H	H	H	Ac	OH	OH	<i>Barnettia kerrii</i>	—	38
56	Markhamioside A	Api	H	H	H	H	H	OH	OH	<i>Markhamia stipulata</i> ,	—	39
57	Markhamioside B	Api	H	Feru	H	H	H	OH	OCH ₃	<i>Markhamia stipulata</i> ,	—	39

58	Markhamioside C	Ara	H	Caf	H	H	H	OH	OH	<i>Markhamia stipulata</i> ,	—	39
59	Markhamioside D	Ara	Caff	Ac	H	H	H	OH	OH	<i>Markhamia stipulata</i> ,	—	39
60	Markhamioside E	Gal	Caff	Ac	H	H	H	OH	OH	<i>Markhamia stipulata</i> ,	—	39
61	Marruboside	H	Caff	Api	Api	H	H	OH	OH	<i>Marrubium vulgare</i>	—	40
62	2",3"-Di- <i>O</i> -acetyl martynoside	H	Feru	H	Ac	Ac	H	OH	OCH ₃	<i>Lippia dulcis</i>	—	41
63	2"- <i>O</i> - β -Apiosylverbascoside	Api	Caff	H	H	H	H	OH	OH	<i>Fernandoa adenophylla</i>	—	42
64	Samioside	H	Caff	H	H	H	Api	OH	OH	<i>Phlomis samia</i>	DPPH radical scavenging and antimicrobial	43
65	Angoroside D	H	Freu	Ara	H	H	H	OH	OH	<i>Scrophularia scorodonia</i>	Immunomodulating activity	44, 45
66	Serratumoside A	H	Freu	H	H	Api	H	OH	OCH ₃	<i>Clerodendrum serratum</i>	—	46
67	Crassoside	Glc	Caff	H	H	H	H	OH	OH	<i>Plantago crassifolia</i>	—	47
68	Isoangoroside C	H	<i>Cis</i> -Feru	Ara	H	H	H	OH	OCH ₃	<i>Scrophularia scorodonia</i>	—	48
69	Incanoside C	H	Feru	H	Glc	H	H	OH	OH	<i>Caryopteris incana</i>	Radical scavenging activity	49
70	Incanoside D	H	Feru	H	Glc	H	H	OH	OCH ₃	<i>Caryopteris incana</i>	Radical scavenging activity	49
71	Incanoside E	H	Feru	H	Glc	H	H	OCH ₃	OH	<i>Caryopteris incana</i>	Radical scavenging activity	49
72	β -(3,4-dihydroxyphenyl)-ethyl- <i>O</i> - α -L-rhamnopyranosyl(1 $\rightarrow$ 3)- β -D-[β -D-xylopyranosyl(1 $\rightarrow$ 6)]-(4- <i>O</i> -isoferulyl)glucopyranoside	H	Isoferu	Xyl	H	H	H	OH	OH	<i>Verbascum sinaiticum</i>	—	50
73	β -(3-hydroxy-4-methoxyphenyl)-ethyl- <i>O</i> - α -L-rhamnopyranosyl(1 $\rightarrow$ 3)- β -D-[β -D-glucopyranosyl(1 $\rightarrow$ 6)]-(4- <i>O</i> -isoferulyl)glucopyranoside	H	Isoferu	Glc	H	H	H	OH	OCH ₃	<i>Verbascum sinaiticum</i>	—	50
74	Martynoside	H	Feru	H	H	H	H	OH	OCH ₃	<i>Cassiope selaginoids</i>	Antioxidative, antimicrobial and inhibit ACE activities	51-54

75	Scrophuloside B1	H	Feru	Ara	H	H	H	OH	OH	<i>Scrophularia nodosa</i>	—	55
76	Scrophuloside B2	H	<i>Cis</i> -Feru	Ara	H	H	H	OH	OH	<i>Scrophularia nodosa</i>	—	55
77	Trichosanthoside A	H	Caff	H	H	H	Xyl	OH	OH	<i>Globularia alypum</i>	Radical scavenging Activity	56
78	Trichosanthoside B	H	Caff	Xyl	H	H	Xyl	OH	OH	<i>Globularia alypum</i>	Radical scavenging Activity	56
79	Isobetonyoside F	H	H	Caff	Api	H	H	OH	OH	<i>Prostanthera melissifolia</i>	—	57
80	6'- β -D-Apiofuranosyl cistanoside C	H	Caff	Api	H	H	H	OCH ₃	OH	<i>Lamiophlomis rotata</i>	—	58
81	<i>Cis</i> -lamiophlomiside A	H	<i>Cis</i> -Feru	Api	H	H	H	OCH ₃	OH	<i>Lamiophlomis rotata</i>	—	58
82	<i>Cis</i> -martynoside	H	<i>Cis</i> -Caff	H	H	H	H	OH	OCH ₃	<i>Penstemon serrulatus</i>	—	59
83	<i>Cis</i> -leucosceptoside A	H	<i>Cis</i> -Feru	H	H	H	H	OH	OH	<i>Penstemon serrulatus</i>	—	59
84	Ferruginoside C	H	Feru	Rha	H	H	H	OH	OCH ₃	<i>Digitalis ferruginea</i>	—	60
85	Incanoside	H	H	Caff	Glc	H	H	OH	OH	<i>Caryopteris incana</i>	Radical Scavenging Activity	61
86	Luteoside A	Api	Caff	Ac	H	H	H	OH	OH	<i>Markhamia lutea</i>	Antivirus	62
87	Luteoside B	Api	H	Caff	H	H	H	OH	OH	<i>Markhamia lutea</i>	Antivirus	62
88	Luteoside C	Api	H	Feru	H	H	H	OH	OH	<i>Markhamia lutea</i>	Antivirus	62
89	6'- <i>O</i> -(<i>E</i>)-Cinnamoylverbascoside	H	Caff	Cinn	H	H	H	OH	OH	<i>Osmanthus austrocaledonica</i>	—	63
90	Galactosylmartynoside	H	Feru	H	Gal	H	H	OH	OCH ₃	<i>Ajuga decumbens</i>	Antivirus	64
91	2-(3-Hydroxy-4-methoxyphenyl)-ethyl- <i>O</i> -(α -L-rhamnosyl)-(1 $\rightarrow$ 3)- <i>O</i> -(α -L-rhamnosyl)-(1 $\rightarrow$ 6)-4- <i>O</i> - <i>E</i> -feruloyl- β -D-glucopyranoside	H	Feru	Rha	H	H	H	OH	OCH ₃	<i>Digitalis purpurea</i>	PKC α -Inhibitory Activity	65
92	Incanosides A	H	H	Feru	Glc	H	H	OH	OCH ₃	<i>Caryopteris incana</i>	—	66
93	Incanosides B	H	H	H	Glc	H	H	OH	OCH ₃	<i>Caryopteris incana</i>	—	66

94	6'-O-Acetyl-martynoside	H	Feru	Ac	H	H	H	OH	OCH ₃	<i>Verbascum undulatum</i>	—	67
95	Ballotetroside	H	Caff	Api	Ara	H	H	OH	OH	<i>Ballota nigra</i>	Antioxidative, immunodulating and cardiovascular activities	68-71
96	Newbouldioside	Api	H	Feru	H	H	H	OH	OH	<i>Newbouldia laevis</i>	No antibacterial and antifungal	72
97	Premnethanosides A	H	Feru	H	Ac	Ac	Glc	OH	OCH ₃	<i>Premna subscandens</i>	—	73
98	Premnethanosides A	H	Cis-Feru	H	Ac	Ac	Glc	OH	OCH ₃	<i>Premna subscandens</i>	—	73
99	Cis-isoverbascoside	H	H	Cis-Caff	H	H	H	OH	OH	<i>Pedicularis semitorta</i>	—	74

Table II. PhGs with or without sugars (other than α -L-rhamnose) at C-3'

No	Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Source	Biological Activity	Ref.
100	2-(4-Hydroxy-3-methoxyphenyl) ethanol 1- <i>O</i> -[β -D-apiofuranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside]	H	H	H	Api	OCH ₃	OH	<i>Fraxinus sieboldiana</i>	TNF- α secretion inhibitory	75
101	2-(3,4-Dihydroxyphenyl) ethanol 1- <i>O</i> -[β -D-apiofuranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside]	H	H	H	Api	OH	OH	<i>Fraxinus sieboldiana</i>	TNF- α secretion inhibitory	75
102	Turrilliosides A	H	H	Caff	Glc(1 $\rightarrow$ 4)Rha	OH	OH	<i>Veronica turrilliana</i>	DPPH radical scavengers	76
103	Turrilliosides B	H	H	Caff	6- <i>O</i> -feruloyl-Glc(1 $\rightarrow$ 4)Rha	OH	OH	<i>Veronica turrilliana</i>	DPPH radical scavengers	76
104	Mongrhoside	H	H	H	Ara	H	OCH ₃	<i>Rhodiola rosea</i> and <i>Rhodiola quadrifida</i>	—	77
105	3- <i>O</i> -Methylpoliumoside	H	H	Feru	Rha' (1 $\rightarrow$ 3)Rha	OH	OH	<i>Leucas indica</i>	Antioxidant activity inhibitor of XO enzyme	78
106	Ternstrosides A	A	H	H	H	OH	OH	<i>Ternstroemia japonica</i>	Antioxidant	79
107	Ternstrosides B	B	H	H	H	OH	OH	<i>Ternstroemia japonica</i>	Antioxidant	79
108	Ternstrosides C	H	A	H	H	OH	OH	<i>Ternstroemia japonica</i>	Antioxidant	79
109	Ternstrosides D	H	H	H	A	OH	OH	<i>Ternstroemia japonica</i>	Antioxidant	79
110	Ternstrosides E	A	H	H	H	OH	H	<i>Ternstroemia japonica</i>	Antioxidant	79
111	Parviflorosides A	Rha	H	Caff	H	OH	OH	<i>Stachys parviflora</i>	—	80
112	Parviflorosides B	Rha	H	H	OH	OH	OH	<i>Stachys parviflora</i>	—	80
113	Heterodontoside	H	H	H	Xyl	H	OCH ₃	<i>Rhodiola heterodonta</i>	—	81
114	Newbouldioside C	5- <i>O</i> -Syringoyl-Api(1 $\rightarrow$ 2)Rha	H	H	Sinapoyl	OH	OH	<i>Newbouldia laevis</i>	—	11
115	6'- <i>O</i> -Coumaroyl-1'- <i>O</i> -[2-(3,4-dihydroxyphenyl)ethyl]- α -D-glucopyranoside	H	H	H	Coum	OH	OH	<i>Globularia alypum</i>	Antioxidant	82
116	2-(4-Hydroxyphenyl)ethyl 1- <i>O</i> - β -D-[5- <i>O</i> -(4-hydroxybenzoyl)]-apiofuranosyl- (1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	5- <i>O</i> -(4-hydroxybenzoyl)-Api	H	OH	<i>Tabebuia impetiginosa</i>		83

117	2-(4-Hydroxyphenyl)ethyl-1- <i>O</i> - β -D-[5- <i>O</i> -(4-hydroxybenzoyl)]-apiofuranosyl- (1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	5- <i>O</i> -(4-hydroxybenzoyl)-Api	H	OH	<i>Tabebuia avellanedae</i>	NO production inhibitor	84
118	Cuneatasides C	H	H	H	Api	OH	OH	<i>Sargentodoxa cuneata</i>	—	85
119	Clerodendronoside	Api	H	Feru	H	H	OH	<i>Clerodendron bungei</i>	—	86
120	Cusianoside A	H	Api	Caff	H	OH	OH	<i>Strobilanthes cusia</i>	—	87
121	Cusianoside B	H	Xyl	Caff	H	OH	OH	<i>Strobilanthes cusia</i>	—	87
122	Scroside D	H	Glc	H	H	OH	OH	<i>Picrorhiza scrophulariiflora</i>	Antioxidant	88
123	2-(4-Hydroxyphenyl)ethyl-1- <i>O</i> - β -D-[5- <i>O</i> -(3,4-dimethoxybenzoyl)]-apiofuranosyl- (1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	5- <i>O</i> -(3,4-dimethoxybenzoyl)-Api	H	OH	<i>Tabebuia impetiginosa</i>	—	89
124	2-(4-Hydroxyphenyl)ethyl-1- <i>O</i> - β -D-[5- <i>O</i> -(4-methoxybenzoyl)]-apiofuranosyl- (1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	5- <i>O</i> -(4-methoxybenzoyl)-Api	H	OH	<i>Tabebuia impetiginosa</i>	—	89
125	2-(4-Hydroxyphenyl)ethyl-1- <i>O</i> - β -D-[5- <i>O</i> -(3,4,5-trimethoxybenzoyl)]-apiofuranosyl- (1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	5- <i>O</i> -(3,4,5-trimethoxybenzoyl)-Api	H	OH	<i>Tabebuia impetiginosa</i>	—	89
126	1- <i>O</i> -3,4-Dimethoxyphenylethyl-4- <i>O</i> -3,4-dimethoxy cinnamoyl-6- <i>O</i> -cinnamoyl- β -D-glucopyranose	H	H	DMC	Cinn	OCH ₃	OCH ₃	<i>Psidium guajava</i>	Antitumor	90
127	1- <i>O</i> -3, 4-Dimethoxyphenylethyl-4- <i>O</i> -3,4-dimethoxy cinnamoyl- β -D-glucopyranose	H	H	DMC	H	OCH ₃	OCH ₃	<i>Psidium guajava</i>	Antitumor	90
128	2-(4-Hydroxy-3-methoxyphenyl)-ethyl- <i>O</i> - β -D-glucopyranoside	H	H	H	H	OCH ₃	OH	<i>Laurus nobilis</i>	—	91
129	Scroside D	H	Glc	Feru	H	OH	OH	<i>Picrorhiza scrophulariiflora</i>	—	92
130	Scroside E	H	Glc	H	Feru	OH	OH	<i>Picrorhiza scrophulariiflora</i>	—	92
131	1'- <i>O</i> - β -D-(3,4-Dihydroxyphenyl)-ethyl-6'- <i>O</i> -vanilloyl-glucopyranoside	H	H	H	Van	OH	OH	<i>CoraUodiscus flabellata</i>	—	93
132	Lancetoside	H	Glc	<i>Trans/Cis</i> -Coum	H	H	OH	<i>Plantago lanceolata</i>	—	94
133	2-(3-Hydroxy-4-methoxyphenyl)-ethyl- <i>O</i> - β -D-glucopyranosyl (1-3) β -D-glucopyranoside	H	Glc	H	H	OH	OCH ₃	<i>Picrorhiza scrophulariiflora</i>	—	95
134	Hemiphroside C	H	Glc	H	Cis-feru	OH	OCH ₃	<i>Hemiphragma heterophyllum</i>	—	96

135	Aragoside	Glc	Ara	Caff	H	OH	OH	<i>Aragoa cundinamarcensis</i>	—	97
136	3,4-Dihydroxyphenylethanol-[8- <i>O</i> - β -D-apiofuranosyl(1 $\rightarrow$ 2)]- β -D-glucopyranoside	Api	H	H	H	OH	OH	<i>CoraUodiscus flabellata</i>	—	98
137	3,4-Dihydroxyphenylethanol-8- <i>O</i> -[(5- <i>O</i> -vanilloyl)- β -D-apiofuranosyl (1 $\rightarrow$ 2)]- β -D-glucopyranoside	5- <i>O</i> -vanilloyl-Api	H	H	H	OH	OH	<i>CoraUodiscus flabellata</i>	—	98
138	3,4-Dihydroxyphenylethanol-8- <i>O</i> -[β -D-apiofuranosyl(1 $\rightarrow$ 3)]- β -D-glucopyranoside	OH	Api	H	OH	OH	OH	<i>CoraUodiscus flabellata</i>	—	99
139	3,4-Dihydroxyphenylethanol-8- <i>O</i> -[4- <i>O</i> -trans-caffeoyl- β -D-apiofuranosyl (1 $\rightarrow$ 3)]- β -D-glucopyranosyl-(1 $\rightarrow$ 6)]- β -D-glucopyranoside	OH	Api	Caff	Glc	OH	OH	<i>CoraUodiscus flabellata</i>	—	99
140	3,4-Dihydroxyphenylethanol-8- <i>O</i> -[β -D-apiofuranosyl(1 $\rightarrow$ 3)]- β -D-glucopyranosyl-(1 $\rightarrow$ 6)]- β -D-glucopyranoside	OH	Api	H	Glc	OH	OH	<i>CoraUodiscus flabellata</i>	—	99
141	Bacopaside B.	Freu	H	H	H	OH	OH	<i>Bacopa monniera</i>	—	100
142	Bacopaside C	5- <i>O</i> -4-Hydroxy-benzoyl-Api	H	H	H	H	H	<i>Bacopa monniera</i>	—	100
143	Monnierasides I	4-Hydroxy-benzoyl	H	H	H	H	OH	<i>Bacopa monniera</i>	—	101
144	Monnierasides II	Feruloyl	H	H	H	OH	OH	<i>Bacopa monniera</i>	—	101
145	Monnierasides III	4-Hydroxy-benzoyl	H	H	H	OH	OH	<i>Bacopa monniera</i>	—	101
146	Persicoside	Glc	Glc	Caff	H	OH	OH	<i>Veronica persica</i>	Radical scavenging activity	102
147	Dracunculifosides O	H	H	H	5- <i>O</i> -Caffeoyl-Api	H	H	<i>Baccharis dracunculifolia</i>	—	103
148	Echipsuroside A	H	H	H	Rha	H	OH	<i>Echinacea purpurea</i>	—	104
149	2'- <i>O</i> -Acetylplantamajoside	Ac	Glc	Caff	H	OH	OH	<i>Wulfenia carinthinca</i>	Andioxidant	105, 106
150	2'- <i>O</i> , 6''- <i>O</i> -Diacylplantamajoside	Ac	6- <i>O</i> -Acetyl-Glc	Caff	H	OH	OH	<i>Wulfenia carinthinca</i>	Andioxidant	105, 106
151	Sayaendoside	Api	H	H	H	H	H	<i>Pisum sativum</i>	Antiproliferative activity	107, 108

152	Phenethyl alcohol β -D-(2'-O- β -D-glucopyranosyl) glucopyranoside	Glc	H	H	H	H	H	<i>Premna subscandens</i>	—	109
153	Isolugrandoside	H	Caff	H	Glc	OH	OH	<i>Fraxinus ornus</i>	—	110
154	Phenethyl alcohol 8-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-apiofuranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside	H	H	H	Glc(1 $\rightarrow$ 2)Api	H	H	<i>Bupleurum falcatum</i>	—	111
155	Phenethyl alcohol 8-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside	Glc	H	H	H	H	H	<i>Bupleurum falcatum</i>	—	111
156	Phlomisethanoside	5-O-Vanilloyl -Api	H	H	H	H	OH	<i>Phlomis grandiflora</i> var. <i>grandiflora</i>	—	112
157	Ferruginoside A	Caff	H	H	Glc	OH	OH	<i>Digitalis ferruginea</i>	—	113
158	Ferruginoside B	H	H	H	Glc	OH	OH	<i>Digitalis ferruginea</i>	—	113
159	Fuhsioside	H	H	H	PT	OH	OH	<i>Veronica fuhsii</i>	—	114
160	Plantalloside	H	Allo	Caff	H	OH	OH	<i>Plantago myosuroides</i>	—	115
161	Lysionotoside.	Rha	Api	Caff	H	OH	OH	<i>Lysionotus pauciflorus</i>	—	116
162	Hattushoside	5-O-Syringoyl-Api	H	H	H	OH	OH	<i>Phlomis pungens</i>	—	117
163	Artselaeroside A	H	Xyl	H	H	H	H	<i>Pedicularis artselaeri</i>	—	118
164	Artselaeroside B	H	Glc	Feru	Rha	OH	OCH ₃	<i>Pedicularis artselaeri</i>	—	118
165	Scroside A	H	Glc'(1 $\rightarrow$ 2)Glc	H	Feru	OH	OCH ₃	<i>Picrorhiza thizoma</i>	—	119
166	Scroside B	H	Glc	H	Feru	OH	OCH ₃	<i>Picrorhiza thizoma</i>	—	119
167	Scroside C	H	Glc'(1 $\rightarrow$ 2)Glc	Feru	H	OH	OCH ₃	<i>Picrorhiza thizoma</i>	—	119
168	Nyctoside A	Xyl	H	Caff	H	OH	OH	<i>Nyctanthes arbor-tristis</i>	—	120

Table III. PhGs with substituent at C-7

No	Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	Source	Biological Activity	Ref.
169	Cistantubulosides C1/C2	H	Rha	Caff	Glc	α/β -OH	OH	OH	<i>Cistanche tubulosa</i>	—	8
170	Lamiusides D	H	Gal(1→2)Rha	Caff	H	OCH ₃	OH	OH	<i>Lamium purpureum</i>	Radical scavenging activity	10
171	Rossicaside F	H	Glc(1→4)Rha	Caff	H	OCH ₂ CH ₃	OH	OH	<i>Boschniakia rossica</i>	—	121
172	Ilicifolioside A	H	Rha	Caff	H	OCH ₂ CH ₃	OH	OH	<i>Acanthus ilicifolius</i>	—	122
173	1'-(4-Hydroxyphenyl)ethane-1',2'-diol 2'-O- β -D-apiofuranosyl-(1→6)- β -D-glucopyranoside	H	H	H	Api	OH	H	OH	<i>Coriandrum sativum</i>	—	123
174	Wedelosin	H	Api(1→4)Rha	Caff	H	OH	OH	OH	<i>Wedelia chinensis</i>	Immuno-regulatory activity	124
175	Suspensaside B	H	H	Caff	Rha	O(CH ₂) ₃ CH ₃	OH	OH	<i>Forsythia suspensa</i>	—	125

Fig. (1). PhGs with 1,4-dioxane

176 Cuneatasides A [85]

177 Cuneatasides B [85]

178 3'''-O-Methyl crenatoside [24, 26, 126]

179 Suspensaside A [125]

180 Isocrenatoside [127]

Fig. (2). PhGs with a secoiridoid moiety

181 Isooleoacteoside [128]

182 Safghanoside E [129]

183 Safghanoside F [129]

184 (8Z)-Nüzhenide [130]

185 Desrhamnosyloleoacteoside [131]

186 Specneuzhenide [132]

Fig. (3). PhGs with glucose at the 4-hydroxyl of the phenylethyl moiety

187 6''-O- β -D-Glucopyranosyloleuropein [133]

188 Neopolyanoside [134]

189 (1,2-Dihydroxyethyl)-2-methoxyphenyl
1-O- β -D-[5-O-(3,4-dimethoxybenzoyl)]
-apiofuranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside [83]

Fig. (4). PhG with core sugar other than glucose

190 3,4-Dihydroxyphenethoxy-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 3)- β -D-(2-*O*-acetyl-4-*O*-caffeoyl)-galactopyranoside [135]

Fig. (5). Compounds with structural features that are not common to PhGs

191 Dopao β -D-2,3-diketoglucopyranoside [136]

192 Dopao β -D-2-ketoglucopyranoside [136]

193 (1'*R*)-1'-(3,4-Dimethoxyphenyl)ethane-1',2'-diol 1'-*O*- β -D-glucopyranoside [137]

194 Ternstrosides F [79]

glucose attached to the phenolic 4-hydroxyl in the phenylethyl moiety (Fig. (3)) [133, 134, 83]. Similar to **(182)**, secoiridoid is connected to C-8 of the aglycone via ester linkage in both compounds **(187)** and **(188)**. Compound **(190)** is an example of PhGs that do not have glucose as their core sugar (Fig. (4)) [135]. Isolated from *Brandisia hancei*, **(190)** has galactopyranose instead of β -glucopyranose in its molecule. Fig. (5) shows compounds with structural features that are not common to PhGs. For example, **(191)** and **(192)** from *Chelone oblique* have the rarely occurring dopaol 2,3-diketo and 2-ketoglycosides [136]. **(193)** forms glycosidic linkage at C-7 rather than C-8 in its phenylethanol moiety [137] while ternstrosides F (**194**) from *Ternstroemia japonica* is one of the few PhGs that have C-6 hydroxyl [79].

3. CHEMOTAXONOMY

As a major group of secondary metabolites produced by plants, PhGs has played an important role in plant chemotaxonomy studies. For example, the presence of acteoside in *Byblis liniflora* (Byblidaceae) plantlets has substantially supported the placement of Byblidaceae in the order Scrophulariales and subclass Asteridae [138]. Given the caffeic acid moiety in its molecule, acteoside is also of chemotaxonomical importance for ajugoid Labiatae [139]. Another example is 2',6''-O-diacetylplantamajoside that was initially isolated from genus *Hemiphragma* and later used as a key chemotaxonomic marker to reveal the relationship between genera *Hemiphragma* and *Wulfenia* [140]. Furthermore, a qualitative and quantitative study on PhGs in the methanol extracts of five species from genus *Phlomis* (Lamiaceae), including *Phlomis nissolii*, *P. leucophracta*, *P. bruguieri*, *P. russeliana* and *P. kurdica*, demonstrated that variations in the content of PhGs can be used for chemotaxonomical study within the same genus [141]. Other studies have also confirmed the utilization of PhGs as taxonomic markers of genus *Orobancha* [142],

Sibthorpia, and *Ellisiophyllum* (Plantaginaceae) [143]. Findings in chemotaxonomy based on PhGs are expected to provide a valuable measure for chemists to source rare PhGs from related species or genera.

4. BIOTRANSFORMATIONS OF PhGs

Biotransformations using cultures of roots or other parts of a plant have been performed in a number of studies to selectively enhance the production of specific PhGs. For example, Wysokinska *et al.* reported that the production of total acteoside and martynoside (**74**) in root cultures of *Catalpa ovata* could be increased significantly comparing to that in the intact plant grown in a greenhouse [144]. In a previous study, a large amount of PhGs (up to 16% dry weight) was isolated from cell suspension cultures of *Syringa vulgaris* L. (Oleaceae) with acteoside as the main component of the hydroxyphenylethanol glycoside fraction [145]. Similar results (1.78-10.43% of dry weight) were obtained when *Plantago lanceolata* leaves were used [94]. Moreover, Skrzypek *et al.* reported that the biomass of *cis*- and *trans*-acteoside, leucosceptoside A, and martynoside (**74**) could be maximized in the cell suspension cultures of *Penstemon serrulatus* after 12-days' of growth [146]. Furthermore, studies by Guo *et al.* showed that the amounts of echinacoside, acteoside, and 2'-acetylacteoside in salt brine *Cistanche salsa* callus are higher than those in the intact plant, indicating that the salt brine *Cistanche salsa* callus can be used in place of the naturally-grown plant to produce the required PhGs [147]. The study also suggested that by optimizing cultivation conditions such as carbon source, temperature, and exposure to light, one can selectively enhance the production of specific PhGs of interest, particularly for those that are produced at a minimal amount in nature [147].

5. BIOLOGICAL ACTIVITIES OF PhGs

In the past decades, a large number of PhGs have been isolated from different plants, many of which showed a variety of pharmacological activities including neuroprotective, antioxidant and radical scavenging, immunoregulating, antitumor, antiviral, antibacterial, hepatoprotective, anti-inflammatory, and analgesic effects. The mechanisms of action and structure-activity relationships (SAR) of some PhGs have also been explored. Although these studies have mostly focused on PhGs identified in the early years, they serve as invaluable clues for exploring the therapeutic potentials of the recently discovered PhGs.

5.1 ANTIOXIDATIVE AND FREE RADICAL SCAVENGING CAPABILITIES

Overproduced free radicals or a weakened natural antioxidant system can often lead to oxidative stress that may eventually result in oxidative injury and diseases. It has been widely recognized nowadays that lowering oxidative stress can provide clinical benefits on a variety of pathological conditions such as cardiovascular diseases, retinal ischemia, AIDs, and neurodegenerative diseases such as stroke, Parkinson's, and Alzheimer's diseases. Antioxidant treatment has thus been regarded as a viable therapy to alleviate the oxidative injury in these disorders. As a group of naturally occurring polyphenols, PhG compounds (as well as PhG extracts) have been studied extensively for their antioxidative activities in recent years. Studies have indeed shown that the antioxidative properties of PhGs underly many of the other biological activities observed for these compounds.

PhG extracts of a number of herbs such as *Plantago major* [148], *Wulfenia carinthiaca* [106], and *Forsythia suspense* [149] have been reported to possess remarkable antioxidative effects as assayed by Briggs-Rauscher (BR) reaction or chemiluminescent and nitroblue tetrazolium methods. A large number of PhG compounds also exhibit antioxidative capabilities. For example, the radical scavenging effect of acteoside has been evaluated in

a number of studies [150-152]. The study by Nektarios *et al.* demonstrated that the 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging capabilities of acteoside are comparable to that of butylated hydroxytoluene and α -tocopherol, indicating the potential of using acteoside as a natural protective agent against oxidative rancidity. Neonuezhenide from the fruits of *Ligustrum lucidum* [153], 2'-acetylacteoside, poliumoside, and brandioside from *Brandisia hancei* [150], have strong antioxidant effects against hemolysis of red blood cells induced by free radicals. Plantamajoside, 2'-O-acetylplantamajoside (**149**) and 2',6''-O-diacetylplantamajoside (**150**) from *Wulfenia carinthiaca* exhibit high antioxidant activities in BR reaction [106] while cistanosides have antioxidative and lipoxygenase-inhibiting activities *in vitro* [154]. Jionoside D from *Clerodendron trichotomum* was found to protect the viability of Chinese hamster lung fibroblast (V79-4) cells exposed to H₂O₂ presumably due to its radical scavenging property [155]. Moreover, Silva *et al.* has attributed the antioxidant activity of olive seed extracts mainly to nuzhenide, a secoiridoid PhG [156].

Oxidation of human low-density lipoproteins (LDL) is considered to be a key step during the progression and development of atherosclerosis [157] and many PhGs have thus been evaluated for their therapeutic potential in this area. Chen *et al.* [158] observed that the crude glycoside fraction of bitter tea (*Ligustrum pedunculare*) markedly protected human LDL from oxidation. Further column chromatography led to the identification of three PhGs, of which two (i.e., lipedoside A-I and lipedoside A-II) protect human LDL from Cu²⁺-mediated oxidation and have scavenging effect on DPPH free radical comparable to that of α -tocopherol [158]. Acteoside, ligupurpurosides A and B from *Ligustrum purpurascens* have also been reported to inhibit microsome lipid oxidation in malondialdehyde test and increased the lag-time of LDL oxidation [159]. Moreover, seven PhGs including caerulescenoside (**33**), 3'-methyl crenatoside, acteoside, isoacteoside,

campneoside II, crenatoside and desrhamnosyl acteoside from the whole plant of *Orobanche caerulescens* are found to suppress conjugated diene formation with higher potency than resveratrol, a natural phenolic antioxidant isolated from grape [26]. Interestingly, some of the PhGs are found to inhibit iron-dependent lipid peroxidation through chelation. An example is the PhGs from *Pedicularis striata* that form sufficiently stable PhGs-Fe²⁺ chelates through phenolic hydroxyl groups under physiological conditions [160]. On the contrary, PhGs extracted from *Ballota nigra* (e.g., verbascoside, forsythoside B, arenarioside, and ballotetroside (**95**)) inhibit Cu²⁺-induced LDL peroxidation without involving a metal-chelating mechanism and their effectiveness was comparable to that of quercetin [69]. PhGs from the aerial parts of *Marrubium vulgare* are found to inhibit copper (Cu²⁺)- and 2,2'-azobis(2-amidinopropane) dihydrochloride-induced LDL oxidation while preserving the morphological aspects of bovine aortic endothelial cells when incubated with minimally oxidized LDL [161].

In some diseases such as cancer and aging, DNA damage induced by oxygen radicals has often been regarded as a causative event. Thus the search for effective radical scavengers prior to DNA damage or agents that can repair the damaged DNA is crucial. A number of studies have shown that PhGs can play a protective role in DNA damage [162-165]. Li *et al.* suggested that acteoside and pedicularioside A can suppress the formation of thymine lesion and are thus potential radioprotectors and anticarcinogens. Repair effects based on electron transfer between the thymine radical anion and PhGs have also been observed for six PhGs from *Pedicularis* species [166]. Using the pulse radiolytic technique, Huang *et al.* further demonstrated the repair activities and the reaction mechanisms of acteoside and cistanoside C toward the oxidizing hydroxyl radical adduct of poly G [167]. Likewise, the antimutagenic activities of lavandulifolioside, acteoside, leucosceptoside A and martynoside (**74**) from *Stachys macrantha* have been investigated in

human lymphocytes by single cell gel electrophoresis or 'comet' assay and the data suggest that the PhGs possess protective effects on DNA damage induced by mitomycin C [52]. Studies by Shi *et al.* further demonstrated that PhGs such as acteoside, angoroside, cistanoside C and pedicularioside A, or their derivatives can repair 2'-deoxyadenosine-5'-monophosphate (dAMP), 2'-deoxyguanosine 5'-monophosphate (dGMP) hydroxyl adducts and TMP radical anions, indicating that PhGs can repair DNA damage in all four structural levels and even DNA fragments [168-172]. More interestingly, the PhGs are found to complete the repair in a time scale of microseconds and may prevent the damaged DNA from being transferred to cells of the next generation [172]. Further studies on this repair mechanism will evidently provide a useful tool to prevent and/or intervene in free radical-related diseases. Other examples of antioxidative PhGs include those from *Phlomis syriaca* and *Phlomis viscose* [173, 174], *Phlomis samia* or *Phlomis monocephala* [175], *Verbascum salviifolium* [176], *Pithecoctenium crucigerum* [177], and *Scutellaria galericulata* [178].

A large number of SAR studies have demonstrated that the phenolic hydroxyls play an important role in the antioxidative activity of PhGs [179-182]. For example, Shi *et al.* suggested that both the number and position of the phenolic hydroxyls could significantly affect the free radical scavenging effects of PhGs [183]. In a later study, Wright *et al.* utilized a theoretical method to correlate the calculated bond dissociation enthalpies of phenolic antioxidants with their free radical scavenging capabilities. The result suggested that strategic placing of the phenolic hydroxyls is of much greater importance than the number of such groups in determining the antioxidant capabilities of the molecule [184]. Meanwhile, studies have shown that other parts of the PhG molecule will also affect the activity. For example, a study on salidroside and its derivatives showed that the length of methylene-chain connected to the benzene ring and the type of sugar connected to the

aglycon moiety are major factors affecting the overall activity [185]. Moreover, Okawa *et al.* compared the activity of acteoside, ligupurpurosides A, B, C and D, and their results showed that PhGs with caffeic acid esters (e.g., acteoside and ligupurpurosides A) are more potent than those with *p*-coumaric acid esters, indicating that the type of phenylpropanoid acids also affects the activity [186].

5.2 NEURO-RELATED ACTIVITIES

Given their antioxidative properties, many PhGs have been evaluated as potential neuro-protective agents. For instance, campneoside II, a compound from *Cistanche tubulosa*, was found to inhibit neurotoxin 1-methyl-4-phenylpyridinium ion (MPP⁺)-induced apoptosis and DNA fragmentation in neurons [187]. Using the MTT assay, osmanthuside B and osmanthuside D were found to have significant neuroprotective activities against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in human neuroblastoma SH-SY5Y cells [188]. Lu *et al.* reported that PhGs including acteoside, leucosceptoside B, pedicularioside A, arenarioside, and buddleoside A (**25**) could improve cell viability and prevent cell death induced by MPP⁺ in primary cultured mesencephalic neurons [19]. A study on ten PhGs including forsythoside B, acteoside, 2'-acetylacteoside, poliumoside, brandioside, echinacoside, isoacteoside, cistanoside H and *E*-tubuloside and *Z*-tubuloside E (**23**) isolated from *Callicarpa dichotoma* raeuschel (Verbenaceae) has shown that these compounds possess significant neuroprotective activities against glutamate-induced toxicity in primary cultures of rat cortical neurons at concentrations from 0.1 to 1.0 μ M [17]. Moreover, tubuloside B isolated from *Cistanche salsa* can markedly attenuate MPP⁺-induced cytotoxicity, DNA fragmentation, and intracellular accumulation of reactive oxygen species (ROS) in rat PC12 pheochromocytomas. Evidently, the neuroprotective

action of tubuloside B is mediated through several pathways, independently or synergistically. In addition to its antioxidative properties [189], tubuloside B may counteract the toxicity of MPP⁺ by inhibiting the opening of mitochondrial permeability transition pore [190]. The compound has also been reported to antagonize TNF α -induced apoptosis in SH-SY5Y cells, suggesting that it may have therapeutic potential in the prevention and treatment of neurodegenerative diseases such as Parkinson's disease [191]. A SAR study by Kim *et al.* suggested that the α,β -unsaturated ester moiety and the *p*-methoxy group in the PhGs play vital roles in PhGs' neuroprotective activity [192]. In addition to neuroprotective activities, neurosedative effects have also been reported for PhGs such as acteoside, forsythoside B and arenarioside [193].

5.3 CYTOTOXIC AND ANTIPROLIFERATIVE EFFECTS

Acteoside has been reported to have moderate cytotoxic activity against normal mouse NIH3T3 fibroblast cells and the virally transformed mouse fibroblast cells (KA3IT) [194]. Moreover, several types of cancer cells are sensitive to the cytotoxic actions of caffeic acid-containing PhGs such as angoroside A, angoroside B, angoroside C, and poliumoside [195]. Further studies on SAR indicated that the *o*-dihydroxyl aromatic system within the molecule is necessary for these PhGs' cytotoxic and cytostatic activities [195]. In another study by Iida *et al.*, poliumoside showed high inhibitory activity with IC₅₀ values ranging from 9 – 42 μ M against DNA polymerases, indicating the potential of using this compound as a lead candidate for the development of antitumor agent targeting DNA polymerases and/or HIV-1 reverse transcriptase [196].

The effect of ester-forming phenylpropanoic acid (e.g., caffeic acid and ferulic acid) and the substituents on the phenethyl moiety (e.g., 3,4-dihydroxyphenethyl or 3-hydroxy-4-methoxyphenethyl) of PhGs on their antiproliferative activities have been

examined in a number of SAR studies [41, 197, 198]. Experimental data showed that the PhGs' antiproliferative activity is largely dependent on the substituents on the phenethyl group, slightly influenced by those on the phenylpropanoic acid, and not affected by the structure of the sugar moiety. It has been suggested that the 3,4-dihydroxyphenethyl moiety is essential for a strong antiproliferative activity [41, 198]. A later study by Emika *et al.* further confirmed this observation. Sayaendoside (**151**) and phenethyl β -D-glucopyranoside from *Mikania hirsutissima* with a phenethyl instead of 3,4-dihydroxyphenethyl group lack significant antiproliferative activity on human peripheral blood mononuclear cells [108]

5.4 HEPATOPROTECTIVE AND ANALGESIC EFFECTS

CCl_4 -induced liver injury has been widely used as an animal model for radical-induced hepato-damage and its prevention [199]. Given their radical scavenging activities, many PhGs have been evaluated for their hepatoprotective effects. For example, acteoside, 2'-acetylacteoside, isoacteoside and tubuloside B exert hepatoprotective activity in both CCl_4 and D-galactosamine liver injury models [200]. They also prevent AST (aspartate aminotransferase D-galactosamine) release and alleviate CCl_4 -induced cytotoxicity more efficiently than silymarin. The study further suggested that the protective effect may be largely due to the caffeoyl residue in the molecule [200]. However, other investigators argued that the phenylethyl moiety also played a key role given the fact that the radical scavenging activity of PhGs could come from aromatic hydroxyl groups in not only caffeoyl but also the phenylethyl moieties [201]. Moreover, acteoside can effectively inhibit TNF- α -mediated hepatic apoptosis and the subsequent necrosis and lethality in D-galactosamine-induced fulminant hepatitis in mice, possibly through an antioxidative mechanism [202].

Acteoside has also been found to have analgesic activities in a number of studies [203, 204]. For example, Nakamura *et al.* reported that acteoside exerts analgesic effect on acetic acid-induced writhing and tail pressure pain in mouse models at oral dosages of 300 mg/kg and 100 mg/kg, respectively [204]. SAR studies showed that the lack of hydroxyl groups in the aglycone or the removal of caffeoyl and phenethyl moieties (e.g., cistanoids F and decaffeoyl acteoside) will attenuate the analgesic activity. Furthermore, the esterification position of caffeoyl moiety may also affect the activity [204].

5.5 ANTIVIRAL, ANTIBACTERIAL, AND ANTI-PROTOZOAL PROPERTIES

Antiviral, anti-HIV-1 activities in particular, have been reported for a number of PhGs. For example, acteoside and its derivatives can markedly inhibit HIV type-1 reverse transcriptase (HIV-1 RT) *in vitro* [205]. Acteoside and isoacteoside possess potent inhibitory activities against HIV-1 integrase with IC₅₀ values of 7.8 and 13.7 μ M, respectively [206], while calceolarioside B has moderate binding affinity for HIV gp41 [207]. Moreover, inhibitory effects on other viruses have also been reported for PhGs. Acteoside has been shown to inhibit vesicular stomatitis virus [208] while neonuezhenide has varying effects on herpes simplex type 1, influenza type A, respiratory syncytial, and parainfluenza type 3 virus [209].

Antibacterial and antimicrobial activity is another major biological property observed for PhGs. Leucosceptoside A from *Leonurus persicus* possesses moderate antibacterial activity against *Staphylococcus epidermidis* [210] while acteoside, forsythoside B, and arenarioside exhibit moderate antimicrobial effects against *Proteus mirabilis* and *Staphylococcus aureus* [211]. More importantly, arenarioside's inhibitory effect on methicillin-resistant *S. aureus* strain can provide a useful tool for the treatment of nosocomial pathogens in hospitals [211]. Other examples of PhGs as antimicrobial agents

include calceolarioside B, martynoside (**74**) [53], crassifolioside [212], and songaroside A [213]. Although no systematic SAR studies have been performed with regard to the antibacterial activities of PhGs, Prusky *et al.* suggested that, similar to the flavonoids, the antifungal/antimicrobial effect of PhGs may be largely due to the presence of phenolic hydroxyls that have high affinity for proteins [214].

In vitro antiprotozoal activity has also been reported for PhGs. PhGs such as acteoside, isoacteoside, forsythoside B, echinacoside, glucopyranosyl-(1→6)-martynoside, integrifolioside B, and angoroside C appear to possess pronounced effect against *Leishmania donovani* [215, 216]. Except for integrifolioside B, the other six PhGs also showed trypanocidal activity against *trypanosoma brucei rhodesiense* while isoacteoside, forsythoside B, and echinacoside were the most potent with IC₅₀ values at low µg/ml range [215, 216].

5.6 ANTI-INFLAMMATORY AND IMMUNOMODULATING ACTIVITIES

Different inflammation models have been used to characterize anti-inflammatory properties of PhGs. Angoroside A, angoroside C, angoroside D (**65**), acteoside, and isoacteoside from *Scrophularia scorodonia* have been evaluated as potential inhibitors of macrophage functions involved in the inflammatory process and the results suggested that the PhGs are indeed the active principles for the overall anti-inflammatory effect of *S. scorodonia*. [45]. Carrageenan-induced mouse paw edema test has been employed to identify PhGs from *Sideritis lycia* as potential anti-inflammatory agents with less side effects such as gastric ulceration [217]. Lin *et al.* reported that acteoside, crenatoside, and rossicaside B could inhibit ROS production (likely through modulation of NADPH oxidase activity and/or the radical scavenging effect) and β2 integrin expression in leukocytes, indicating that these PhGs can serve as potential anti-inflammatory agents during oxidative

stress [218].

Moreover, purpureaside A from the leaves of *Digitalis purpurea* was found to inhibit lipopolysaccharide (LPS)-induced nitric oxide synthase (iNOS) expression in macrophages by suppressing activator protein-1 but not nuclear factor- κ B (NF- κ B) [219]. Seven PhGs from the stems of *Cistanche deserticola* were found to reduce or inhibit nitrite accumulation in LPS-stimulated J774.1 cells or mouse peritoneal exudate macrophages [220]. It has been suggested that the anti-inflammatory effects of the tested PhGs may be due to their nitrite radical-scavenging activity. The study by Sahpaz *et al.* revealed that acteoside, forsythoside B, arenarioside, and ballotetroside (**95**) from *Marrubium vulgare* possess inhibitory activity toward the Cox-2 enzyme [70]. More interestingly, three of the tested PhGs, including acteoside, forsythoside B, and arenarioside exhibit higher inhibitory potencies on Cox-2 than on Cox-1. Since side effects resulting from non-selective Cox-1 inhibition have often been observed for non-steroidal anti-inflammatory drugs in the market, the selectivity of these PhGs may be of great value for the development of an effective anti-inflammatory agent.

Immunomodulating effects have also been reported for PhGs. Using [3 H]TdR target release assay, Cai *et al.* demonstrated that *p*-hydroxyphenethyl- α -D-glucoside from the fruits of *Ligustrum lucidum* can significantly increase the cytotoxicity of natural killer (NK) cells *in vitro* and protect NK activity from inhibition caused by cyclophosphamide [221]. Moreover, cistanosides have been shown to improve the phagocytotic index of macrophages and increase the weight of immune organs in mice [157]. Immuno-enhancing effect has also been reported for forsythoside A by Liu *et al.* as the compound dose-dependently augments the proliferation of mouse splenic lymphocytes activated by concanavalin A [222].

5.7 EFFECTS ON THE CARDIOVASCULAR SYSTEM

Many PhGs have been evaluated for their beneficial effects on the cardiovascular system. Acteoside, leucosceptoside A, martynoside (**74**), isoacteoside, and isomartynoside were found to remarkably inhibit angiotensin converting enzyme activities [54]. It was thus suggested that the antihypertensive effect of their source herb, *Clerodendron trichotomum*, may be attributed to the presence of these PhGs [54]. Significant negative chronotropism, prolongation of the P-Q, Q-T intervals and QRS complex, and decrease of blood pressure have been observed for lavandulifolioside, making the compound a potential antihypertensive agent [223]. Plantaionoside D inhibits adriamycin-induced apoptosis in H9C2 cardiac muscle cells via inhibition of ROS generation and NF- κ B activation. The compound can thus be a potential agent that protects cardiotoxicity in adriamycin-exposed patients [224]. Likewise, forsythiaside from the fruits of *Forsythia suspense* exerts slow relaxation activity against norepinephrine (NE)-induced vasocontraction of rat aorta. The inhibition is likely due to a decrease in calcium influx from the extracellular space caused by NE [225]. The compound also inhibits the activity of porcine pancreatic elastase [226]. Moreover, forsythoside B and alyssonoside can counteract the free radical-induced inhibition of endothelium-dependent relaxation in response to acetylcholine [227]. This protective effect can be mainly attributed to the free radical scavenging property of the PhGs. Furthermore, the inhibition of copper-oxidized LDL-induced endothelin-1 liberation by acteoside, forsythoside B, arenarioside, and ballotetroside (**95**) indicates that these PhGs may be potential therapeutic tools for controlling atherosclerosis [71]. In another study by He *et al.*, acteoside, 2'-acetylacteoside, poliumoside, and brandioside from *Brandisia hancei* showed antiproliferative activity on cultured A7r5 rat aortic smooth muscle cells, suggesting that the PhGs may have beneficial effects on arteriosclerosis [228].

5.8 MISCELLANEOUS ACTIVITIES

Various other biological properties have also been reported for PhGs. These include inhibition on enzymes of the arachidonate cascade in calcium-stimulated mouse peritoneal macrophages and human platelets and suppression on the release of prostaglandin E₂ and production of thromboxane B₂ by salidroside [229]; decrease of uric acid formation through inhibiting xanthine oxidase, a key enzyme involved in the hyperuricemia-related disorders by isoacteoside [230]; inhibition on the germination of dicotyledons *Lactuca sativa* and *Raphanus sativus* but stimulation on that of the monocotyledon *Allium cepa* by 1-*O*- β -D-glucopyranosyl-2-(3-hydroxyphenyl)-ethanol [231]. Moreover, some PhGs are known to affect the scent formation in flowers [232]. An example is 2-phenylethyl β -D-glucopyranoside that has been used as a fragrance enhancer for cut flowers [233].

6. CONCLUSION

The polyphenolic structural feature and the resulting diverse biological and pharmacological properties of the PhGs are particularly attractive to those engaged in drug discovery. Concerted efforts in the past decade have yielded a large panel of PhGs whose biological functions have yet to be fully explored. Nevertheless, their pharmacological potentials can be gleaned from known PhGs. As a group of naturally-occurring non-enzymatic antioxidants, PhGs have potential therapeutic values in the treatment of a wide range of oxidative-stress-mediated pathological conditions such as neurodegenerative, cardiovascular, and inflammatory diseases. Full exploitation of the therapeutic potentials of PhGs awaits the identification of more novel compounds in this structural class as well as the elucidation of their SAR trend.

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ABBREVIATIONS

PhGs	= Phenylethanoid glycosides
BR	= Briggs-Rauscher
SAR	= Structure-activity relationships
DPPH	= 1,1-diphenyl-2-picrylhydrazyl
LDL	= Low-density lipoproteins
MPP ⁺	= 1-Methyl-4-phenylpyridinium ion
MTT	= 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
ROS	= Reactive oxygen species
HIV	= Human immunodeficiency virus
LPS	= Lipopolysaccharide
iNOS	= Inducible nitric oxide synthase
Cox	= Cyclooxygenase
NE	= Norepinephrine

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