Phenylethanoid Glycosides: Research Advances in Their Phytochemistry, Pharmacological Activity and Pharmacokinetics

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Abstract: Phenylethanoid glycosides (PhGs) are widely distributed in traditional Chinese medicines as well as in other medicinal plants, and they were characterized by a phenethyl alcohol (C$_6$-C$_2$) moiety attached to a β-glucopyranose/β-allopyranose via a glycosidic bond. The outstanding activity of PhGs in diverse diseases proves their importance in medicinal chemistry research. This review summarizes new findings on PhGs over the past 10 years, concerning the new structures, their bioactivities, including neuroprotective, anti-inflammatory, antioxidant, antibacterial and antivirus, cytotoxic, immunomodulatory, and enzyme inhibitory effects, and pharmacokinetic properties.

Keywords: phenylethanoid glycosides; novel structures; bioactivity; pharmacokinetics

1. Introduction

Phenylethanoid glycosides (PhGs) are a class of water-soluble compounds widely distributed in traditional Chinese medicines (TCMs), as well as other medicinal plants. They have been detected in roots, stems, leaves, flowers, fruits and seeds without organ selectivity, while their concentrations in each organ may vary a lot [1,2]. As their names suggest, PhGs are characterized by a phenethyl alcohol (C$_6$-C$_2$) moiety attached to a β-glucopyranose/β-allopyranose via a glycosidic bond. The core structures are often abundantly decorated with substituents such as aromatic acids (e.g., caffeic acid, coumaric acid, cinnamic acid, ferulic acid, and isoferulic acid) and various saccharides (e.g., rhamnose, xylose, apiose, glucose, lyxose, allose and arabinose) through ester or glycosidic linkages, respectively. The outstanding activity of PhGs in diverse diseases proves their importance in medicinal chemistry research. Several reviews on PhGs regarding their isolation and purification, structure elucidation, chemotaxonomy and biotransformations, and pharmacological activities have been reported [3,4]. Recently, interest in PhGs has been growing, with a significantly increasing volume of literature describing PhGs’ novel structures, diverse bioactivities, and evident roles in the prevention and treatment of various human diseases as well as their pharmacokinetics having been reported. Such rich information prompted us to review papers on novel PhG structures, their pharmacological activities and pharmacokinetics published in the last decade.

2. Phytochemistry

Since a 2008 review [4], more than 100 new PhGs have been isolated and identified. Compared with the known PhGs reported in [4], some of the new ones differed in their core structures, while others differed in the number and/or position of the substituents. The new PhGs with a typical phenethyl alcohol (C$_6$-C$_2$) moiety attached to a β-glucopyranose/β-allopyranose are listed in Table 1.
Table 1. The new phenylethanoid glycosides with typical phenethyl alcohol moieties attached to a β-glucopyranose/β-allopyranose.

| Compound | Structure |
|----------|-----------|
| 1-51     | ![Structure 1-51](image1) |
| 65-102   | ![Structure 65-102](image2) |
| 52-64    | ![Structure 52-64](image3) |

**Sugars:**
- Glc = β-D-glucopyranose
- Ara = α-L-arabinopyranose
- Gal = β-D-galactopyranose
- Rha = α-L-rhamnopyranose
- All = β-D-allopyranose
- Xyl = β-D-xylopyranose
- Api = β-D-apiofuranose
- Lyx = α-L-lyxopyranose

**Acyl groups:**
- Coumaroyl
- Caffeoyl
- Feruloyl
- Vanilloyl
- Acetyl
- cis-Feruloyl
- cis-Coumaroyl
- cis-Caffeoyl
- Glycosmyl
- Syringoyl
| No. | Compounds | 
|-----|-----------|
| 1   | Acanmontanoside | OH OH H H H 4-O-Syringoyl-Rha Caffeoyl H Acanthus montanus | a
| 2   | Kansanoside A | H H H Gal H H Xyl Asclepias syriaca | a
| 3   | Bacomoside A | OH OH =O p-hydroxy-benzoyl H H H Bacopa monniera b
| 4   | Bacomoside B₁/B₂ | OH OCH₃ Caffeoyl H H H B. monniera Inhibitory effects on Aβ₄₂ aggregation [7]
| 5   | Himaloside A | OCH₃ OH Acetyl Glc[1→4]Rha Caffeoyl H Boschniakia himalaica Antibacterial activity [8]
| 6   | Himaloside B | OH OH H H H H cis-Caffeoyl B. himalaica Antibacterial activity [8]
| 7   | Himaloside C | OH OH H Acetyl 2,3,4-tri-O-Acetyl-Rha Coumaroyl Glc C. deserticola Anti-inflammatory activity [11]
| 8   | Cistanoside K | OH OH H H H H coumaroyl C. deserticola Anti-inflammatory activity [11]
| 9   | Cistanoside L | OH OH H H H H trans-cis-Coumaroyl Glc C. deserticola | a
| 10  | Cistanoside I | OH OH H H H H C. deserticola | a
| 11  | Cistanoside J | OH OH H H H H Coumaroyl C. deserticola | a
| 12  | Cistanoside K₁/K₂ | OH OH Acetyl Rha Caffeoyl H C. tubulosa | a
| 13  | Cistanoside K₃/K₄ | OH OH OCH₃ H H Rha Caffeoyl H C. tubulosa | a
| 14  | Cistanoside K₅/K₆ | OH OH Acetyl Rha Feruloyl H C. tubulosa | a
| 15  | Cistanoside K₇/K₈ | OH OH H Acetyl trans/cis-Coumaroyl Glc C. tubulosa | a
| 16  | Cistanoside L | OH OH H H H H Rha C. tubulosa | a
| 17  | Cistanoside M | OH OH H H H H Rha C. tubulosa | a
| 18  | Cistanoside N | OH OH H H H H Rha C. tubulosa | a
| 19  | Cistanoside O | OH OCH₃ H H H H Rha C. tubulosa | a
| 20  | 3,4-di-O-acetylmaurynoside | OCH₂OH OCH₃ H H H H 3,4-di-O-Acetyl-Rha Feruloyl H C. sinensis | a
| 21  | 7-(3-methoxyl-4-hydroxy-phenyl)-7-methoxyethyl-3α-L-rhamnopyranosyl-4'-(8E)-7-(4-hydroxy-phenyl)-8-propenoate | OCH₂OH OCH₃ H H Rha C. setosum Hepatoprotective effect [15]
| 22  | Purpureaside D | OH OH H H H H Feruloyl Rha Digitalis purpurea Antioxidant activity [17]
| 23  | Purpureaside E | OH OH H H H H Gla Feruloyl Rha D. purpurea Antioxidant activity [17]
| 24  | Forsythenside K | OH OH H H H H Coumaroyl Rha Forsythia suspensa Antiviral activity [18]

Table 1. Cont.
| No. | Compounds | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ | Source | Bioactivity | Reference |
|-----|-----------|----|----|----|----|----|----|--------|-------------|-----------|
| 26  | Lianqiaoxinside A | OH | OH | H  | H  | H  | Rha | F. suspensa | Antibacterial activity | [19] |
| 27  | 2-[(3,4-Dihydroxyphenyl)-2-oxo-ethyl]-O-α-L-haminoxyranosyl-(1→6)-(4-O-caffeoyl)β-D-glucopyranoside | OH | OH | H  | H  | H  | Caffeoyl | Rha | F. suspensa | . b | [20] |
| 28  | Forsythoside A | OH | H  | H  | H  | H  | 4-O-Glc-Caffeoyl | Rha | F. suspensa | . b | [20] |
| 29  | Isoforsythoside | OH | H  | Caffeoyl | H  | H  | Rha | F. suspensa | Antioxidant and antibacterial effects | [21] |
| 30  | Forsythoside H | OH | Caffeoyl | H  | H  | Rha | F. suspensa | . | [22] |
| 31  | Forsythoside I | OH | Caffeoyl | H  | H  | Rha | F. suspensa | . | [22] |
| 32  | Forsythoside J | OH | Caffeoyl | H  | H  | Xyl | F. suspensa | . | [22] |
| 33  | Calceolarioside A-2′-α-L-rhamnopyranoside | OH | H  | Rha | H  | Caffeoyl | H  | Frexenus mandshurica | . | [23] |
| 34  | 3′′-O-Methyllupaneoside I | OH | OCH₃ | H  | Rha | Fertuloyl | H  | Incarvillia compacta | Hepatoprotective and antioxidant effects | [24] |
| 35  | 6′-O-(4-O-caffeoyl)cylohexanacetyl)acteoside | OH | OCH₃ | H  | Rha | Caffeoyl | cis-1,4-Dihydroxy-cyclohexanacetyl | Jacaranda cana | Antioxidant capacity | [25] |
| 36  | 6′-O-(1-Hydroxy-4-oxo-cyclohexanacetyl)acteoside | OH | H  | Rha | Caffeoyl | 1-Hydroxy-4-oxo-cyclohexanacetyl | J. cana | Antioxidant capacity | [25] |
| 37  | Fucatoside A | OH | H  | Api | H  | Caffeoyl | H  | Lantana fasciculirta | . b | [24] |
| 38  | Fucatoside B | OH | H  | Xyl | Api | Caffeoyl | H  | L. fasciculrtat | . b | [24] |
| 39  | Fucatoside C | OH | H  | Api | Api | Caffeoyl | H  | L. fascicula | Anti-inflammatory effect | [26] |
| 40  | Raduloside | OH | H  | Api | Caffeoyl | Api(1→4)Xyl | L. radula | . b | [27] |
| 41  | Leonoside E | OH | H  | Arat(1→2)Rha | H  | H  | Leonurus japonicus | Hepatoprotective activity | [28] |
| 42  | Leonoside F | OH | H  | Rha | H  | Glc | L. japonicus | Hepatoprotective activity | [28] |
| 43  | 6′,(4-Hydroxyphenyl)ethyl-4-O-caffeoyl-O-[β-D-apiofuranosyl-(1→2)]β-D-glucopyranoside | H  | OH | H  | Api | H  | Caffeoyl | H  | Lepisorus contortus | Cytotoxicity | [29] |
| 44  | 6′,[(3,4-Dihydroxyphenyl)ethyl-4-O-caffeoyl-O-[β-D-apiofuranosyl-(1→2)]β-D-glucopyranoside | OH | H  | H  | H  | H  | Caffeoyl | L. contortus | Cytotoxicity | [29] |
| 45  | 6′,[(3,4-Dihydroxyphenyl)ethyl-4-O-caffeoyl-O-[β-D-apiofuranosyl-(1→2)]β-D-glucopyranoside | OH | H  | H  | Caffeoyl | H  | L. contortus | . b | [29] |
Table 1. Cont.

| No. | Compounds                                                                 | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ | R₇ | Source | Bioactivity | Reference |
|-----|---------------------------------------------------------------------------|----|----|----|----|----|----|----|--------|-------------|-----------|
| 46  | β-(3,4-Dihydroxyphenyl)ethyl-3-[(E)-3,4-di-O-[β-D-apiofuranosyl]-(1→2)[β-D-glucopyranosyl| OH | OH | H  | Api| Caffeoyl| H  | H  | L. contortus| Cytotoxicity| [29]     |
| 47  | β-(4-Hydroxyphenyl)ethyl-3-[(E)-3,4-di-O-[β-D-apiofuranosyl]-(1→2)[β-D-glucopyranoside| H  | OH | H  | Api| Caffeoyl| H  | H  | L. contortus|             | [29]     |
| 48  | Lagotiside A OH OH H H 4-O-CH₃-Xyl Caffeoyl H Lagetis brevituba |     |     |     |     |     |     |     |        |             | [30]     |
| 49  | Yulanoside A OH OH H Rha Rha Caffeoyl Glc(1→4)Glc Magnolia salicifolia |     |     |     |     |     |     |     |        |             | [31]     |
| 50  | Yulanoside B OH OH H H Rha Caffeoyl Glc(1→4)Glc M. salicifolia |     |     |     |     |     |     |     |        |             | [31]     |
| 51  | 2'-Rhamnoechinacoside OH OH H Rha Rha Caffeoyl Glc M. salicifolia |     |     |     |     |     |     |     |        | a-Glucosidase inhibitory effect and cytotoxicity | [31,32]  |
| 52  | Magnoloside D OH OH H Rha H H Caffeoyl M. officinalis |     |     |     |     |     |     |     |        | Antioxidant activity, a-glucosidase inhibitory effect and cytotoxicity | [32,33]  |
| 53  | Magnoloside E OH OH H Api H H Caffeoyl M. officinalis |     |     |     |     |     |     |     |        | Antioxidant activity, a-glucosidase inhibitory effect and cytotoxicity | [32,33]  |
| 54  | Magnoloside F OH OH H Rha H Caffeoyl Glc M. officinalis |     |     |     |     |     |     |     |        | a-Glucosidase inhibitory effect and cytotoxicity | [32]     |
| 55  | Magnoloside G OH OH H Api H Caffeoyl Glc M. officinalis |     |     |     |     |     |     |     |        | Cytotoxicity | [32]     |
| 56  | Magnoloside H OH OH H Api Caffeoyl H Glc M. officinalis |     |     |     |     |     |     |     |        | a-Glucosidase inhibitory effect and cytotoxicity | [32]     |
| 57  | Magnoloside I OH OH H Api Cumaroyl H Glc M. officinalis |     |     |     |     |     |     |     |        | a-Glucosidase inhibitory effect | [32]     |
| 58  | Magnoloside J OH OCH₃ H Rha Caffeoyl H Glc M. officinalis |     |     |     |     |     |     |     |        | Cytotoxicity | [32]     |
| 59  | Magnoloside K OH OH H Rha Feruloyl H Glc M. officinalis |     |     |     |     |     |     |     |        | a-Glucosidase inhibitory effect and cytotoxicity | [32]     |
| 60  | Magnoloside L OH OH H Api Caffeoyl H H M. officinalis |     |     |     |     |     |     |     |        | Cytotoxicity | [32]     |
| 61  | Magnoloside M OH OH H Rha H Caffeoyl H M. officinalis |     |     |     |     |     |     |     |        |             | [32]     |
| 62  | Magnoloside N OH O-Glc H Rha Caffeoyl H Glc M. officinalis |     |     |     |     |     |     |     |        |             | [32]     |
| 63  | Magnoloside O OH OH H H H H Glc(1→4)Rha(1→4)-Syringoyl M. officinalis |     |     |     |     |     |     |     |        | Cytotoxicity | [32]     |
| 64  | Magnoloside P OH OH H H H H Glc(1→4)Rha(1→4)-Vanillyl M. officinalis |     |     |     |     |     |     |     |        | Cytotoxicity | [32]     |
| 65  | Savaside A OH OH OH Rha H H Caffeoyl Monochasma seriati |     |     |     |     |     |     |     |        | Anticomplement activity | [34]     |
| No. | No. | Compounds | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ | R₇ | Source | Bioactivity | Reference |
|-----|-----|-----------|-----|-----|-----|-----|-----|-----|-----|--------|-------------|-----------|
| 66  | 66  | Savaside B | OH  | OH  | OH  | H   | H   | Caffeoyl | H   | M. savatieri | Anticomplement activity | [34] |
| 67  | 67  | Savaside C | OH  | OH  | OH  | H   | H   | Feruloyl | H   | M. savatieri | Anticomplement activity | [34] |
| 68  | 68  | Savaside D | OH  | OH  | OH  | Rha | H   | H   | Coumaroyl | M. savatieri | Anticomplement activity | [34] |
| 69  | 69  | Savaside E | OH  | OH  | OH  | Rha | H   | H   | Feruloyl | M. savatieri | Anticomplement activity | [34] |
| 70  | 70  | Rashomoside A | OH  | OH  | H   | H   | Xyl | Caffeoyl | Glc | Meihana articulata | | [35] |
| 71  | 71  | Tazettoside D | H   | OCH₃ | H   | H   | H   | H   | Glc | Narcissus tazetta var. chinensis | Melanogenesis inhibitory activity | [36] |
| 72  | 72  | 3-Hydroxy-4-methoxy-β-phenylethoxy-O-[2,3-di-acetyl-α-L-rhamnopyranosyl(1→3)]4-O-cis-feruloyl-[β-D-apiofuranosyl(1→6)]-β-D-glucopyranoside | OH  | OCH₃ | H   | H   | H   | 2,3-di-O-Acetyl-Rha | cis-Feruloyl | Api Philmis umbrosa | Cytotoxic activity | [37] |
| 73  | 73  | 3’’’-Acetyl-O-betonyoside D | OH  | OCH₃ | H   | H   | H   | 3-O-Acetyl-Rha | Feruloyl | Api P. umbrosa | Cytotoxic activity | [38] |
| 74  | 74  | 2’’’’,3’’’-Diacetyl-O-betonyoside D | OH  | OCH₃ | H   | H   | H   | 2,3-di-O-Acetyl-Rha | Feruloyl | Api P. umbrosa | Cytotoxic activity | [38] |
| 75  | 75  | 3’’’’,4’’’-Diacetyl-O-betonyoside D | OH  | OCH₃ | H   | H   | H   | 3,4-di-O-Acetyl-Rha | Feruloyl | Api P. umbrosa | Cytotoxic activity | [38] |
| 76  | 76  | Stewartioside | OH  | OH  | H   | H   | Rha | Api(1→4)Rha | Caffeoyl | Rha Ph. steutartii | α-Glucosidase inhibitory activity | [39] |
| 77  | 77  | 3-(3-Hydroxy-4-methoxyphenyl) ethanol-1-O-[α-L-rhamnopyranosyl(1→3)]-β-D-glucopyranoside | OH  | OCH₃ | H   | H   | H   | H   | Plantago depressa | | - | [40] |
| 78  | 78  | 2-(3,4-Dihydroxyphenyl)ethanol 1-O-[α-L-rhamnopyranosyl(1→3)]-β-D-glucopyranoside | OH  | OH  | H   | H   | H   | All | H   | Caffeoyl | P. scutatic | Antioxidative effect | [41] |
| 79  | 79  | Isocassifolioside | OH  | OH  | H   | Rha | Rha | H   | Caffeoyl | R. uliginosa | | | [42] |
| 80  | 80  | Lavandulifolioside B | OCH₃ | OH  | H   | H   | Ara(1→2)Rha | 4-O-CH₃-Feruloyl | H   | Stachys leucanthemifola | | | [43] |
| 81  | 81  | Poliumoside B | OH  | OH  | H   | H   | Ara(1→2)Rha | Caffeoyl | Rha Ph. pulvistem | Antioxidant activity | | | [44] |
| 82  | 82  | 1-(3,4-Dihydroxyphenethyl)-O-[α-L-rhamnopyranosyl(1→3)]-β-D-glucopyranoside | OH  | OH  | H   | H   | Lys(1→2)Rha | H   | Feruloyl | T. chamadris | Antioxidant activity | [45] |
| 83  | 83  | Chionoside A | OH  | OH  | H   | Ara | Glc | Feruloyl | H   | Veronica thomsonii | | | [46] |
| 84  | 84  | Chionoside B | OH  | OCH₃ | H   | Ara | Glc | Feruloyl | H   | V. thomsonii | | | [46] |
| 85  | 85  | Chionoside C | OH  | OH  | H   | Ara | 6-O-Feruloyl-Glc | Caffeoyl | Glc | V. thomsonii | | | [46] |
| 86  | 86  | Chionoside D | OH  | OH  | H   | Ara | Glc | Caffeoyl | Glc | V. thomsonii | | | [46] |
| 87  | 87  | Chionoside E | OH  | OH  | H   | Ara | Glc | Feruloyl | Glc | V. thomsonii | | | [46] |
| 88  | 88  | Chionoside F | OH  | OH  | H   | Ara | Glc | Caffeoyl | Rha | V. thomsonii | | | [46] |
| 89  | 89  | Chionoside G | OH  | OCH₃ | H   | Glc | Glc | Caffeoyl | H   | V. pulonarius | | | [46] |
Table 1. Cont.

| No. | Compounds          | R_1 | R_2   | R_3 | R_4 | R_5   | R_6 | R_7 | Source          | Bioactivity | Reference |
|-----|-------------------|-----|-------|-----|-----|-------|-----|-----|----------------|-------------|-----------|
| 90  | Chionoside I      | OH  | OCH_3 | H   | Glc | Glc   | Feruloyl | H   | V. thomsonii and V. pulvinaris | - | [46] |
| 91  | Isochionoside J    | OH  | OH    | H   | H   | Glc(1→2)Glc | H   | Caffeoyl | V. thomsonii | - | [46] |
| 92  | Isoaragoside       | OH  | OH    | H   | Ara | Glc   | H   | Caffeoyl | V. thomsonii | - | [46] |
| 93  | Isochionoside K    | OH  | OCH_3 | H   | Ara | Glc   | H   | Caffeoyl | V. thomsonii | - | [46] |
| 94  | Isochionoside A    | OH  | OH    | H   | Ara | Glc   | H   | Feruloyl | V. thomsonii | - | [46] |
| 95  | Isochionoside G    | OH  | OCH_3 | H   | Glc | Glc   | H   | Caffeoyl | V. pulvinaris | - | [46] |
| 96  | Isochionoside I    | OH  | OCH_3 | H   | Glc | Glc   | H   | Feruloyl | V. thomsonii and V. pulvinaris | - | [46] |
| 97  | Helioside A        | OH  | OH    | H   | Ara | Glc   | Caaffeoyl | Xyl | V. lavandula | - | [47] |
| 98  | Helioside B        | OH  | OH    | H   | Ara | 6-O-Caffeoyl-Glc | Caaffeoyl | Xyl | V. lavandula | - | [47] |
| 99  | Helioside C        | OH  | OH    | H   | Ara | Glc   | Feruloyl | Xyl | V. lavandula | - | [47] |
| 100 | Helioside D        | OH  | OH    | H   | Ara | 6-O-Coumaroyl-Glc | Caaffeoyl | H   | V. ruelli | - | [48] |
| 101 | Helioside E        | OH  | OH    | H   | Ara | 6-O-Caffeoyl-Glc | Caaffeoyl | H   | V. ruelli | - | [48] |
| 102 | Helioside F        | OH  | OH    | H   | Xyl | Glc   | Caaffeoyl | Glc | V. hulkmee | - | [48] |

* Not determined; † Show no activities at the given pharmacological models.
In the table references for the first reports on specific PhGs as new compounds are given, and the plant sources and biological activities reported for the specific PhGs are also included. Most of the isolated new PhGs were glucopyranosides, and the allopypranosides, which are rarely found in the plant kingdom, were mainly isolated from Magnolia officinalis [32]. Generally, glucose, galactose, xylose, apiose, arabinose and rhamnose were the most frequently occurring saccharides, while lyxose only appeared in compound 82 from Teucrium chamaedris [45]. Aside from the most frequently occurring substituents at C-3/4/7 of the phenylethanoid moiety, which were hydroxy and methoxy groups, a glucose moiety occurred at the C-4 of aglycone of compound 62 from M. officinalis [32]. Additionally, the most frequently occurring aromatic acids that form esters with the glucose/allose were caffeic, ferulic, coumaric, vanillic and syringic acids.

Figure 1 illustrates the new PhGs having varied core structures or special substituents. PhGs with a 7,2'-epoxy moiety are rare in the plant kingdom, e.g., compound 103 from Forsythia suspensa which is reported to possess antioxidant as well as antimicrobial activities [49], and compound 104 from Tarphochlamys affinis which was shown to have antioxidant as well as anti-HBV activities [50]. Compound 105 from Jacaranda mimosifolia with antioxidant activity is an example of a PhG with a substituent at C-8 [51]. Compound 106 with melanogenesis inhibitory activity as well as compounds 107 and 108 from Narcissus tazetta var. chinensis are examples of PhGs with substituents at C-2 [36]. Compounds 109 and 110 from F. suspensa are examples of PhGs with substituents at C-2 and C-5 of the phenylethyl moiety [20]. There were also adducts of other kinds of compound units fused to PhGs. Compounds 111–114 from F. suspensa with neuroprotective effects are four unusual adducts of a flavonoid unit fused to a phenylethanoid glycoside through a pyran ring or carbon-carbon bond [20]. Compounds 115 and 116 from Strobilanthes cusia are adducts of an indole alkaloid group fused to a phenylethanoid glycoside [52].

![Figure 1](image-url)
3. Pharmacological Activity

The pharmacological activities of the PhGs are discussed by two ways. The pharmacological activities of the new PhGs, mainly focused on the hepatoprotective, antioxidant activity, cytotoxicity, anti-inflammatory and \( \alpha \)-glucosidase inhibitory, were listed in Table 1, while the pharmacological activities of the old PhGs which are listed in Table 2 were introduced in the following.

Table 2. The old phenylethanoid glycosides whose pharmacological effects were reported after 2008.
Table 2. Cont.

| No. | Compounds                | R¹ | R² | R³ | R⁴  | R⁵ | R⁶ | R⁷ |
|-----|--------------------------|----|----|----|-----|----|----|----|
| 134 | Decaffeoylacteoside      | OH | OH | H  | H   | Rha| H  | H  |
| 135 | Teucrioside              | OH | OH | H  | H   | Lyx(1→2)Rha| Caffeoyl| H  |
| 136 | Lamiuside A              | OH | OH | H  | H   | Gal(1→2)Rha| Caffeoyl| H  |
| 137 | 2'-Acetyllacteoside      | OH | OH | Acetyl| H   | Rha| Caffeoyl| H  |
| 138 | Plantamajoside           | OH | OH | H  | H   | Glc| Caffeoyl| H  |
| 139 | Tubuloside B             | OH | OH | Acetyl| Rha| H  | Caffeoyl|    |
| 140 | Tyrosol galactoside      | H  | OH | H  | H   | H  | H  | H  |

3.1. Neuroprotective Effects

Parkinson’s disease is characterized by a selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and consequently a reduction in striatal dopamine levels [53]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to cause Parkinsonism in rodents and non-human primates [54,55]. It can cause a partial lesion of the substantia nigra and a significant reduction in striatal dopamine levels [56], and the toxicity of MPTP depends on its biotransformation to its active metabolite 1-methyl-4-phenylpyridinium (MPP⁺) [57]. The potential neuroprotective and behavioral rescue effects of echinacoside (117) were evaluated in a mouse model of MPTP-induced dopaminergic neuronal damage. In which, an HPLC analysis was conducted to monitor the changes in the levels of striatal dopamine and its metabolites. The results showed that the reductions in the levels of dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) were partially prevented by pre-treatment of 117 (20 mg/kg) (dopamine, 0.86 ± 0.05 ng/mg tissue, p < 0.01; DOPAC, 0.93 ± 0.06 ng/mg tissue, p < 0.05). Tyrosine hydroxylase is the rate-limiting enzyme in dopamine biosynthesis. Immunostaining of the substantia nigra using an anti-tyrosine hydroxylase antibody demonstrated pre-treatment of 117 (20 mg/kg) for 15 days significantly reduced MPTP-induced tyrosine hydroxylase-positive dopaminergic neuron loss (p < 0.05). In addition, the pre-treatment with 117 can significantly reduce caspase-3 and caspase-8 activation induced by MPP⁺ in cerebellar granule neurons, which was regarded to be a possible mechanism on neuroprotection of 117 [58].

Pedicularioside A (118), leucosceptoside A (119), isoacteoside (120), acteoside (121), and arenariside (122) were studied to assess their effects on MPP⁺-induced cell death in rat mesencephalic neurons [59]. Compound 118 had the greatest neuroprotective effect among the five tested compounds. The pre-treatment with 118 inhibited MPP⁺-induced loss and death of dopaminergic neurons, and the immunohistochemistry results indicated that 118 inhibited expression of caspase-3 gene and cleavage of poly (ADP-ribose) polymerase in cultures exposed to MPP⁺. All suggested that the inhibition of caspase-3 gene expression of 118 protected mesencephalic neurons from MPP⁺-induced cell death.

Considerable evidence supported that oxidative stress worked as a common pathogenetic mechanism in Alzheimer’s disease (AD) [60,61]. In AD, oxidative stress was suspected to be mainly generated by β-amyloid peptide (Aβ) [62], and heme oxygenase-1 (HO-1) was a crucial factor in the response to oxidative injury, protecting neurons against Aβ-induced injury. Wang studied the neuroprotective mechanisms of 121 against Aβ25-35-induced cell death in PC12 cells. It showed that 121 was an activator of NF-E2-related factor 2 (Nrf2) and inducer of HO-1 expression. Compound 121 attenuated Aβ25-35-induced neurotoxicity by induction of HO-1 via extracellular regulated kinase (ERK) and PI3K/Akt signaling [63]. Similarly, the neuroprotective effects of salidroside (123) following traumatic brain injury were mediated, at least in part, through activation of the PI3K/Akt signaling pathway [64]. In another study, the neuroprotective effect of 121 on Aβ25-35-induced neurotoxicity in SH-SY5Y cells was investigated. A 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl- tetrazolium bromide (MTT) reduction assay showed that 20 and 30 µg/mL of 121 significantly blocked cytotoxic effects of Aβ25-35 on cell viability and the result was also confirmed by calcein-AM staining assay through analysis of morphological nuclear changes and DNA fragmentation. Meanwhile, pretreatment with 20 µg/mL of 121 decreased the number of apoptotic cells and scavenged reactive oxygen species (ROS). The result indicated that 121 could protect SH-SY5Y cells against Aβ25-35-induced cell injury.
by attenuating ROS production and modulating apoptotic signal pathway through Bcl-2 family, cytochrome c, and caspase-3 [65]. Peng et al. [66] investigated the effects of 121 in improving learning and memory using a mouse model of senescence induced by a combination of D-galactose and AlCl₃. Compound 121 was administered intragastrically at doses of 30, 60 and 120 mg/kg/day for 30 days after AD was induced. The results showed that the latency of step down was shortened in AD model mice and the number of errors decreased after treatment with all doses of 121. Neurons and Nissl bodies in the hippocampus were increased significantly with higher doses (60 and 120 mg/kg/day) of 121. The content of nitric oxide (NO), the activity of nitric oxide synthase and the expression of caspase-3 protein were decreased by 120 mg/kg/day of 121 compared with that in the AD model group [66]. In a previous study, anti-amnesic activities of 121 using scopolamine-induced amnesic mice with both passive avoidance and Morris water maze test were examined. In both tests, the prolonged oral treatment of 121 (0.1 and 1.0 mg/kg body weight respectively for 10 days) significantly improved the memory deficits, while, the acute treatment of 121 (1.0 and 2.5 mg/kg body weight for 1 day) showed positive effect only in the passive avoidance test [67].

As reported, the anti-apoptotic action of 117 was partially dependent on its anti-oxidative effects [68,69]. Kuang’s experiment indicated that 117 increased cell viability and decreased the apoptotic ratio by reducing ROS generation in H₂O₂-injured rat PC12 cell. In addition, compound 117 prevented H₂O₂-induced increase of the Bax/Bcl-2 ratio by down-regulating Bax protein expression and up-regulating Bcl-2 protein expression. The result suggested that 117 showed significant neuroprotective effects on H₂O₂-injured PC12 cell through the mitochondrial apoptotic pathway [70]. Similarly, the antioxidant property and neuroprotective effects of isocampneoside II (131) were studied on H₂O₂-induced oxidative injury in PC12 cells. Compound 131 inhibited cell apoptosis by decreasing the level of superoxide anion radical, inhibiting Bax/Bcl-2 ratio, and attenuating the decrease of superoxide dismutase (SOD) and catalase activity [71].

3.2. Antioxidant Activity

ROS are inevitably generated during the normal metabolism of living organisms, but excessive production leads to oxidative stress damage to cellular structures [72]. Oxidative stress is associated with the etiology of a wide range of chronic and acute disease such as malignant tumors, inflammation, cataracts, Parkinson’s and Alzheimer’s disease, hypertension, diabetes, atherosclerosis, cardiovascular diseases, cell death, and some immune disorders and the aging process [72,73]. PhGs have been reported to possess antioxidant properties. Forsythoside B (125), leucosceptoside B (126) and 121 were isolated from Verbascum xanthophoeniceum and exhibited potent antioxidant activities in 2, 2'-diphenyl-1-picrylhydrazyl (DPPH), oxygen radical absorbance capacity (ORAC₅₅), hydroxyl radical averting capacity (HORAC₅₅), ferric-reducing antioxidant power (FRAP) and superoxide anion radical scavenging assays [1]. In another study, Harput et al. reported calceorioside A (127) as well as 121 showed strong radical scavenging effects against DPPH, NO and superoxide anion radical comparable to that of known antioxidants [74]. Recently, DPPH· scavenging, anti-LP assays, ABTS⁺· scavenging, OH scavenging, superoxide anion radical scavenging, Cu²⁺-chelating and FRAP assays were used to evaluate the antioxidant activities of poliumoside (128), alyssonoside (129), brandioside (130), 121, 125 and their derivatives, and the tested compounds were all screened out as antioxidants [75]. The structure-activity relationship between PhGs and their antioxidant activities indicated that the ortho-dihydroxyphenyl group was the important group, and the steric hindrance, the number as well as the position of phenolic hydroxyl were also thought to play an important effect [76].

3.3. Anti-Inflammatory Effect

Pseudomonas aeruginosa is the major pathogen implicated in sepsis and pneumonia [77,78]. Total phenylethanoid glycosides (TPG) from Monochasma savatieri prolonged survival rate of mice with P. aeruginosa or Staphylococcus aureus infection-induced sepsis in vivo. Meanwhile, TPG could reduce the bacterial colony-forming units in lung tissue in mouse model. In addition, TPG (60–180 mg/kg)
had significantly reduced xylene-induced ear edema and cotton pellet-induced granulomat formation at a dose-dependent manner. Furthermore, the treatment of TPG (1.5 g/kg) for 15 days did not cause any death of rat and no organic toxicity at the dose equal to approximately 284 times of clinical dose used [79]. It was reported that compound induced HO-1 in macrophages through p38 mitogen-activated protein kinase (MAPK)/Nrf2 signaling and decreased the release of high mobility group box 1 (HMGB1) in lipopolysaccharide (LPS)-stimulated Raw264.7 cells and in cecal ligation and puncture (CLP)-induced septic mice. In vitro, compound 121 not only inhibited the release of HMGB1, the production of inducible nitric oxide synthase and NO, but also induced HO-1 expression in a concentration-dependent manner; in vivo, it increased survival and decreased the HMGB1 levels of serum and lung in CLP-induced sepsis [80]. In another study, the anti-inflammatory activity, the anti-nociceptive activity, and the wound healing activity of 121 were studied using a carrageenan-induced hind paw edema model in vivo, a p-benzoquinone-induced abdominal constriction test, and incision and excision models in vivo, respectively [81]. It was previously reported that 121 was more active than ibuprofen in the writhing test (67.6% and 50.0% at equimolar doses) and showed similar effects in the tail flick (topic and oral) at equivalent dose to ibuprofen [82]. Moreover, compound 121 was found to be active in a carrageenan-induced hind paw edema model and in p-benzoquinone-induced writhing in mice [83]. Penido et al., revealed that 121 exhibited a potent inhibitory effect on LPS-induced total leucocyte, neutrophil and eosinophil accumulation in the pelural cavity along with a potent antiulcerogenic activity against diclofenac-induced gastric ulcers at 100 mg/kg [84]. Meanwhile, the histological scores indicated that treatment with 121 ameliorated intestinal inflammation in both acute and chronic dextran sulphate sodium-induced colitis in vivo through inhibition of oxidative burst activity [85]. Cell adhesion molecules (CAMs) play a role in the pathogenesis of atherosclerosis and inflammation. Compounds and 6-O-acetyl-acteoside (132) inhibited IL-1β-activated expression of intercellular CAM-1 and vascular CAM-1 (VCAM-1) in human umbilical vein endothelial cells (HUVECs). Compounds 121 and dose-dependently inhibited VCAM-1 gene promoter activity in IL-1β-activated HUVECs and their inhibition on IL-1β-activated expression of CAMs was manifested by decreased phosphorylation of ERK and c-Jun N-terminal kinase (JNK) [86]. Georgiev et al., studied anti-inflammatory properties of and forsythoside (124) towards human keratinocytes. Compounds 121 and 124 were both equally effective inhibitors of IL-8 release at 50 mM, with more than 90% reduction of IL-8 at spontaneous levels. Meanwhile, they significantly and dose-dependently impaired the release of IFN-γ-induced MCP-1 and IP-10 as well as significantly reduced background and IFN-γ-induced levels of IL-8 mRNA [87]. In addition, the protective effect of 123 on ethanol-induced acute gastric ulcer and H2O2-induced gastric epithelial cell damage were investigated. Intragastrical treatment with 123 inhibited the overproduction of pro-inflammatory cytokines (interleukin-6, interleukin-1β and tumor necrosis factor-α), enhanced antioxidant activity and alleviated acute gastric ulcer as well as gastric epithelial cell damage through the MAPK/NF-κB pathway [88].

3.4. Antibacterial and Antivirus Activity

The antimicrobial activity of TPG from M. savatieri was studied in vivo and in vitro. In vitro, TPG showed significant bacteriostatic properties against S. aureus, P. aeruginosa, Escherichia coli, Enterococcus faecalis, and Streptococcus pneumoniae at a concentration between 0.0625 and 16 mg/mL [79]. The anti-influenza virus effect of TPG from Ligustrum purpurascens was reported in vivo and in vitro. In vivo, C57BL/6J mice were given oral administration of TPG once daily for five successive days. TPG significantly decreased the mouse lung index (p < 0.05), alleviated influenza-induced lethality and clinical symptoms, and subsequently enhanced mouse survival (p < 0.05). In vitro, TPG inhibited influenza A virus H1N1 infection of MDCK cells in a hemagglutination assay [89]. Besides, many pure PhGs also possessed potent antibacterial activity. Compounds 121 and 125 showed considerable antibacterial activities against all strains of S. aureus with the minimum inhibitory concentration (MIC) values ranging from 64 µg/L to 256 µg/L. Particularly, the activities of 121 (MIC = 2.1 × 10⁻⁴ and
4.1 \times 10^{-4} \text{ M}) and 125 (MIC = 3.4 \times 10^{-4} \text{ M}) against SA 1199B (NorA) and XU 212 (TetK/MecA), respectively, were comparable to those of the positive control, norfloxacin (MIC = 1.0 \times 10^{-4} \text{ and } 2.5 \times 10^{-5} \text{ M}) [90]. In addition, 4'''-O-acetylacteoside (133) and 121 possessed significant inhibition of the formation of bacterial biofilms by E. coli UTI89 [91]. The antifungal/antimicrobial effect of PhGs may be largely due to the presence of phenolic hydroxyls which have high affinity with proteins [92].

3.5. Anti-Tumor Activity

The effects of 123 on the growth of human breast cancer in vitro and in vivo were evaluated, and it was found that 123 inhibited the proliferation of breast adenocarcinoma (MCF-7) cells with half maximal inhibitory concentration (IC_{50}) value of 19.48 \mu \text{M}, and promoted the apoptosis of MCF-7 cells in a dose-dependent manner by increasing the activity of caspase, up-regulating the Bax expression, and down-regulating the Bcl-2 expression. In addition, compound 123 significantly diminished not only the weight but also the volume of tumor \((p < 0.05)\) in a nude mouse mode. Compound 123 inhibited the intracellular ROS formation and MAPK pathway activation, which may contribute to the inhibition of tumor growth [93]. Compound 121 was reported to be a potent anti-cancer drug in the treatment of fibrosarcoma metastasis. It inhibited phorbol-12-myristate-13-acetate-induced matrix metalloproteinase-9 expression via \text{Ca}^{2+}-dependent calmodulin-dependent protein kinase (CaMK)/ERK and JNK/nuclear factor-\kappa B (NF-\kappa B)-signaling pathways [94]. Cytotoxic activities of 121 and 127 against human larynx epidermoid carcinoma, human rhabdomyosarcoma and human MCF-7 cell lines were determined with the IC_{50} from 36.24 \mu \text{g/mL} to 64.6 \mu \text{g/mL}, and apoptotic cell death was observed in histological analysis [74]. In another study, compounds 119, 120, 121, 125, 129, and decaffeoyl-acteoside (134) from Marrubium thessalum were assayed by MTT and \text{3}H-thymidine incorporation assays, and 120 and 121 showed tumor toxicity, while, they also showed low toxicity against peripheral blood mononuclear cells [95].

3.6. Immunomodulatory Effect

Autoimmune hepatitis (AIH) is a severe form of hepatitis. Studies have indicated that inflammatory cytokines and T lymphocytes play important roles in the pathogenesis of AIH [96,97]. Concanavalin A-induced hepatitis in a mouse model was regarded as the immune-mediated liver injury that resembles AIH occurring in human [98]. Hu et al., reported the intravenous (i.v.) injection of 123 dramatically reduced the levels of alanine aminotransferase and aspartic transaminase in the above mentioned mouse model, and partly suppressed the secretion of proinflammatory cytokines through downregulating the activity of NF-\kappa B. Meanwhile, compound 123 altered the distribution of CD4^{+} and CD8^{+} T lymphocyte in the liver and spleen through regulating CXCL-10 and decreased the severity of liver injuries [99]. Song extracted TPG from L. purpurascens and tested the immune enhancement effect of the TPG using serum hemolysin antibody, phagocytosis, splenocyte antibody production, and NK cells activity assays. Mice treated with TPG showed an increase in the haemagglutination titre, the antibody production of spleen cells, MΦ phagocytosis of chicken RBCs and NK cell activity [100]. Huang et al., established a screening model of immunological activity by using dendritic cells as target cells to investigate the effects of 120 and 121 on the phenotypic and functional maturation of dendritic cells. Expressions of major histocompatibility complex (MHC) class II and costimulatory molecules were used as indicators of successful maturation, and dendritic cells treated with 120 and 121 expressed high level of class II MHC and costimulatory molecule CD86 (B7-2). In addition, increased naïve T cell stimulatory activity and decreased endocytosis further confirmed the functional maturation of dendritic cells [101].

3.7. Enzyme Inhibitory Activity

Prescott et al. found that 121, teucrioside (135) and lamiuside A (136) (caffeoyl phenylethanoid glycosides) were direct calcineurin inhibitors when assayed both in the presence and absence of calmodulin using \text{p}-nitrophenyl phosphate as substrate [102]. In Georgiev’s study, compound 125
and the phenylethanoid fractions from the Devil’s claw cultures showed higher butyrylcholinesterase inhibitory activity than that of galanthamine [103]. Compound 131 was found to significantly inhibit recombinant human aldose reductase with an IC$_{50}$ value of 9.72 $\mu$M. Furthermore, it inhibited sorbitol formation in a rat lens incubated with a high concentration of glucose [104]. Meanwhile, the effect of pure PhG on improving glucose tolerance was also performed in vivo and in vitro. Compounds 117 and 121 inhibited the increase in postprandial blood glucose levels in starchloaded mice at doses of 250–500 mg/kg p.o. and also significantly improved glucose tolerance in starchloaded mice after 2 weeks of continuous administration at doses of 125 and/or 250 mg/kg/day p.o. without producing significant changes in body weight or food intake. In vitro, nine of pure PhGs demonstrated potent rat lens aldose reductase inhibitory activity. In particular, 2′-acetyl-acteoside (137) (0.071 $\mu$M) was similar to that of epalrestat (0.072 $\mu$M), a clinical aldose reductase inhibitor [105]. In an alloxan-induced diabetic mice model, compound 123 significantly reduced fasting blood glucose, total cholesterol, triglyceride and methane dicarboxylic aldehyde levels, and at same time increased serum insulin levels, SOD, glutathione peroxidase and catalase activities [106].

3.8. Other Pharmacological Effects

The effect of 121 on a 42-mer amyloid $\beta$ protein aggregation was examined by using the thioflavin-T assay, transmission electron microscopy, and circular dichroism spectroscopy. Compound 121 strongly inhibited the aggregation of 42-mer amyloid $\beta$ protein in a dose-dependent manner [107]. In another study, compound 121 appeared an inhibitory effect on DHT-induced secretion of both free and total prostate-specific antigen at all tested concentration in an in vitro model of human prostate epithelium [108]. He et al. studied the vasorelaxant activity of 117 and the results highlighted that 117 could evoke a significant endothelium-dependent vasorelaxation action mediated through the NO-cGMP pathway in an isolated rat thoracic aorta ring [109].

4. Pharmacokinetics

4.1. Pharmacokinetics of Echinacoside (117) and Acteoside (121)

Compounds 117 and 121 are the major PhGs in Herba Cistanchis, and 117 is widely present in plants. 117 contained additional glucose linking to C-6 of core saccharide compared with 121, and both of them exhibited good bioactivities [58,59,64,65]. In Caco-2 cell monolayer model, compounds 117, 120 and 121 were primarily transported via poorly absorbed passive diffusion down a concentration gradient without efflux [110], which was consistent with the result that the caffeic acid conjugates permeated poorly through the Caco-2 monolayers [111]. Though the absorption of 117 was poor, it was significantly increased when 117 was combined with verapamil and clove oil both in situ and in vitro [112].

PhGs were characterized by low intestinal absorption due to their physicochemical characteristics such as molecular sizes, degrees of polymerization and solubilities [113], but it is a growing recognition that not only the absorbed PhGs but also their metabolites may contribute to their pharmacological activities [114,115]. For example, the hydrolyzing metabolites of 117 and 121, such as hydroxytyrosol (HT) and 3-hydroxyphenylpropionic acid (3-HPP), possessed antioxidant [116,117], neuroprotective [118–120], and anti-inflammatory activities [121,122]. Identification of 117’s metabolites produced by human intestinal bacteria, biliary metabolites as well as urinary and fecal ones was reported. Eight phase II metabolites of parent compound (methyl ethers, glucuronides, and minor sulfates) were isolated and identified unambiguously from rat bile sample after i.v. administration of 117 [123]. Unlike the metabolites in rat bile, besides the phase II metabolites of parent compound, the degradation products and their glucuronic acid, sulfate, and methyl conjugations were identified in rat urine and feces [124]. PhGs were reported to be transformed by the intestinal bacteria before being absorbed into blood [125]. Compound 117 was found to be stable in simulated gastric juice and intestinal juice, whereas it could be metabolized by intestinal bacteria. Thirteen metabolites
of compound 117 and five possible metabolic pathways, including hydroxylation, dehydroxylation, reduction, deglycosylation, and acetylation were identified using UPLC-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS) with MSÈ technology and MetaboLynx software. In addition, HT and 3-HPP were found to be bioactive metabolites of 117. The fact that HT and 3-HPP possessed biological functions similar to those of 117, could potentially explain that 117 has prominent bioactivity but poor bioavailability [126].

Up to thirty-five metabolites were observed in the urine samples of rats orally administered with compound 121, through processes of oxidization, glucuronidation, sulfation, and methylation. Interestingly, the metabolism of 121 occurred much quickly than those of the degradation products, while the concentrations of metabolites from the degradation products were much higher than that of 121 [127]. The metabolic profiles of 121 produced by human or rat intestinal bacteria or intestinal enzyme in vitro were also reported. 3-HPP (56.13%), HT (24.77%) and reduction 121 or its isomers (18.07%) were the main products of 121 produced by the action of human bacteria, while 3-HPP (55.75%) and 134 (36.31%) were the main products of 121 produced by rat bacteria. The content of metabolite produced by intestinal enzyme was lower than that produced by intestinal bacteria, which indicated that intestinal bacteria had more impact on the absorption and metabolism of 121 than that of intestinal enzyme [128,129].

Further pharmacokinetic study was also reported to offer suitable references in PhGs’ clinical applications. Compound 121 was absorbed fast with low peak area, and the integral area under drug concentration-time curve (AUC) was small, which indicated few 121 were absorbed into the circulatory system. Its moderate elimination made less possibility of organ injury [130,131]. Interestingly, double peaks were seen from concentration-time curve of 121 in rat plasma [131,132]. And its absolute bioavailability was 0.12% [133]. The absorption of 117 was also fast with lower peak area, and elimination was faster than that of 121, but the absolute bioavailability of 117 with a value of 0.83% was a bit higher than that of 121 [134]. The different results of 117 and 121 may be ascribed to their structural difference, i.e., more than one glucose existed in the C-6 of 117, which meant that 117 was easier to be hydrolyzed and resulted in lower peak area as well as faster elimination. Another issue was that the value of $T_{\text{max}}$ of 117 obtained from the study performed by Yang [135] was prolonged to 90 min compared to Jia’s study [134]. Jia’s study was conducted in three groups of rats collected to develop a full pharmacokinetic profile whereas in Yang’s study the full pharmacokinetic profile was obtained from a group of rats.

With the development of analysis and extraction technology, more and more sensitive and specific methods were reposted. What’s more, simultaneous determination of more than one chemical marker and their pharmacokinetic studies were also reported. The microemulsion liquid chromatography (MELC) method [136] and the two-phase hollow fiber liquid phase microextraction coupled with a magnetofluid technique [137] for simultaneous determination of 117, 120, 121 and tubuloside B (139) in rat plasma after oral administration of Cistanche salsa extract by HPLC were developed. In the MELC method, the calibration curve for the four PhGs was linear in the range of 10–1000 ng/mL with the correlation coefficients greater than 0.9994. The RSDs of intra-day and inter-day precision were below 8.64% and the limits of detection (LOD) for the four PhGs were 0.4–1.3 ng/mL (S/N = 3). Under the MELC method, the calibration curve for PhGs was linear in the range of 0.1–100 ng/mL with correlation coefficients greater than 0.9996. The RSDs of intra-day and inter-day precision were below 8.74% and the LOD for the four PhGs were 8–15 pg/mL (S/N = 3).

4.2. Pharmacokinetics of Salidroside (123) and p-Tyrosol

Guo et al. [138] established an HPLC-tandem mass spectrometry method to determine 123 and its aglycone metabolite p-tyrosol in rat plasma after i.v. (50 mg/kg) and intragastric gavage (i.g.) (100 mg/kg) administration of 123 to rats. Both 123 and p-tyrosol were detected after i.v. administration, the $T_{1/2}$ of elimination phase was prolonged 1.34 fold to 1.64 ± 0.30 h for p-tyrosol, comparing with that of 0.70 ± 0.21 h for 123. According to AUC$_{0-\infty}$ data, about 2% of 123 was present as the aglycone
metabolite, \( p \)-tyrosol, in plasma. On the other hand, only 123 was detected after \( i.g. \) administration, with \( T_{1/2} \) value at 1.32 ± 0.22 h. It indicated that 123 was eliminated quickly after both \( i.v. \) and \( i.g. \) administrations in vivo. In addition, 123 may metabolize to \( p \)-tyrosol after \( i.g. \) administration, whereas it may be further metabolized to other metabolites, and resulted in undetectable \( p \)-tyrosol in the plasma sample [138]. The speculation was verified by Hu’s experiment, in which 123 and its deglycosylation phase I metabolite \( p \)-tyrosol were further metabolized to glucuronidation and sulfation products and mainly excreted through the urine excretion pathway [139]. Later, Guo’s research team studied the metabolism of 123 and \( p \)-tyrosol in liver tissues after \( i.v. \) administration of 123 (50 mg/kg) to rats, in which \( T_{1/2} \) values were 0.54 ± 0.06 h and 0.92 ± 0.03 h for 123 and \( p \)-tyrosol, respectively. In addition, the higher mean residence time and clearance (CL) values of \( p \)-tyrosol suggested that \( p \)-tyrosol was eliminated more slowly than 123 in liver tissues [140]. These differences in the pharmacokinetics parameters of 123 and \( p \)-tyrosol might be attributed to their chemical properties. Compound 123 is made up of aglycone \( p \)-tyrosol and a glucopyranose through glycosidic linkage, which makes it more water-soluble and consequently leads to a more rapid elimination than its aglycone [141]. The same goes for the deconjugation of flavonoid glucuronides, which could also lead to prolonged circulation and enhanced bioactivity in in vitro studies [141,142]. The elimination of 123 in rats was fast but slow (\( T_{1/2}, 120.0 \text{ min} \)) in beagle dogs after a single \( i.v. \) at a dose of 75 mg/kg [143], which indicated species difference existed in metabolism of 123. In addition, different dosages and administrative patterns might affect the bioavailability of 123. The bioavailability of 123 was calculated as 51.97% at dosages of 100 mg/kg \( i.g. \) and 50 mg/kg \( i.v. \) administration [138], 32.1% at dosages of 12 mg/kg oral and \( i.v. \) administration [144] and 98.0% at dosages of 25 mg/kg oral and 5 mg/kg \( i.v. \) administration [145].

4.3. Pharmacokinetics of Forsythoside (124)

It was found that 124 was rapidly absorbed into the circulation system and reached its peak concentration (\( C_{\text{max}} \), 122.2 ± 45.4 ng/mL) at around 20 min following oral administration (100 mg/kg) in rats. Similarly, its absolute bioavailability was also quite low with a value of 0.5% [146]. The potential hydrolysis in the gastrointestinal tract, poor permeability through the intestinal epithelial membrane and first-pass effect in the liver might be responsible for the low bioavailability of 124. Though the low permeability of 124 leads to low oral bioavailability of 124 [147,148], water-soluble chitosan at dosage of 50 mg/kg improved the bioavailability of 124 and the antioxidant activity in vivo [149]. Meanwhile, the metabolism and bioactivity studies of 124 also showed that its metabolites HT and dihydrocaffeic acid exhibited more potent anti-complement, antimicrobial and antiendotoxin effects than itself [150].

The pharmacokinetic characteristics of 124 in dogs after \( i.v. \) administration of 5, 10 or 20 mg/kg of 124, respectively, were also reported. The AUC and \( C_{\text{max}} \) increased proportionally with the increasing doses, but CL and \( T_{1/2} \) were not dose-dependence. The result that 124 was eliminated quickly and its \( T_{1/2} \) was short, clued to that 124 should be given by continuous \( i.v. \) infusion to maintain clinical effect. Meanwhile, the relative large values of distribution volume (\( V_d \), 1.10–1.90 L/kg) suggested that 124 was easily to distribute into tissues, which was beneficial to the treatment of infectious diseases in tissues [151]. It’s worth noting that \( T_{1/2} \) and \( V_d \) of 124 in dogs were different from those in rats [152], the species difference existed and deep reason needed further investigation.

The pharmacokinetics and hepatobiliary excretion of 124 in rats were also reported. The results indicated that hepatobiliary excretion was an important excretion path for 124. Furthermore, the disposition of 124 in blood and bile suggested that there was rapid exchange and equilibration between the blood and hepatobiliary systems [153].

A comparative pharmacokinetic study of 124 in rats after administration of Shuang-huang-lian (SHL) solutions via \( i.v. \), peroral or intratracheal routes was reported [154]. The plasma concentration of 124 reached the peak at 45 min with \( C_{\text{max}} \) of 35.0 ± 7.1 ng/mL after oral administration of 1000 mg/kg SHL solutions. The absolute bioavailability was determined to be 0.72% for 124. Whereas, the intratracheal delivery produced the peak plasma concentration within 5 min, and the absolute
bioavailability of 124 via pulmonary route was determined to be 25.8%. The absorption characteristic of 124 from the respiratory tract was distinct from that via the peroral route. Compared to peroral administration, pulmonary delivered chemical markers more rapidly and thoroughly absorbed.

4.4. Pharmacokinetics of Other PhGs

Plantamajoside (138) was a unique compound that characterizes Plantago asiatica. The mean plasma concentration-time profile of 138 in rats after oral administration of 10 g/kg (dry herb weight equivalent) was reported. The pharmacokinetic results showed 138 was quickly absorbed in rats with the time of 16.7 min to maximum plasma concentration (C\text{max}, 172.3 \pm 35.1 ng/mL). The elimination rate constants was 0.28 \pm 0.01 L/h and T\text{1/2} was 2.46 \pm 1.0 h \[132\]. Pharmacokinetics of tyrosol galactoside (140) following oral and i.v. administration both at a dose of 60 mg/kg were performed \[155\]. The oral bioavailability of 140 was about 27.9%, which was similar to that of compound 123 calculated at dosages of 12 mg/kg oral and i.v. administration \[144\].

5. Conclusions

The structural diversity of PhGs and the resulting biological properties, including neuroprotective, anti-inflammatory, antioxidant, anti-aging, memory enhancement, antibacterial, antiviral, cytotoxic, immunomodulatory, and enzyme inhibitory effects are attractive to those engaged in drug discovery. Pure PhGs and herbs rich in PhGs have been shown to possess multiple medical functions in vitro and in vivo. The poor permeability through the intestinal epithelial membrane, hydrolysis by enzymes in the gastrointestinal tract, and interaction with the enriched intestinal bacteria are the three possible reasons for the poor bioavailability of PhGs. Metabolic studies revealed that PhGs could be presumed to act as prodrugs, which were easily hydrolyzed in vivo and mainly metabolized into degradation products. There is a growing recognition that not only the absorbed parent PhGs, but also their metabolites may have the potential to be the effective ingredients, while most pharmacokinetic studies have focused on prototype compounds rather than their metabolites, so intensive studies of metabolite pharmacokinetics are required to shed light on the mechanisms underlying their systemic health effects of these compounds and confirm their clinical potential.

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