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Vietnamese Ginseng (*Panax vietnamensis* Ha and Grushv.): Phylogenetic, Phytochemical, and Pharmacological Profiles

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ABSTRACT
Vietnamese ginseng (VG) (*Panax vietnamensis*, Araliaceae) is indigenous in the central highlands of Vietnam and the southernmost distribution in the *Panax* genus. Compared to the long history of use and overall research on Korean ginseng and American ginseng, the up-to-date publication on VG is relatively much less extensive. The studies on VG have been reported focusing on phylogenetic analysis, phytochemistry, and pharmacological activity. To date, there is no systematic review of VG. In this review, the phytochemical profile including 52 individual saponins of VG is described, it becomes noteworthy that ocotillol-type ginsenosides including majonoside R1 and majonoside R2 are unique and dominate in the title plant of the *Panax* spp. In addition, various pharmacological activities of VG extracts and components are summarized and discussed.
Key words: Araliaceae, ginseng, ginsenoside, majonoside R2, *Panax vietnamensis*, Vietnamese ginseng

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INTRODUCTION

Vietnamese ginseng (VG) *(Panax vietnamensis* Ha and Grushv.) [Figure 1] is one of 11 *Panax* species in the Araliaceae family, which was found in the highlands of Central Vietnam, especially surrounding Ngoc Linh Mountain, in 1973 and recognized officially in 1985.[1] This is the southernmost species in distribution of *Panax* genus and in respect to meaning of ginseng as "cure for all" or "all-healing," it is traditionally used by the local people as a miraculous, tonic herb drug and for the treatment of various serious diseases including hepatitis, diabetes, and cancer.[2,3]

Since its discovery, investigation on VG has been being carried out comprehensively, especially, in the areas of chemical composition and pharmacological activity; but in respect to other well-known *Panax* sp. such as Korean ginseng (KG, *Panax ginseng),* American ginseng (AG, *Panax quinquefolium),* and Sanchi ginseng *(Panax notoginseng* [PN]), and it is much less extensive. According to PubMed database, the number of publication on VG is <100 while that of KG, for example, is in thousands. Phytochemically, there have been 52 saponins, known as ginsenosides, reported from VG and ocotillol-type ginsenosides such as majonosides R1 and R2 are among major compounds. Of them, majonoside R2 (MR2) was found to exhibit liver protective and anticancer effects, etc., In this chapter, we briefly summarize the research results in chemistry, pharmacology, and taxonomy of VG.

Phylogeny of Vietnamese Ginseng

Phylogenetic analysis of VG has been studied lately following researches on chemical constituents and pharmacological effects. In 2001, based on the analyses of 18S ribosomal RNA gene and matK gene sequence of VG and other *Panax* species, Komatsu *et al.* revealed the phylogenetic tree that VG was sympatric with other *Panax* species and had close relationship with *Panax japonicus* and *Panax pseudoginseng*.[4] In another study, based on the similarity of the nucleotide sequence of 18S ribosomal RNA gene and matK gene, a variety of VG, *P. vietnamensis* var. *fuscidicus* was discovered in the Southern part of Yunnan Province, China.[5] Very recently, the complete chloroplast genome sequence of VG was generated by *de novo* assembly using whole-genome next-generation sequences, which further supports that VG was in the same clade with the well-known *Panax* members PG, AG, and PN.[6]

Chemical Constituents

The published phytochemical results have been spotlighted on the underground part (root and rhizome) of VG. Since first report in 1993,[7] to date, 52 individual saponins mostly belonging to dammarane triterpene type have been characterized yet, and they can be further classified into protopanaxadiol (PPD), protopanaxatriol (PPT) and occotillol (OT) subtypes except for two oleanane-type saponins (ginsenoside Ro and hemsloside Ma3) [Figure 2a-c].[7–11]

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Figure 1: Vietnamese ginseng (Vietnamese ginseng, *Panax vietnamensis* Ha and Grushv). (a) Sketch of Vietnamese ginseng and natural distribution of Vietnamese ginseng in Vietnam (cite: http://www.botanyvn.com); (b) Color sketch of Vietnamese ginseng[3]

Among them, ginsenoside Rb_1 (G-Rb_1), Rb_2 (G-Rb_2), Rd (G-Rd), Re (G-Re), Rg_1 (G-Rg_1), majonoside R1 (MR1), MR2, notoginsenoside R_1, vinaginsenoside R1 (VR1), vinaginsenoside R2, and vinaginsenoside R11 are the major saponins in VG [Figure 2b]. In raw or nonprocessed material, it became evident that saponin content of VG is not only higher in yield but also more divert in both structure skeleton and number than those of AG and KG. In AG and KG roots, the numbers of saponins are <40 and belonging to PPD and PPT types. In particular, VG dominates OT-type saponins such as MR1, MR2, VR1, and VR2 with >50% total saponin content and that MR2 with very high yield (*ca* 5%) is remarkable [Figure 3].[12] These findings could be implicated in chemotaxonomy of VG and *Panax* species.

Ginseng has been used more widely in forms of red ginseng by heating process or steaming. Likewise, steamed VG was recently studied and upon steaming, the results showed that contents of polar ginsenosides, such as Rb_1, Rc, Rd, Re, and Rg_1, were rapidly decreased, whereas less polar ginsenosides such as Rg_3, Rg_5, Rk_1, Rk_3, and Rh_4 were increased by quantitative high-performance liquid chromatography HPLC analysis. However, OT saponins, which have no glycosyl moiety at the C-20 position, were relatively stable on steaming.[13]

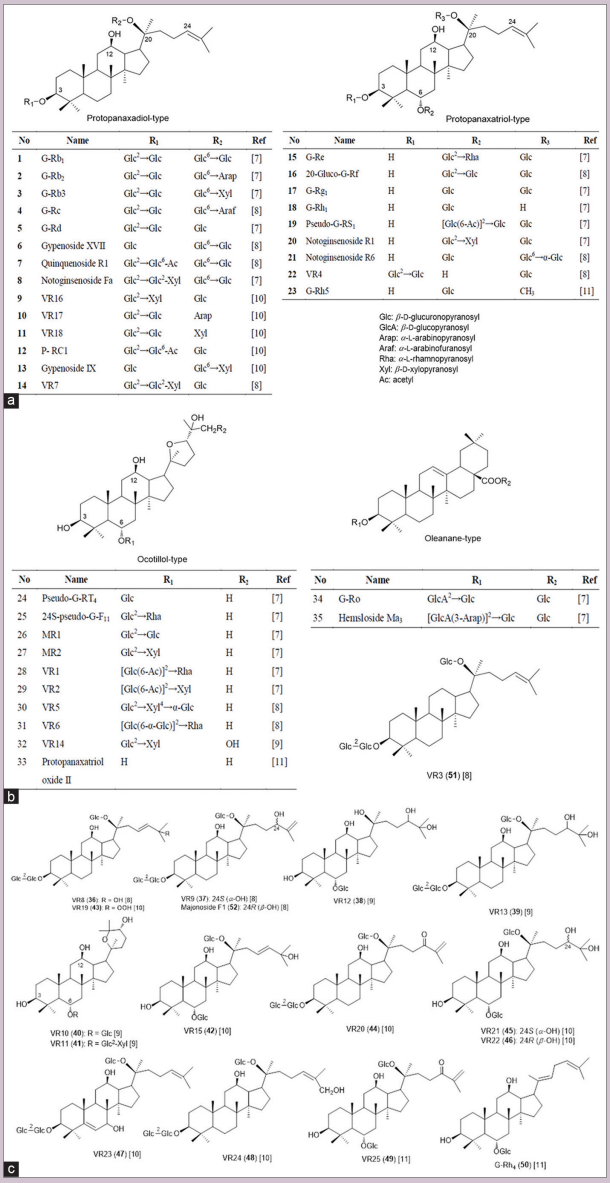
Pharmacological Activities

Anticancer activity

The most studied pharmacological activity anticancer of VG is both cancer chemopreventive and cancer chemotherapeutic effects and correlated with OT ginsenosides.

Yamasaki reported that the crude VG extract and its major saponin components (MR1, MR2, G-Rb_1, G-Rb_2, G-Rd, G-Re, and G-Rg_1) showed *in vitro* the inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by whether 12-0-tetradecanoylphorbol-13acetate (TPA) or fumonisin B_1 without toxicity on normal cell.[14] It is noteworthy that MR2, as the major saponi, exhibited the strongest inhibitory effects on EBV-EA activation and be relatively more active than glycyrrhizic acid from licorice which is known as a potent antitumor promoter.[15] In addition, *in vivo* study revealed the inhibitory effect of MR2 on the two-stage carcinogenesis test (initiation and promotion) of several tumor models of mouse skin induced by 7,12-dimethylbenz[a] anthracene/TPA, nitric oxide/TPA, and peroxynitrite/TPA and mouse hepatic liver induced by N-nitrosodiethylamine/phenobarbital.[16]

VG showed antiproliferative activity against A549 lung cancer cells, and upon steaming, the antiproliferative activity of the convention product significantly increased. Enhanced anticancer potential was evidenced



No	Name	R_1	R_2	Ref
1	G-Rb_1	Glc^2→Glc	Glc^6→Glc	[7]
2	G-Rb_2	Glc^2→Glc	Glc^6→Arap	[7]
3	G-Rb3	Glc^2→Glc	Glc^6→Xyl	[7]
4	G-Rc	Glc^2→Glc	Glc^6→Araf	[8]
5	G-Rd	Glc^2→Glc	Glc	[7]
6	Gypenoside XVII	Glc	Glc^6→Glc	[8]
7	Quinquenoside R1	Glc^2→Glc^6-Ac	Glc^6→Glc	[8]
8	Notoginsenoside Fa	Glc^2→Glc^2-Xyl	Glc^6→Glc	[7]
9	VR16	Glc^2→Xyl	Glc	[10]
10	VR17	Glc^2→Glc	Arap	[10]
11	VR18	Glc^2→Glc	Xyl	[10]
12	P- RC1	Glc^2→Glc^6-Ac	Glc	[10]
13	Gypenoside IX	Glc	Glc^6→Xyl	[10]
14	VR7	Glc^2→Glc^2-Xyl	Glc	[8]

No	Name	R_1	R_2	R_3	Ref
15	G-Re	H	Glc^2→Rha	Glc	[7]
16	20-Gluco-G-Rf	H	Glc^2→Glc	Glc	[8]
17	G-Rg_2	H	Glc	Glc	[7]
18	G-Rh_1	H	Glc	H	[7]
19	Pseudo-G-RS_1	H	$[Glc(6\text{-}Ac)]^2$→Glc	Glc	[7]
20	Notoginsenoside R1	H	Glc^2→Xyl	Glc	[7]
21	Notoginsenoside R6	H	Glc	Glc^6→α-Glc	[8]
22	VR4	Glc^2→Glc	H	Glc	[8]
23	G-Rh5	H	Glc	CH_3	[11]

Glc: β-D-glucuronopyranosyl
GlcA: β-D-glucopyranosyl
Arap: α-L-arabinopyranosyl
Araf: α-L-arabinofuranosyl
Rha: α-L-rhamnopyranosyl
Xyl: β-D-xylopyranosyl
Ac: acetyl

No	Name	R_1	R_2	Ref
24	Pseudo-G-RT_4	Glc	H	[7]
25	24S-pseudo-G-F_{11}	Glc^2→Rha	H	[7]
26	MR1	Glc^2→Glc	H	[7]
27	MR2	Glc^2→Xyl	H	[7]
28	VR1	$[Glc(6\text{-}Ac)]^2$→Rha	H	[7]
29	VR2	$[Glc(6\text{-}Ac)]^2$→Xyl	H	[7]
30	VR5	Glc^2→Xyl^4→α-Glc	H	[8]
31	VR6	$[Glc(6\text{-}\alpha\text{-}Glc)]^2$→Rha	H	[8]
32	VR14	Glc^2→Xyl	OH	[9]
33	Protopanaxatriol oxide II	H	H	[11]

No	Name	R_1	R_2	Ref
34	G-Ro	$GlcA^2$→Glc	Glc	[7]
35	Hemsloside Ma_3	$[GlcA(3\text{-}Arap)]^2$→Glc	Glc	[7]

Figure 2: (a) Saponin constituents from Vietnamese ginseng (1–23). (b) Saponin constituents from Vietnamese ginseng (24–35 and 51). (c) Saponin constituents from Vietnamese ginseng (36–50 and 52)

by chemical degradation and conversion of the original saponins to less polar ginsenosides such as Rg_3, Rg_5, Rk_1, Rk_3, and Rh_4 during the steaming process except for the content of OT saponins, which are reasonably thermostable.[13]

The cellular mechanism of VG against cancer was also studied. The effects of MR2 on the cell cycle of Raji cells treated with TPA were examined by flow cytometry and found out the evidence of influencing in the S and G2+M phases.[14,16] Taken together, the major OT saponin content MR2 in VG had potential in chemopreventive therapeutics.

Hepatoprotective activity

Another pharmacological activity of VG and its constituents is hepatoprotection, which has been investigated in both cell and tissue models. In 2000, Nguyen *et al.* found that the saponin extract of VG partly prevented CCl_4-induced hepatotoxicity in mice.[17] In a following study, Tran *et al.* reported also a potent hepatocytoprotective effect of the VG

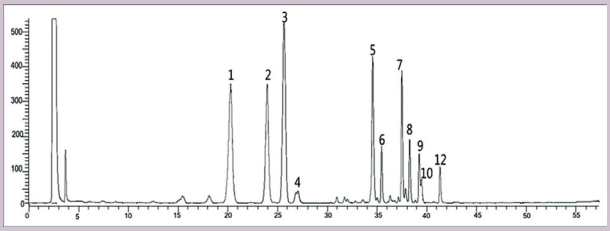


Figure 3: Typical chromatogram of Vietnamese ginseng extracted by high--performance liquid chromatography--(ELSD) Evaporative light scattering detector. Chromatographic and analytical conditions were shown in Le *et al*.[13] Peak identities: 1, MR1; 2, Rg_1 + Re; 3, MR2; 4, unknown 1; 5, vinaginsenoside R1 + vinaginsenoside R2; 6, unknown 2; 7, Rb_1; 8, Rc; 9, Rh2; 10, Rh_1; 12, Rd

extract against D-GalN/tumor necrosis factor-alpha (TNF-α)-induced cell death and further demonstrated that the hepatocytoprotective effect of VG is due to the presence of OT-type saponins, which are typical in chemical profile of the material.[11] The major OT-type member, MR2, was found to protect the mouse hepatocytes by lowering the level of the activated liver enzymes sGPT and sGOT in liver injury model in mice and the underlying protective mechanism was associated with apoptosis from apoptotic morphology, nuclei DNA fragmentation, and chromatin condensation in MR2-treated cells.[18]

In further studies, MR2 significantly decreased the production of TNF-α on D-galactosamine/lipopolisaccharide (D-GalN/LPS)-treated mice, which plays vital role for liver damage, together with improving the hepatocyte viability.[18] Taken together, it could be concluded that MR2 showed the hepatoprotective activity via both inhibition of TNF-α production by activated macrophages and direct inhibition of apoptosis induced by TNF-α.

Antistress activity

Traditionally, VG has been used to enhance and recover physical strength, which was closely related to antistress activity. The antistress activity of VG was first evidenced from antifatigue and adaptogenic effects.[19] In following study, Huong *et al.* reported the positive effects of VG and its major saponin, MR2, on behavioral and pathophysiological responses induced by psychological stress in mice using the communication box method and underlying neuronal mechanism.[20–22]Pretreatment with VG extract and MR2 suppressed the antinociception caused by the stress. Since both flumazenil and picrotoxin completely blocked the antagonistic effects of MR2 on opioid antinociception, it is likely the MR2 suppresses the stress-induced antinociception due to the modulation of the activity of opioid systems.[23–25] Similarly, pretreatment with VG extract and MR2, diazepam, or naloxone exhibited protective actions against the stress-induced gastric lesions. In addition, VG extract, VG saponin, and MR2 were found to restore the hypnotic activity of pentobarbital to the level of unstressed control mice. In mechanism, the effect of MR2 is likely acting as antagonist on the $GABA_A$-benzodiazepine receptor complex.[21–26]

These findings revealed the antistress effects of VG extract, and especially, MR2, in psychosomatic disorders caused by psychological stress[27] and further support its potential in medicinal use.

CONCLUSIONS AND FUTURE PERSPECTIVES

In general, in correlation with other *Panax* sp., the published result on VG has been less extensive in all research aspects. In this chapter, we summarized the up-to-date profile of phylogeny, phytochemistry, and pharmacological activity of VG.

A total of 52 ginsenosides have been identified from raw underground parts of VG and the OT saponins are typical constituents. The chemical constituents of steamed VG and the aerial parts (leaf, stem, and flower) have whether just preliminarily analyzed or not been carried out systematically, together with development of chromatographic techniques, there is interesting space for more studies and potential of novel compounds from VG.

Certain pharmacological actions of VG have been observed on the central nervous and immune systems as evidenced by antistress, anticancer, and hepatoprotective activities in this review. There are general lacks of not only evaluation of various pharmacological activities such as effects on the endocrine and cardiovascular system but also respective underlying mechanism of biological activities of detailed constituents/extracts from VG also should become interests in natural product researchers.

It is the fact that source of VG is an issue, which is mainly from nature or natural growing other than field cultivation. Once sustainable biotechnological production of VG is facilitated, the following studies for utilization of VG will become feasible.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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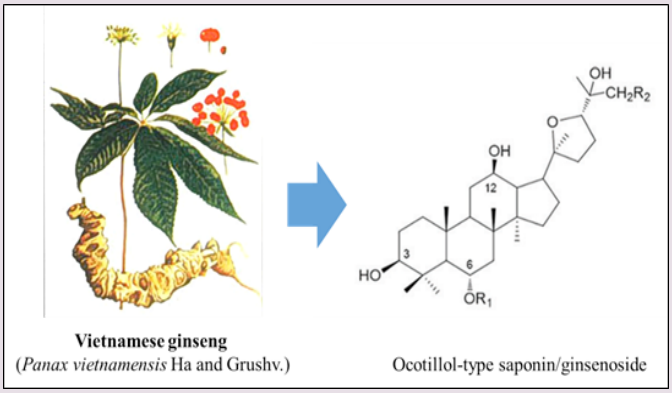
GRAPHICAL ABSTRACT



SUMMARY

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