Chemical Composition and Pharmacological Activities of Vietnamese Ginseng, *Panax vietnamensis*

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ABSTRACT

From the underground part of *Panax vietnamensis* Ha *et* Grushv., commonly known as Vietnamese ginseng, 50 triterpene glycosides including 24 new dammarane saponins named vina-ginsenosides-R_1-24 were isolated and identified. The structure of the new saponins was elucidated based on chemical and spectroscopic evidence. The saponin composition of Vietnamese ginseng is almost similar to that of ginseng (*Panax ginseng* C.A. Meyer) and other cultivated *Panax* spp. However, the content of ocotillol-type saponins, especially that of the major saponin, majonoside-R_2 (5.29% yield), was surprisingly very high. The pharmacological activities of Vietnamese ginseng are essentially similar to those of ginseng. In addition, it has marked antibacterial activity against pathogenic *Streptococcus* spp. and is effective in treatment of granular angina. The chemical composition and pharmacological activities have made Vietnamese ginseng an interesting member of *Panax* spp. from chemotaxonomical and pharmacological points of view.

Introduction

Panax species occur in the nothern hemisphere from Central Himalaya to North America through China, Korea and Japan.[1,2] This genus includes well-known medicinal plants such as *Panax ginseng* C.A. Meyer (ginseng), *P. notoginseng* (Burk.) F. H. Chen (Sanchi ginseng), and *P. quinquefolium* L. (American ginseng), and studies on this genus have been elaborated extensively.

In 1973, a wild *Panax* species was discovered at Ngoc Lay, Kon Tum Province, Central Vietnam, at the elevation of 1,800 m above sea level.[3] Subsequent investigations revealed that this herb was a "secret medicine" of the Sedang ethnic group living in high mountains of the Truong Son Range, and it has been regarded as a life-saving medicinal plant used for treatment of many serious diseases and enhancement of physical strength. In 1985, the plant was designated as *Panax vietnamensis* Ha *et* Grushv.,[4,5] a new *Panax* species, and readily turned out to be an important medicinal plant of Vietnam with the common name Vietnamese ginseng.

The present review article deals with the chemical composition and pharmacological activities of this plant.

Chemical Composition of Vietnamese Ginseng

Saponins

The saponin composition of Vietnamese ginseng has been studied extensively, since saponins are regarded as the main active component of *Panax* spp.

From the underground part of *P. vietnamensis* growing wild, which consists of a large rhizome having a small root at its end, 50 compounds were isolated and identified. Besides daucosterin (β -sitosteryl 3-O- β -D-glucopyranoside), twenty-five known and twenty-four new saponins were isolated and structurally identified.[6-12]

Each of known saponins was unambigously identified by comparison of optical rotation, thin-layer chromatographic behavior, ^{1}H- and ^{13}C-NMR spectra, and mass spectra (as trimethylsilyl ethers) with those of a corresponding authentic sample or references. They are as follows (yield as a percentage of the dried material is shown in parenthesis).

- Protopanaxadiol saponins: ginsenoside-Rb_1 (**1**, 2.0), ginsenoside-Rb_2 (**2**, 0.012), ginsenoside-Rb_3 (**3**, 0.11), ginsenoside-Rc (**4**, 0.013), ginsenoside-Rd (**5**, 0.87), pseudo-ginsenoside-RC_1 (**6**, 0.001), gypenoside-IX (**7**, 0.001), gypenoside-XVII (**8**, 0.036), quinquenoside-R_1 (**9**, 0.012), notoginsenoside-Fa (**10**, 0.072), and majoroside-F_1 (**11**, 0.003, protopanaxadiol-type saponin with a modified side chain).

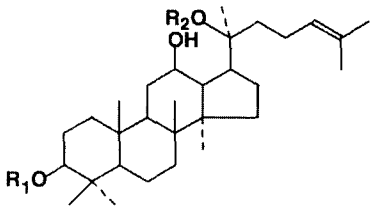
- Protopanaxatriol saponins: ginsenoside-Re (**12**, 0.17), 20-gluco-ginsenoside-Rf (**13**, 0.01), ginsenoside-Rg_1 (**14**, 1.37), ginsenoside-Rh_1 and 20(R)-ginsenoside-Rh_1 (**15**, 0.008, as an epimeric mixture), pseudo-ginsenoside-RS_1 (= monoacetyl ginsenoside-Re, **16**, 0.013), notoginsenoside-R_1 (**17**, 0.36), and notoginsenoside-R_6 (**18**, 0.01).

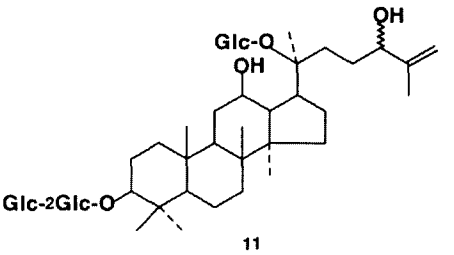
- Ocotillol-type saponins (dammarane saponins having a hydroxyisopropyl tetrahydrofuran ring): pseudo-ginsenoside-RT_4 (**19**, 0.065), 24(S)-pseudo- ginsenoside-F_{11} (**20**; 0.005), majonoside-R_1 (**21**, 0.14), and majonoside-R_2 (**22**, 5.29), the major saponin.

- Oleanolic acid saponins: ginsenoside-Ro (= Chikusetsu-saponin-V, 23, 0.038), and hemsloside-Ma_3 (**24**, 0.052).

The structures of the known saponins are shown in Figure 1. Most of the known saponins have been isolated from other *Panax* spp., though gypenosides-IX (**7**) and -XVII (**8**) were first isolated from *Gymnostemma pentaphyllum* Makino, Cucurbitaceae, by Takemoto *et al.*[13] One exception is hemsloside-Ma_3 (**24**), which was previous isolated from *Hemsleya macrosperma* C. Y. Wu, Cucurbitaceae.[14] It should be noted that that this is the first identification of hemsloside-Ma_3 in a *Panax* species.

The new dammarane saponins isolated from Vietnamese ginseng were named vinaginsenosides-R_1 - R_{24} (**25** - **48**, respectively). Their structures were established based on chemical and spectro-





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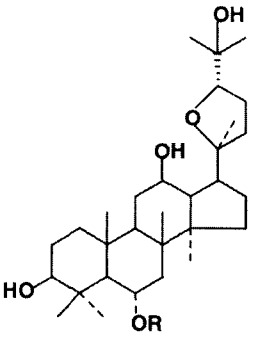
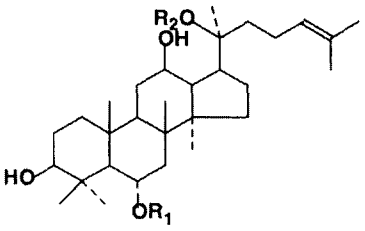
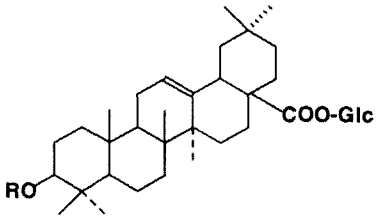
	R_1	R_2
1	-Glc2-Glc	-Glc6-Glc
2	-Glc2-Glc	-Glc6-Ara(p)
3	-Glc2-Glc	-Glc6-Xyl
4	-Glc2-Glc	-Glc6-Ara(f)
5	-Glc2-Glc	-Glc
6	-Glc2-Glc6-Ac	-Glc
7	-Glc	-Glc6-Xyl
8	-Glc	-Glc6-Glc
9	-Glc2-Glc6-Ac	-Glc6-Glc
10	-Glc2-Glc2-Xyl	-Glc6-Glc



	R
19	-Glc
20	-Glc2-Rha
21	-Glc2-Glc
22	-Glc2-Xyl



	R_1	R_2
12	-Glc2-Rha	-Glc
13	-Glc2-Glc	-Glc
14	-Glc	-Glc
15	-Glc	-H
16	-Glc2-Rha (6-Ac)	-Glc
17	-Glc2-Xyl	-Glc
18	-Glc	-Glc6-αGlc



	R
23	-GlcA2-Glc
24	-GlcA2-Glc (3-Ara(p))

Figure 1. Known Triterpene Saponins from *Panax vietnamensis.*
(Ara(f): α-L-arabinofuranosyl; Ara(p): α-L-arabinopyranosyl
α-Glc: α-glucopyranosyl; Glc: β-D-glucopyranosyl
Rha: α-L-rhamnopyranosyl, Xyl: β-D-xylopyranosyl
GlcA: β-D-glucoronopyranosyl; Ac: acetyl)

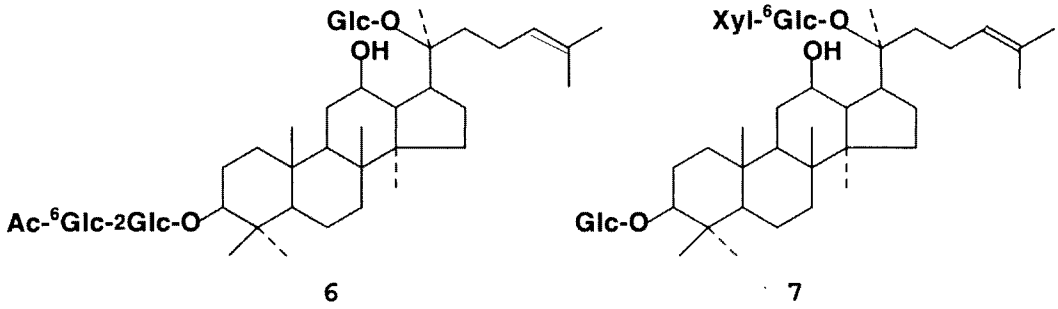


Figure 1 (contd.). Known Triterpene Saponins from *Panax vietnamensis*.

scopic evidence. Various techniques of one and two-dimentional NMR including ^{1}H-^{1}H COSY, HETCOR, HMBC, HSQC, NOESY, ROESY showed their efficacy in structure elucidation of the new saponins. The structures of the new saponins and their yields (as a percentage of the dried material) are given in Figure 2. Of these new compounds, vina-ginsenoside-R_3 **(27)** is the first naturally occuring glycoside of dammarenediol II. Vina-ginsenoside-R4 **(28)** was noted as the first example of protopanaxatriol saponins having the glycosyl linkage at C-3 of the aglycone. Vina-ginsenosides-R5 (29) and R_6 **(30)** provided two more examples of the few saponins containing the α-glucosyl linkage. Vina-ginsenosides-R_{10} **(34)**, -R_{12} **(36)**, -R_{13} **(37)**, R_{14} **(38)**, R_{15} **(39)**, -R_{19} **(43)**, -R_{20} **(44)**, -R_{23} **(47)**, and -R_{24} **(48)** are the saponins with new dammarane aglycones.

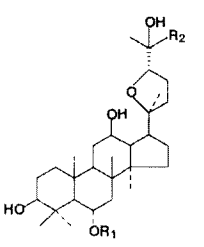
Previously, South Yunnan, China and the northern provinces of Vietnam near the China-Vietnam border seemed to be the southern limit of the distribution of the *Panax* genus. However, Vietnamese ginseng was discovered in a region which is more southward than the known limit of the distribution. Furthermore, since the temperate climate seemed to be a requirement for the distribution of *Panax* spp., it is interesting that the plant grows in a tropical region.

Table 1. Saponin Contents (yield %) of P. *vietnamensis* and Related Wild *Panax* spp.

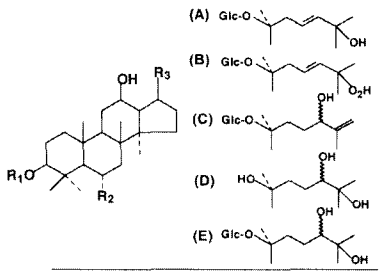
Aglycone type	Bhutanese *PPH*			Nepalese Specimen			*PJM* (Zu-Tzishen)	*PV*
	Tz	P	K	C	G	D		
20(S)-ppd	0.5	0.2	1.1	4.3	6.6	0.88	0.7	3.1
20(S)-ppt	0.5	1.3	---	0.4	0.7	0.94	0.04	2.0
Ocotillol	0.3	0.02	---	0.06	0.2	0.19	0.17	5.6
Oleanolic acid	3.7	7.0	8.2	---	---	0.94	1.2	0.09
Total yield	5.0	8.5	9.3	4.8	7.5	3.0	2.1	10.8

[ppd: protopanaxadiol; ppt: protopanaxatriol; *PPH: Panax pseudoginseng* subsp. *himalaicus;*
Tz: Tzatogang (Bhutan, 3,100 m); P: Pari-la (Bhutan, 2,600-3,550m); K: Khosa (Bhutan, 1,800 m);
C: specimen C collected at Chame (2,700 m); G: specimen G collected at Ghorapani (2,743 m);
D: specimen D collected in Central Nepal; *PJM:Panax japonicus* var. *major; PV: Panax vietnamensis]*

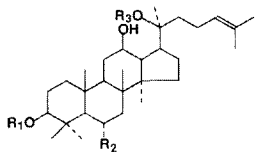
It has been revealed that the underground part of *Panax* spp. growing wild in the Eastern Himalayas through Southwestern China and Japan, except a very few species collected in Nepal, bears a large rhizome and contain mainly oleanolic saponins along with a small amount of dammarane saponins (Table 1). On the other hand, *P. ginseng* (ginseng), *P. quinquefolium* (American ginseng), and P. *notoginseng* (Sanchi ginseng), which are now cultivated plants and have carrot-like roots, contain mainly dammarane saponins with (or without) a relatively small amount of oleanolic acid saponins (Table 2).



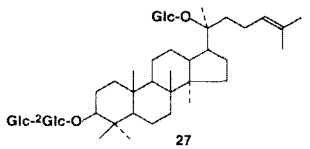
	yield %	R_1	R_2
25	0.033	-Glc^2-Rha (6 Ac)	$-CH_3$
26	0.014	-Glc^2-Xyl (6 Ac)	$-CH_3$
29	0.008	-Glc^2-Xyl^{4}-αGlc	$-CH_3$
30	0.006	-Glc^2-Xyl (6 αGc)	$-CH_3$
38	0.02	-Glc^2-Xyl	$-CH_2OH$



	yield %	R_1	R_2	R_3
32	0.004	-Glc^2-Glc	-H	(A)
39	0.003	-H	-O-Glc	(A)
43	0.003	-Glc^2-Glc	-H	(B)
33	0.004	-Glc^2-Glc	-H	(C)
36	0.005	-H	-O-Glc	(D)
37	0.002	-Glc^2-Glc	-H	(E)
45	24(*S*) 0.002	-H	-O-Glc	(E)
46	24(*R*) 0.002	-H	-O-Glc	(E)



	yield %	R_1	R_2	R_3
28	0.004	-Glc^2-Glc	-OH	-Glc
31	0.01	-Glc^2-Glc^2-Xyl	-H	-Glc
40	0.001	-Glc^2-Xyl	-H	-Glc
41	0.001	-Glc^2-Glc	-H	-Ara
42	0.001	-Glc^2-Glc	-H	-Xyl



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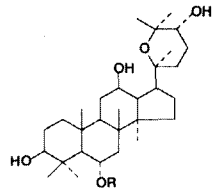
(0.009)



	yield %	R
34	0.007	-Glc
35	0.03	-Glc^2-Xyl

Figure 2. New Dammarane Saponins from *Panax vietnamensis.*

(Ara:α-L-arabinopyranosyl; Rha: α- L-rhamnopyranosyl
α-Glc: α-glucopyranosyl Glc: β-D-glucopyranosyl
Xyl: β-D-xylopyranosyl; Ac: acetyl)

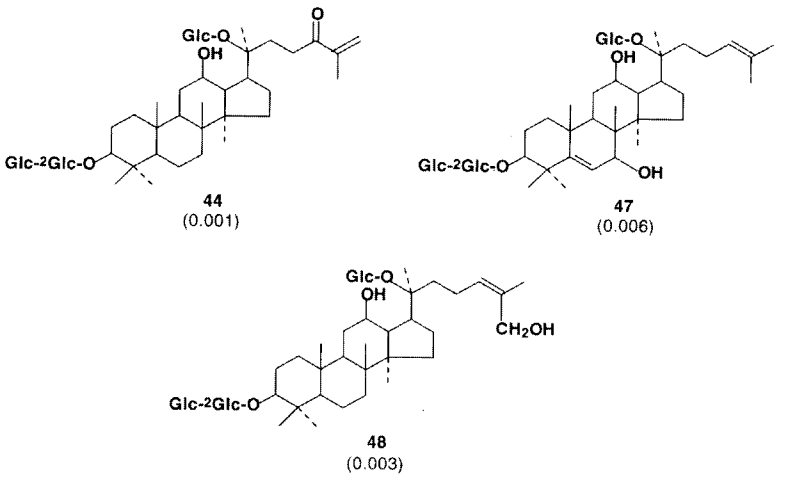


Figure 2 (contd.). New Dammarane Saponins from *Panax vietnamensis*

Despite having a large horizontally elongated rhizome, the underground part of *P. vietnamensis* contains a large amount of dammarane saponins together with a very small amount of oleanolic acid saponins. The saponin composition of Vietnamese ginseng is similar to that of the cultivated *Panax* species. It also includes most of the main dammarane saponins found in the cultivated *Panax* plants, such as ginsenosides-Rb_1 **(1)**, -Rd **(5)**, - Re **(12)**, -Rg_1 **(14)**, and notoginsenoside-R_1 **(17)**. In addition, the yield of saponins from Vietnamese ginseng is obviously higher than that of other *Panax* spp. However, the yield of ocotillol-type saponins, especially majonoside-R_2 **(22)**, is surprisingly very high (more than 5% and *ca.* half of the total yield of saponins). It should be noted that ocotillol-type saponins were isolated from American ginseng in small quantity but have not been isolated from ginseng and Sanchi ginseng as yet.

Experimental cultivation of *P. vietnamemis* has been carried out. The study on the saponin compo-

Table 2. Saponin Contents (yield %) of *P. vietnamensis* and Cultivated *Panax* spp.

Aglycone type	*P. ginseng*	*P. notoginseng*	*P. quinquefolium*	*P. vietnamensis*
20(S)-ppd	2.9	2.1	2.7	3.1
20(S)-ppt	0.6	2.4	1.2	2.0
Ocotillol	---	---	0.04	5.6
Oleanolic acid	0.02	---	0.07	0.09
Total yield	3.5	4.5	4.0	10.8

[ppd: protopanaxadiol; ppt: protopanaxatriol]

sition of the cultivated plant revealed that it contained almost the same saponin composition with that of the wild plant. [15] It is noteworthy that the underground part of the cultivated plant is a fascicle of carrot-like roots instead of a large rhizome.

The characteristic saponin composition has made Vietnamese ginseng an interesting member of *Panax* spp., not only from a chemotaxonomical point of view but also from pharmacological view points.

Polyacetylene compounds

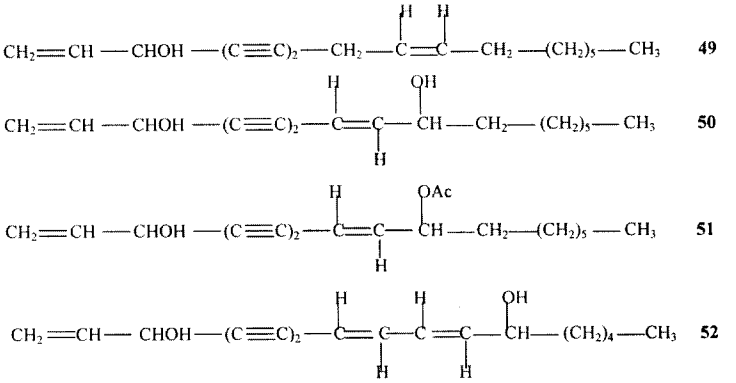


Figure 3. Polyacetylene Compounds from Rhizomes and Roots of *P. vietnamensis*

Seven polyacetylene compounds were isolated from the underground part of *P. vietnamensis*. Besides two main compounds were identified as falcarinol **(49)** and heptadeca-1,8(E)-diene-4,6-diyne-3,10-diol **(50)**, three others were suggested to be isomers and derivatives of heptadeca-1,8(E)-diene-4,6-diyne-3,10-diol. Two new compounds were structurally characterized as 10-acetoxy-heptadeca-8(E)-ene-4,6-diyn-3-ol **(51)** and heptadeca-1,8(E),10(E)-triene-4,6-diyne-3,12-diol **(52)**[16]. Recently, polyacetylene alcohols have drawn much attention of scientists since they have been proven to be cytotoxic against some cultured cancer cells.

Other consituents

An *n*-hexane fraction from the extraction of Vietnamese ginseng was used for analysis of fatty acid by gas chromatography. The fatty acid constituents of *P. vietnamensis* included palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, *etc.*, which are similar to those of ginseng. The content of linoleic acid and linolenic acid, which have been considered as vitamine F, was very high (42.7% of the total lipid).[12]

P. vietnamensis was shown to contain 17 amino acids including lysine, histidine, arginine, aspartic acid, threonine, serine, glutamic acid, prolin, leucine, isoleucine, *etc.* Many of them are essential amino acids for human body.[12]

An analysis of the composition of micro-elements showed the presence of several known biologically active elements such as K, Mg, Fe, Co, B, Mn, Se, etc.[12]

Pharmacological Activities of Vietnamese Ginseng

A systematic study on pharmacological activities of Vietnamese ginseng has been carried out in comparison with those of ginseng.[5,12] The results obtained showed that it induced a number of biological activities similar to those of ginseng. Important pharmacological activities of Vietnamese ginseng extract carried out in animals can be summarized as follows.

- Stimulating the central nervous system (CNS) in small doses, and depressing CNS and showing antipsychotic action in large doses.
- Enhancing physical strength and showing analeptic, antifatigue and adaptogenic actions (protection against stress, hepatic toxins *etc.*).
- Increasing the weight of male and female sexual organs.
- Anti-arteriosclerotic action, hypertensive action to hypotension-induced animals.
- Hypoglycemic action.
- Enhancing the phagocytic activity of phagocytes.

In additon, the extract showed antibacterial effects against pathogenic *Streptococcus* spp. without causing damages on useful microorganisms of intestinal tract.[4,12] The antibacterial and antifungal activities of two main polyacetylene compounds from *P. vietnamensis,* falcarinol and heptadeca-1,8(E)-diene-4,6-diene-3,10-diol, were also reported.[17] In addition, *P. vietnamensis* extract increased the content of cytochrom P-450 in liver microsomes.[12] These biological activities are characteristic for Vietnamese ginseng in comparison with those of ginseng.

Table 3. Characteristic Pharmacological Activities of *P. vietnamensis.*

Pharmacological activity	Related symtom or disease
- Enhancing physical strength, antifatigue	Asthenia
- Stilamuting CNS	Neurasthenia
- Increasing the weight of male and female genital organs	Sexual asthenia
- Increasing erythrocyte number, hemoglobins and hematocrite	Anemia
- Antibacterial and expectorant effect	Granular angina
- Hypoglycemic effect	Diabetes
- Improving heart contractility due to electrolyte disturbance	Arrythmia
- Decreasing blood cholesterol	Arteriosclerosis
- Hypertensive action	Hypotension
- Adaptogenic effect	Stress

Majonoside-R_2, the major saponin of *P. vietnamensis* with ocotillol structure, has also been subjected to pharmacological studies. Majonoside-R_2, as well as Vietnamese ginseng, was proven to have protective effects on footshock stress- and psychological stress-induced antinociception.[18,19] Majonoside-R_2 attenuated the antinociception caused by opoid antagonists and conditioned fear stress.[20]

Recently, T. Konoshima *et al.* reported the anti-tumor promoting activity in *vitro* and *in vivo* of majonoside-R_2. Majonoside-R_2 exhibited strong inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) (50% inhibition at 100 molar ratio/TPA). This activity was much higher than that of glycyrrhetic acid which is known to be a potent anti-tumor promoter. In *in vivo* assays, majonoside-R_2 exhibited an inhibitory effect on the two-stage carcinogenesis test of mouse skin tumor using 7,12-dimethyl-benz[a]anthracene (DMBA) as an intiator, and TPA as a promoter. The papilloma production promote by TPA was significantly decreased and delayed by the pre-treatment of 85 nmol of majonoside-R_2. The activity of majonoside-R_2 was revealed to be higher than that of glycyrrhetic acid.[21]

Clinical evaluation of *P. vietnamensis* extract for aged patients and post-operation patients were also conducted at Institute of Gerontology, Hanoi, and Central Army Hospital and Sanatorium for Patients in Covalescence, Ho Chi Minh City, Vietnam.[4,12] The positive results reported included general tonic effects, anti-fatigue action, increase of appetite and better sleep, improvement of muscular force, mental state, memory and articulation, relief from chronic granular angina, bronchial asthma and cough, *etc.*

The characteristic pharmacological activities and related symptoms or diseases for which *P. vietnamensis* can be useful are summarized in Table 3.

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