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Review

Saponins in the genus *Panax* L. (Araliaceae): A systematic review of their chemical diversity

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ABSTRACT

The *Panax* genus is a crucial source of natural medicines that has benefited human health for a long time. Three valuable medicinal herbs, namely *Panax ginseng*, *Panax quinquefolius*, and *Panax notoginseng*, have received considerable interest due to their extensive application in clinical therapy, healthcare products, and as foods and food additives world-wide. *Panax* species are known to contain abundant levels of saponins, also dubbed ginsenosides, which refer to a series of dammarane or oleanane type triterpenoid glycosides. These saponins exhibit modulatory effects to the central nervous system and beneficial effects to patients suffering from cardiovascular diseases, and also have anti-diabetic and anti-tumor properties. To the end of 2012, at least 289 saponins were reported from eleven different *Panax* species. This comprehensive review describes the advances in the phytochemistry of the genus *Panax* for the period 1963–2012, based on the 134 cited references. The reported saponins can be classified into protopanaxadiol, protopanaxatriol, octillol, oleanolic acid, C17 side-chain varied, and miscellaneous subtypes, according to structural differences in sapogenins. The investigational history of *Panax* is also reviewed, with special attention being paid to the structural features of the six different subtypes, together with their ^{1}H and ^{13}C NMR spectroscopic characteristics which are useful for determining their structures and absolute configuration.

Contents

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1. Introduction

The genus *Panax* L. (Araliaceae) has been an important source of natural medicines for a long period of human history. *Panax ginseng* C.A. Meyer (Abbreviated as **PG**, known as Asian or Korean ginseng) first appeared in the Oracle bone script (1600–1100 BC), and was later recorded in the "Shen Nong's Herbal Classic", the first Chinese pharmaceutical monograph, as the folk medicine given the top grade due to its excellent tonifying effects (Chen et al., 2008; Park et al., 2012). By contrast, *Panax quinquefolius* L. (**PQ**, American ginseng) grows in the wild and is currently widely cultivated in Canada and the USA. Despite its high chemical similarity with *P. ginseng*, *P. quinquefolius* instead exhibits heat-clearing and refreshing functions as a medicinal tonic. *Panax notoginseng* (Burkill) F.H. Chen (**PN**, Sanchi ginseng) is another reputable folk medicine which was recorded in detail in Ben-Cao-Gang-Mu, and is a potent agent for promoting blood circulation (Ng, 2006). The traditional Chinese medicines (TCMs) originating from these three *Panax* species, together with their diversified preparation products, are thus ranked among the most preferred natural medicines worldwide. As for their bioactive ingredients, the saponins occurring in the *Panax* genus have been extensively studied (Qi et al., 2011). In addition to the above three valuable species, however, new saponins were reported from several other *Panax* plants, i.e., *Panax japonicus* C.A. Meyer (**PJ**, Japanese ginseng, Zhu-Jie-Shen) (Zou et al., 2002a,b, etc.), *P. japonicus* var. *major* (Burk.) C.Y. Wu & K.M. Feng (**PJvm**, Zhu-Zi-Shen) (Chan et al., 2011; Morita et al., 1982, 1986), *Panax vietnamensis* Ha & Grushv. (**PV**, Vietnamese ginseng) (Duc et al., 1993, 1994a,b, 1999), *Panax stipuleanatus* Tsai & K.M. Feng (**PS**) (Liang et al., 2010), *Panax bipinnatifidus* Seem. (**PB**, Yu-Ye-San-Qi) (Tung et al., 2011), *P. japonicus* var. *bipinnatifidus* (Seem.) C.Y. Wu & K.M. Feng (**PJvb**) (Wang et al., 1989a), *Panax pseudo-ginseng* subsp. *himalaicus* Hara (**PpGh**) (Namba et al., 1986; Tanaka and Yahara, 1978; Tanaka et al.,1985), and *P. pseudo-ginseng* var. *angustatus* Hara (**PpGa**) (Kohda et al., 1991), respectively. The results, based on these phytochemical studies, have laid a solid foundation for a better understanding of their pharmacological activities and for comprehensive quality control of the *Panax* species within these and other natural medicines.

Multiple subtypes of plant secondary metabolites, involving saponins, organic acids/esters, polysaccharides, amino acids, sterols, flavonoids, carbenes, etc., have been found as natural constituents in the *Panax* plants. Undoubtedly, the saponin constituents, also known as ginsenosides, are the main bioactive ingredients responsible for the pharmacological efficacy of *Panax* species-derived natural medicines. Ginsenosides are the oligosaccharide glycosides of either dammarane or oleanane type triterpenoids, which have been demonstrated as agonists to steroidal receptors (Leung and Wong, 2010). Based on the structure differentiation of the sapogenins, the known ginsenosides can be reasonably classified into six different subtypes: the protopanaxadiol type (PPD), protopanaxatriol type (PPT), octillol type (OT), oleanolic acid type (OA), C17 side-chain varied type, and a series of miscellaneous triterpenes, respectively. Of these, the PPD, PPT, OA, and OT types are four most common subtypes for *Panax* saponins. Fig. 1 shows the structures of the PPD, PPT, OT, and OA sapogenins and their preferred glycosylation sites, as well as the attached saccharides.

Several reviews are currently available concerning the progress that has been made in research on saponins or in ginseng analyses (Baek et al., 2012; Connolly and Hill, 2003; Qi et al., 2011; Vincken et al., 2007). However, a systematic review that summarizes all the isolated *Panax* saponins has never been reported. Herein, a comprehensive review of the literature reporting new saponin structures from diverse *Panax* species between 1963 and 2012 is presented. To this point, at least 289 saponins have been isolated in pure form from either eleven different *Panax* species or relevant processed products, such as red ginseng (**RG**) (Kasai et al., 1983, etc), Sun ginseng (**SG**) (Park et al., 2002a,b), and acid-processed PN leaves or roots (Chen et al., 2006; Teng et al., 2004). The new sapogenins, i.e., three anti-tumor dammarane-type sapogenins (Zhao et al., 2011), are excluded in this review. With the aim to provide more direction for structure determination of the saponins in the *Panax* genus, the ^{1}H and ^{13}C NMR spectroscopic characteristics of each subtype, particularly with respect to their stereochemistry, are also outlined.

2. Subtype classification of the saponins isolated from the *Panax* genus

The structure of a saponin comprises a sapogenin moiety and one or two glycosyl units and/or chains. The reported *Panax* saponins are herein classified into PPD, PPT, OT, OA, C17 side-chain varied, and miscellaneous subtypes in light of their determined sapogenin structures. Some common structural features for these six subtypes originate from the nature of the sugar and of the acyl substituents. Glucose (Glc), glucuronic acid (GlcA), rhamnose (Rha), xylose (Xyl), and arabinose (Ara) are five different monosaccharides composing the *Panax* saponins, of which an arabinose occurs either in the pyran (*p*-Ara) or furan (*f*-Ara) configuration (Fig. 1). Furthermore, the saccharide residues, in particular the glucose moiety, are prone to undergo tailoring acylation reactions, including by acetyl ($+C_2H_2O$), butenoyl ($+C_4H_4O$), octenyl ($+C_8H_{12}O$), and malonyl ($+C_3H_2O_3$) residues. Table 1 and Fig. 2 show the full structure information for the PPD, PPT, OT, and OA type saponins (**1**–**150**), and the structures for the C17 side-chain varied subtype as well as the miscellaneous saponins (**151**–**289**) are given in Table 2 and Fig. 3. For those saponins with a defined absolute configuration at C-20 or C-24, or with an unusual α-D-glucopyranosyl linkage, this information is annotated in the bracket after the corresponding compound in Figs. 2 and 3. By use of the "Find" function, the full information of a known saponin, comprising its trivial name, molecular formula, botanical source, and the literature reporting its NMR spectroscopic data, can be traced in Tables 1 and 2. The key common structure features, as well as the characteristic ^{1}H and ^{13}C NMR spectroscopic features, are discussed in the following sections for each subtype and some important compounds.

2.1. Protopanaxadiol type (PPD, **1–66**)

Among all of the known saponins reported from the *Panax* genus, 66 compounds possess a 20(*S*)-/20(*R*)-protopanaxadiol sapogenin conjoined with one to six monosaccharides. The structures of the PPD type saponins display three discernable features: (1) preferred glycosylation site(s) at C-3 and/or C-20 (Fig. 1); (2) the linear linkage of the glycosyl chains; and (3) acylation occurring at the 6-OH of the terminal glucose for a 3-sugar chain. In an exceptional case, chikusetsusaponin FK7 (**1**), isolated from *P. japonicus*, has a glucose unit attached to C-19 (Yoshizaki and Yahara, 2012a). Four compounds, namely chikusetsusaponins VI (**2**), FK4 (**3**), FK5 (**4**), and FK6 (**5**), have branched saccharide chains (Kohda et al., 1991; Yoshizaki and Yahara, 2012a). Quinquenoside III (**6**) (Yoshikawa et al., 1998) and yesanchinoside J (**7**) (Zou et al., 2002a) are derivatized with an acetyl at the 6-OH of the primary glucose moiety attached to C-3.

Ginsenosides Rb1 (**8**), Rb2 (**9**), Rc (**10**), and Rd (**11**), originally isolated from the roots of *P. ginseng* (Sanada et al., 1974a), are also present in the roots of *P. quinquefolius* (Sanada and Shoji, 1978a) and *P. notoginseng* (Yoshikawa et al., 1997a,b), but their content