

Ginseng in Traditional Herbal Prescriptions

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Panax ginseng Meyer has been widely used as a tonic in traditional Korean, Chinese, and Japanese herbal medicines and in Western herbal preparations for thousands of years. In the past, ginseng was very rare and was considered to have mysterious powers. Today, the efficacy of drugs must be tested through well-designed clinical trials or meta-analyses, and ginseng is no exception. In the present review, we discuss the functions of ginseng described in historical documents and describe how these functions are taken into account in herbal prescriptions. We also discuss the findings of experimental pharmacological research on the functions of ginseng in ginseng-containing prescriptions and how these prescriptions have been applied in modern therapeutic interventions. The present review on the functions of ginseng in traditional prescriptions helps to demystify ginseng and, as a result, may contribute to expanding the use of ginseng or ginseng-containing prescriptions.

Keywords: *Panax ginseng*, Herbal prescription, Historical documents, Modern pharmacological experiments, Translational approaches

INTRODUCTION

In ancient times, medical practitioners treated patients through shamanism or used materials that were available in their area, such as plants, animals or alcohol. However, these practitioners may not have utilized therapeutic knowledge, and patients may have not received satisfactory medical care. Over time, by trial and error, therapeutic strategies using readily available materials were established, as demonstrated by evidence unearthed from ancient tombs (e.g., the Mawangdui tomb), including the Wushier Bing Fang (五十二病方). Over time, medical information accumulated, and medical practitioners used many suitable medicinal plants or animals for the treatment of diseases, including ginseng. Ginseng is a medicinal plant that has been used in medical practices for more than 2,000 years [1]. The Shennong Bencao Jing (Shen-

nong's Herbal Classic, 神農本草經), one of the first books specializing in herbal medicine, was edited in the 1st century AD. In this text, ginseng was first recognized as a medicinal herb by medical practitioners (Fig. 1). In addition, in the Shang-Han Lun (translated as the treatise on diseases caused by cold factors, 傷寒論), Zhong Jing Zhang (張仲景) described the use of ginseng in herbal prescriptions. However, because ginseng has been cultivated since the 15th century, the type of ginseng that appeared in the Shennong Bencao Jing may have been different from that which is currently in use. In previous centuries, wild ginseng would have been collected from mountainous areas; thus, this plant is commonly referred to as mountain ginseng. Several excellent accounts of mountain ginseng have been presented in the literature.

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For instance, mountain ginseng has been used to save lives in Korea [1].

Since standardized ginseng extract G115 was first prepared by Pharmaton Ltd., Lugano-Bioggio, Switzerland, ginseng has been widely used as an active ingredient in modern medicine. For example, the German Commission E approved ginseng as a tonic for invigoration and fortification to treat fatigue, debility or declining sexual capacity. Moreover, ginseng has been approved to enhance concentration and for use during convalescence [2]. These uses were reaffirmed by the World Health Organization in 1999. Ginseng has several beneficial properties, including providing the nourishing effects, anti-fatigue, or immune-enhancing effects, as mentioned in the traditional descriptions of the Shennong Bencao Jing. Therefore, the characteristics of ginseng described in historical documents, such as the Shennong Bencao Jing, the Bencao Gangmu (本草綱目, which was written by Shizhen Li [李時珍] during the Ming Dynasty), and the Hyangyak-jibseongbang (鄉藥集成方) or the Donguibogam (東醫寶鑑, which was published during the Chosun Dynasty), should be examined. The role of ginseng in traditional prescriptions should also be analyzed to expand the use of ginseng in modern medicine. In addition, investigations on the experimental evidence in pharmacological studies of ginseng-based traditional

prescriptions would yield information on how traditional knowledge or historical accounts described in the aforementioned documents can be interpreted in contemporary medical terms.

Panax ginseng is a traditional medicinal plant that has been used therapeutically for millennia in East Asia. In Korea, China, and Japan, ginseng is the most valuable of all medicinal herbs. The name *Panax* means “all healing,” which describes the traditional belief that ginseng can heal all aspects of the body. The most common ginsengs are ginseng (*P. ginseng* Meyer), Chinese ginseng (*P. notoginseng* [Burk.] FH Chen), and American ginseng (*P. quinquefolium* L.).

Among the ginseng varieties, *P. ginseng* has been extensively researched and has received the most attention. *P. ginseng* is sensitive to the temperature and soil of the cultivated area. Therefore, *P. ginseng* is cultivated in limited areas, including Korea, the Manchuria region of China (the region of Dongbei), and the maritime province of Siberia in Russia. Although it is not known whether historical documents described cultivated or wild ginseng, in the present review, we discuss historical accounts concerning *P. ginseng*, the role of *P. ginseng* in traditional prescriptions, and experimental evidence from pharmacological and clinical studies of traditional prescriptions containing *P. ginseng* (Table 1).

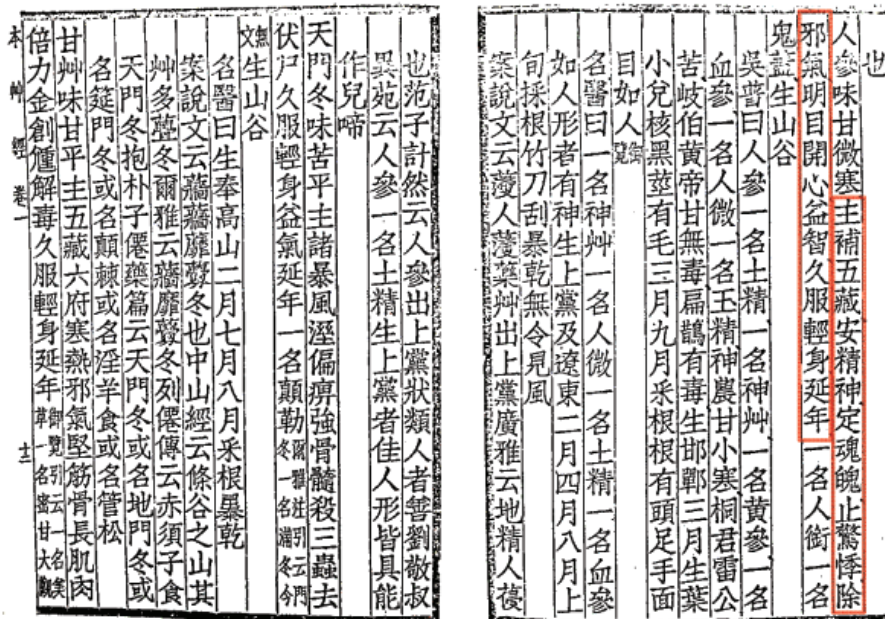


Fig. 1. The description of ginseng in the Shennong Bencao Jing (神農本草經), which explains the function of ginseng. The pharmacological functions of ginseng, which was regarded as a high-grade herb, were first described in the Shennong Bencao Jing. The Shennong Bencao Jing was written in the 1st century by an unknown author.

Table 1. Summary of the pharmacological activities of ginseng-containing prescriptions described in the Shang-Han Lun in either animal or human studies

Name of formula (in Korean)	Name of formula (in Chinese)	Name of formula (in Japanese)	Species	Pharmacological evaluation	References
Banhasasim-tang 半夏瀉心湯	Ban-Xia-Xie-Xin-Tang	Hangeshashin-to	Human	Dyspepsia	[3]
			Human	Diarrhea	[4,5]
Sosiho-tang 小柴胡湯	Xiao-Chai-hu-Tang	Shosaiko-to	Mice	Diarrhea	[6]
			Rat	Anaphylaxis	[7]
			Human	Hepatic injury	[8-14]
			Rat	Hepatic injury	[15-21]
			Mouse	Hepatic injury	[22]
			Rat	Immune modulation	[23]
			Mouse	Immune modulation	[24-32]
Insam-tang 人蔘湯	Ren-Shen-Tang	Ninjin-to	Mouse	Diabetes	[33]
Guibi-tang 歸脾湯	Gu-Pi-Tang	Kihi-to	Rat	Dementia	[34]
			Mouse	Dementia	[35]
			Rat	Osteopenia	[36]
Sipjeondaebotang 十全大補湯	Shi-Quan-Da-Bu-Tang	Juzentaiho-to	Rat	Thrombocytopenic purpura	[37,38]
			Mouse	Dementia	[39]
			Human	Atopic dermatitis	[40]
			Human	Anemia	[41,42]
			Human	Otitis	[43]
			Mouse	Cancer	[44-46]
			Rat	Cancer	[47]
Bojungikki-tang 補中益氣湯	Bu-Zhong-Yi-Qi-Tang	Hochuekki-to	Mouse	Immune modulation	[48-54]
			Human	Fatigue	[55,56]
			Mouse	Fatigue	[57,58]
			Rat	Diabetes	[59]
			Human	Immune modulation	[60-64]
			Mouse	Immune modulation	[65-73]
			Hamster	Cancer	[74]
			Mouse	Lung injury	[75]
			Human	Inflammation	[76,77]
			Mouse	Inflammation	[78]
			Rat	Osteopenia	[79]
			Human	Atopic dermatitis	[80]
			Rat	Liver injury	[81]
			Mouse	Antibacterial	[82]
			Mouse	Anemia	[83]
Insamyangyoung-tang 人蔘養營湯	Ren-Shen-Yang-Rong-Tang	Ninjinyouei-to	Rat	Liver injury	[81]
			Mouse	Amnesia	[84]
			Mouse	Immune modulation	[85-88]
			Rat	Immune modulation	[89]
			Mouse	Colitis	[90]
			Rat	Liver injury	[91]
			Dog	Gastrointestinal motility	[92,93]
Daegeonjung-tang 大建中湯	Da-Jian-Zhong-Tang	Daikenchu-to	Rat	Gastrointestinal motility	[94-96]
			Mouse	Gastrointestinal motility	[97,98]
			Human	Gastrointestinal motility	[99,100]
			Guinea pig	Blood flow	[101,102]
			Human	Blood flow	[103]
			Rat	Blood flow	[104]
			Rat	Diabetes	[105]
			Mouse	Amnesia	[106]
			Rat	Spinal cord injury	[107]
			Rat	Liver injury	[108]
Siho-ga-yonggolmoryeu-tang 柴胡加龍骨牡蠣湯	Chai-Hu-Jia-Long-Gu-Muli-Tang	Saikokaryukotsuborei-to	Rat	Cerebral ischemia	[109-113]
			Rabbit	Atherosclerosis	[114]
Sihokyeji-tang 柴胡桂枝湯	Chai-Hu-Gui-Zhi-Tang	Saikokeishi-to	Rat	Gastric ulcer	[115]
			Rat	Liver injury	[116,117]
			Mouse	Hepatic drug-metabolizing enzyme activity	[118]
Bekho-ga-Insam-tang 白虎加人蔘湯	Bai-Hu-Jia-Ren-Shen-Tang	Byakkokaninjin-to	Rat	Pancreatitis	[119-122]
			Rat	Water balance	[123]
			Mouse	Water balance	[124]
			Rat	Salivary secretion	[125]
			Mouse	Salivary secretion	[126]
			Mouse	Atopic dermatitis	[127,128]
			Mouse	Antihyperglycaemia	[129]
Ome-whan 烏梅丸	Wu-Mei-Wan	Ubai-gan	Rat	Colitis	[130,131]

本草綱目 上品 卷第一

甘藷(一) 無毒。主溫中，下氣，煩滿，短氣，傷寒，欬嗽，止渴，通經脈，利血氣，解百藥毒，為九土之精。安和七十二種石，一千二百種草。一名蜜甘，一名美草，一名蜜草，一名路(二)。生河西積沙山及上郡二月、八月除日採根，暴乾，十日成。唐、乾、苦參為之使。惡遠志、反大戟、芫花、甘遂、海藻。(綱目) 《本草綱目》注為除之才文。按此文《本草綱目》注曰有者疑。

(一) 甘藷 補益千金寶。《大綱》卷六。
 (二) 名路。《和名》同，其說各本一作「一名路草」，又《急就篇》顏師古注云「甘藷，一名蜜草，一名路，一名蜜，一名蜜」。
 (三) 元、乾、苦參為之使，惡遠志，反大戟、芫花、甘遂、海藻。(綱目) 《本草綱目》注為除之才文。按此文《本草綱目》注曰有者疑。

人參(一) 微溫，無毒。主治腸胃中冷，心腹鼓痛，胸膈逆滿，霍亂吐逆，調中，止消渴通血脈，破堅積(二)，令人不忘。一名神草，一名人微，一名土精，一名血參。如人形者有神。生上黨及遼東。二月、四月、八月月上旬採根，竹刀刮，暴乾，無令見風。唐、乾、苦參為之使。惡遠志、反藜蘆。

(《本經》原文)
 人參，味甘，微寒。主補五藏，安精神，定魂魄，止驚悸，除邪氣，明目，開心益智。久服輕身延年。一名人街，一名鬼蓋。生山谷。
 (一) 人參 補益御覽卷九一、《千金翼》。
 (二) 破堅積，《本草綱目》作「補堅積」。

Fig. 2. The description of ginseng in the Mingyi Bielu (名醫別錄), which explains the function of ginseng. The Mingyi Bielu was written by Hongjing Tao.

A RETROSPECTIVE ON GINSENG IN HISTORICAL DOCUMENTS

The pharmacological functions of ginseng, which was considered a high-grade herb, were first described in the Shennong Bencao Jing. Ginseng can nourish or tonify 5 vital organs of the body (the spleen, lung, heart, kidney, and liver), has sedative properties, is used for palpitations to restore a normal pulse, dispels pathogenic factors, improves visual acuity and mental activity, and enhances longevity with long-term intake (Fig. 1). The Shennong Bencao Jing was written in the 1st century by an unknown author, and the Mingyi Bielu (名醫別錄), which described 365 different types of herbs, was written by Hongjing Tao (陶弘景, AD 456-536). Hongjing Tao also published a book titled the Bencaojing Jizhu (本草經集注), in which 730 kinds of herbs were discussed. In the Mingyi Bielu, additional properties of ginseng were described, including curing internal coldness, pain in the chest or abdomen, sensations of fullness in the chest, vomiting, and diarrhea. Ginseng can also be used to

本草綱目 上品 卷第一

人參(一) 微溫，無毒。主治腸胃中冷，心腹鼓痛，胸膈逆滿，霍亂吐逆，調中，止消渴通血脈，破堅積(二)，令人不忘。一名神草，一名人微，一名土精，一名血參。如人形者有神。生上黨及遼東。二月、四月、八月月上旬採根，竹刀刮，暴乾，無令見風。唐、乾、苦參為之使。惡遠志、反藜蘆。

(《本經》原文)
 人參，味甘，微寒。主補五藏，安精神，定魂魄，止驚悸，除邪氣，明目，開心益智。久服輕身延年。一名人街，一名鬼蓋。生山谷。
 (一) 人參 補益御覽卷九一、《千金翼》。
 (二) 破堅積，《本草綱目》作「補堅積」。

勞七傷，虛損衰羸，止嘔咳，補五臟六腑，保中守神，消胸中痰，治肺痿及痢疾，冷氣逆上，傷寒不下，食凡虛而多夢，紛紜者加之。氣止煩躁，變酸水，消食開胃。調中治氣，殺金石藥毒，明治肺胃腸氣不足，肺氣虛促，短氣少氣，補中緩中，瀉心脾，開中火邪。止渴生津，液元治男婦一切虛證，發熱自汗，眩暈頭痛，反胃吐食，痰涎滑瀉，久痢小便頻數，淋瀝，勞倦內傷，中風中痰，痰癆，吐血，嗽血，下血，血淋，血崩，胎前產後諸病。

發 明 宏 景 曰 人 參 性 溫 補 氣 壯 陽 益 精 補 血 養 心 益 神 治 虛 損 衰 羸 止 嘔 咳 補 五 臟 六 腑 保 中 守 神 消 胸 中 痰 治 肺 痿 及 痢 疾 冷 氣 逆 上 傷 寒 不 下 食 凡 虛 而 多 夢 紛 紜 者 加 之 氣 止 煩 躁 變 酸 水 消 食 開 胃 調 中 治 氣 殺 金 石 藥 毒 明 治 肺 胃 腸 氣 不 足 肺 氣 虛 促 短 氣 少 氣 補 中 緩 中 瀉 心 脾 開 中 火 邪 止 渴 生津 液 元 治 男 婦 一 切 虛 證 發 熱 自 汗 眩 暈 頭 痛 反 胃 吐 食 痰 涎 滑 瀉 久 痢 小 便 頻 數 淋 瀝 勞 倦 內 傷 中 風 中 痰 痰 癆 吐 血 嗽 血 下 血 血 淋 血 崩 胎 前 產 後 諸 病

Fig. 3. The description of ginseng in the Bencao Gangmu (本草綱目), which explains the function of ginseng. The Bencao Gangmu is the most complete and comprehensive pre-modern herbal text.

relieve thirst and feelings of solidness, to enhance cognitive function, and to improve blood circulation (Fig. 2). These pharmacological properties of ginseng were also described in the Bencao Gangmu, which is the most complete and comprehensive pre-modern herbal textbook. In addition, Shizhen Li (李時珍, 1518-1593) discussed several symptoms treatable with ginseng, including general weakness, spontaneous sweating and fever, vertigo and headache, regurgitation and vomiting, alternating fever and chills, chronic diarrhea, increased urination or stranguria, fatigue, externally contracted wind or hot attack, cramps, vomiting blood (hematemesis), bleeding from the rectum, bloody urinary leakage, abnormal uterine bleeding, and discomfort before or after parturition (Fig. 3). Several published documents have also referred to the descriptions in the Shennong Bencao Jing, Mingyi Bielu, and Bencao Gangmu. The Hyangyak-jibseongbang was published during the Chosun Dynasty and referred to the pharmacological activities of ginseng described in the Mingyi Bielu. The Donguibogam, which was added



Fig. 4. The description of ginseng in the Donguibogam (東醫寶鑑), which explains the function of ginseng. The Donguibogam also describes additional activities of ginseng as well as the functions listed in the Bencao Gangmu.

to the World Heritage List in 2009 by UNESCO, also described the activities of ginseng, including those described in the Shennong Bencao Jing (i.e., the use of ginseng to cure general weakness, acute vomiting with diarrhea [cholera], hiccups and vomiting, atrophic lung disease and phlegm) (Fig. 4). In addition to the aforementioned texts, many published works have described similar activities. Therefore, *P. ginseng* was likely considered a medicinal herbal for the treatment of general weakness, acute vomiting with diarrhea, anxiety or mental health. It is unclear whether ancient medical practitioners such as Shizhen Li (李時珍), Zhong Jing Zhang (張仲景), or Jun Heo (許浚) knew the functions of ginseng. However, the pharmacological activities listed in historical documents are also supported by recent experimental and clinical studies (vide infra).

Although the pharmacological activities of ginseng were described in the Shennong Bencao Jing, illustrations of the variety of ginseng used at that time were not provided. The Bencao Gangmu described ginseng used

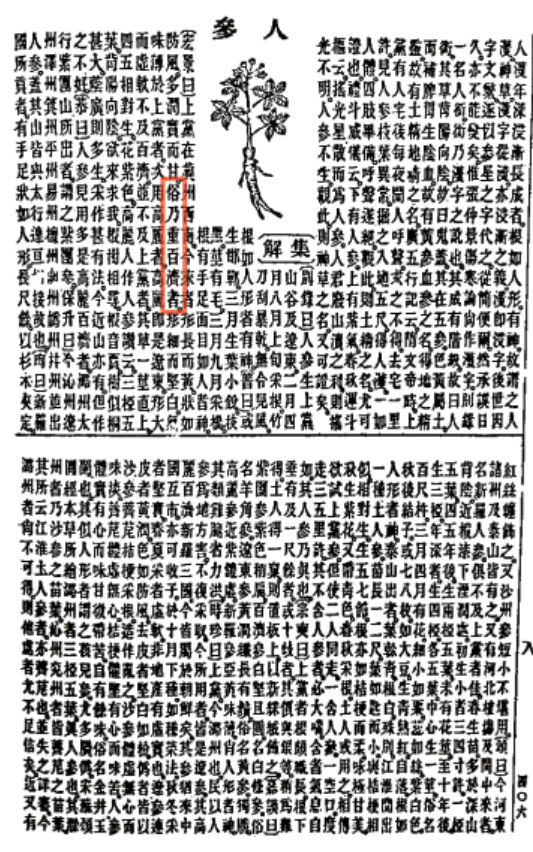


Fig. 5. The description of ginseng in the Bencao Gangmu, which explains the origin of ginseng. Baekje (百濟) represents the Baekje Dynasty, which governed the western part of the Korean Peninsula from 18 BC to AD 666.

in the Baekje Dynasty, and, in this case, an illustration was provided (Fig. 5). The Baekje Dynasty (百濟, 18 BC-AD 660) governed the western part of the Korean Peninsula and actively traded with China, suggesting that the Korean Peninsula might have been suitable for the cultivation of ginseng and that Korean ginseng may have been used in herbal prescriptions prior to the Ming Dynasty. However, the illustration of ginseng in the Bencao Gangmu differs slightly from that of the Bencao Baiyao (本草備要), which was written by Wang Ang (汪昂) in 1694 during the Qing Dynasty. The illustration in the Bencao Baiyao is very similar to *P. ginseng* (Fig. 6). Wang Ang edited the Bencao Baiyao and included herbs from the Shennong Bencao Jing and the Bencao Gangmu. In the Bencao Gangmu, the shape of the ginseng root was described as resembling the human body or the extremities of the human body. Therefore, although the depiction of ginseng differs slightly among historical documents, the description provided in the Bencao Gangmu may have referred to *P. ginseng*.

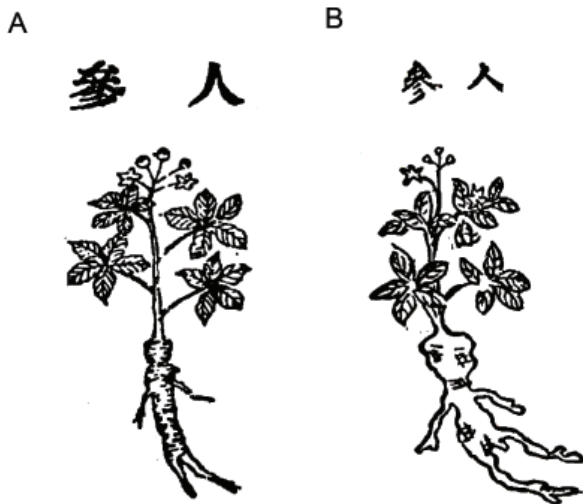


Fig. 6. Illustrations of ginseng from historical documents. (A) Illustrations of ginseng from the Bencao Gangmu (本草綱目) and (B) the Bencao Baiyao (本草備要) are presented.

THE PHARMACOLOGICAL ACTIVITIES OF *PANAX GINSENG* IN TRADITIONAL PRESCRIPTIONS

Among the 113 prescriptions (18.6%) described in the Shang-Han Lun, which was written by Zhong Jing Zhang (150-219 AD), 21 prescriptions contained ginseng, including Banhasasim-tang (半夏瀉心湯, Ban-Xia Xie-Xin Tang in Chinese or Hangeshashin-to in Japanese) and Soshiho-tang (小柴胡湯, Xiao-Chai-hu Tang in Chinese or Sho-saiko-to in Japanese). The Shang-Han Lun covers specific symptoms of disorders and their corresponding treatments and is designated as one of the four fundamental texts of traditional Chinese medicine [132]. In addition, among the 3,944 prescriptions (16.6%) in the Donguibogam, which was written by Jun Heo, 653 prescriptions containing ginseng as an ingredient.

Several traditional prescriptions were prepared from ginseng, which was used for its restorative, tonic, nootropic, and anti-aging properties, or for dispelling pathogenic factors, as described in the Shennong Bencao Jing. Among ginseng-containing prescriptions, the classic and basic prescription is Sagunja-tang (四君子湯, Sijunzi Tang in Chinese or Shikunshi-to in Japanese). Sagunja-tang was prescribed for conditions such as hypodynamia, lassitude and anorexia. As a main ingredient in Sagunja-tang, ginseng exerts various pharmacological activities, such as organ tonification and restorative activities, as described in the Shennong Bencao Jing and Bencao Gangmu. These pharmacological activities were also accomplished by Sipjeondaabo-tang (十全大補湯, Shi-

quan-da-bu-tang in Chinese or Juzen-taiho-to in Japanese), which was composed of 10 types of herbs, including four herbs (Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Glycyrrhizae Radix et Rhizoma) from Sagunja-tang, four herbs (Angelicae Gigantis Radix, Cnidii Rhizoma, Paeoniae Radix, Rehmanniae Radix Preparata) from Samul-tang (四物湯, Si-Wu-Tang in Chinese, and Shimotsu-to in Japanese) and additional herbal materials, such as Astragali Radix (*Astragalus membranaceus*) and Cinnamomi Cortex (*Cinnamomum cassia*). Sipjeondaabo-tang was prescribed to patients who suffered from weakness or spontaneous sweating, which were described as being treatable with ginseng in the Bencao Gangmu. In addition, Doksam-tang (獨參湯, Dushen Tang in Chinese or Dokujin-to in Japanese), which was only composed of ginseng, was used for seriously ill patients [133], as depicted in the Shi Yao Shen Shu (十藥神書), which was written by Ke-Jiu Ge (葛可久) in 1348 during the Yuan Dynasty. In the Shennong Bencao Jing, ginseng was said to dispel pathogenic factors. In the Donguibogam, Talmjung-san (identical to Doksam-tang) was also used for the elimination of pathogenic factors. Recently, An et al. [134] reported the effects of ginseng formulae on stable chronic obstructive pulmonary disease, which represents a pattern of Qi deficiency involving either the lung or the spleen. For seriously ill patients, ginseng can also be used with Aconiti root, which is found in Sambu-tang (參附湯, Shen Fu Tang in Chinese), as described in the Fu Ren DA Quan Liang Fang (婦人大全良方), which was written by Zi-Ming Chen (陳自明) during the Song Dynasty. In the aforementioned formulae, ginseng is the main active ingredient and exerts restorative, tonic or nourishing effects on hypodynamia and ameliorates the effects of serious illness, as described in the Shennong Bencao Jing and the Bencao Gangmu.

Although Jeongji-whan prescription (定志丸, Dingzhi Wan in Chinese) is listed in the Yixue Xinwu (醫學心悟), which was written by Goupeng Cheng (程國彭) in 1732, this prescription has not been certified as a herbal prescription in Japan. However, in the mid-1990s, the Nishiyama group in Japan reported the effects of DX-9386, which possesses ingredients that are identical to those of Jeongji-whan, on brain function [135]. The Jeongji-whan prescription was described as being active against anxiety, palpitation, and amnesia, and ginseng was used as the main ingredient. Kami-guibi-tang (加味歸脾湯, Jia Wei Gu Pi Tang in Chinese or Kami-kihi-to in Japanese), or Guibi-tang (歸脾湯, Gu Pi Tang in Chinese or Kihi-to in Japanese), was described in classical literature

as being effective for the treatment of insomnia, anemia, amnesia, depression, and neurosis [35]. Tohda et al. [35] suggested that Guibi-tang is an attractive candidate as an anti-dementia drug. Thus, although the improvement in brain function was not solely dependent on ginseng, these prescriptions made use of the effects of ginseng on anxiety, amnesia, and palpitation, which were described in the Shennong Bencao Jing.

In particular, the Mingyi Bielu stated that ginseng relieves thirst (Sogal in Korean, Xiao Ke in Chinese or Shoukatsu in Japanese, 消渴), and the Bencao Gangmu referred to the description of ginseng in the Mingyi Bielu. As described in historical documents, the symptoms of thirst are similar to those of diabetes. Baekho-ga-Insam-tang (白虎加人蔘湯, Byakko-ka-ninjin-to in Japanese or Bai Hu Jia Ren Shen Tang in Chinese), which was a Shang-Han Lun formula, relieves thirst caused by internal fever [126].

In addition to the aforementioned pharmacological properties, ginseng can also be used to alleviate diarrhea and vomiting. Insam-tang (人蔘湯, Ninjin-to in Japanese or Ren Shen Tang in Chinese), which is composed of Ginseng Radix, Glycyrrhizae Radix, Atractyloides Rhizome, and Zingiberis Rhizome, has been used for the treatment of diarrhea or anorexia and tonifies the Qi of the spleen. In Banhasasim-tang, ginseng is used as a co-ingredient [6]. Even when included as co-ingredient in Banhasasim-tang, ginseng enhances Qi and contributes to the alleviation of diarrhea or intestinal catarrh. Recently, Taiwanese doctors investigated the most common prescriptions from the Shang-Han Lun. Banhasasim-tang and Soshiho-tang (Sho-saiko-to in Japanese and Xiao Chai Hu Tang in Chinese) were prescribed at 10.24% and 9.11% in the Shan-Han Lun formulae, respectively.

Additionally, in the Shennong Bencao Jing, ginseng is listed as an anti-aging factor. Kyungok-Ko, a sticky extract composed of Ginseng Radix, Rehmannia juice, Hoelen (*Poria Sclerotium*), and honey, was described as having anti-aging activities when administered for an extended period of time [136]. Thus, various pharmacological activities of ginseng were described along with those of other active ingredients.

In Doksam-tang, the ginseng content is equal to 37.5 g, and ginseng is the active ingredient in this prescription [137]. According to the German Commission E, crude preparations of 1 to 2 g of dried root powder of ginseng can be taken every day for up to three months. A decoction can be prepared by simmering 3 to 9 g of dried ginseng root in 720 to 960 mL of water [138]. In decoction, ginseng is included at a dosage of 3 to 9 g as the main

ingredient in most prescriptions, except for Doksam-tang. In some formulations, such as Kami-guibi-tang or Guibi-tang, ginseng is included at a dosage of 15 g [137]. Thus, ginseng has been used at dosages ranging from 3 to 37.5 g. In chemical drugs, the amount of intake rarely exceeds 5 to 10 times the usual dose. Adverse effects or toxicity caused by ginseng overdose should be avoided. However, *P. ginseng* is well tolerated, and its adverse effects are mild and reversible [139].

THE USE OF GINSENG-CONTAINING PRESCRIPTIONS IN MODERN PHARMACOLOGICAL EXPERIMENTS

Over the last several decades, traditional Chinese medicine has become a significant form of complementary and alternative medicine used by patients in Europe and North America [140]. In addition to traditional Chinese medicine, traditional Japanese medicine (Kampo) and traditional Korean medicine (Hanbang), which are referred to as traditional herbal medicine in this review, have been accepted as a form of complementary and alternative medicine by patients [141,142]. In Western medicine, randomized clinical trials are generally accepted as the most reliable approach to testing the efficacy of medicines and treatments; however, in traditional herbal medicine, clinical evidence was observed and recorded descriptively in the literature [143]. Although the theoretical frameworks of Western medicine and traditional herbal medicine are different, scientific studies on the efficacy of traditional herbal medicine using randomized clinical trial techniques are becoming more popular [143]. Such evidence-based medicine integrates the best evidence from research with clinical expertise and patient values [142]. Using clinical trials or basic scientific research, the efficacy of traditional prescriptions for specific diseases can be determined, which has the potential to expand the use of traditional formulae.

Western research models are used in Japan to study traditional medicine, and the approach is based on conventional Western disease nosology and conventional immunology [142]. To date, most traditional herbal medicine experiments have been performed *in vivo* on animals or humans by Japanese scientists, and the results have been published in peer-reviewed international journals. Sipjeondaebo-tang is the most commonly investigated herbal medicine by scientists and clinicians. Traditionally, Sipjeondaebo-tang, a decoction with 10 medicinal herbs, has been used to treat patients with anemia, anorexia, or fatigue. The pharmacological activities of Sipjeondaebo-

tang affect the systemic immune functions of T and B cells, macrophages and NK cells and cells of the hematopoietic and intestinal immune system. Nakamoto et al. evaluated the effects of Sipjeondaebo-tang in patients receiving hemodialysis with erythropoietin-resistant anemia [41]. Their results showed that Sipjeondaebo-tang improved erythropoietin-resistant anemia in end-stage renal disease patients, and similar findings were observed in the perioperative period [144]. In addition, Sipjeondaebo-tang exerted a protective influence against intractable and recurrent infections in immature immune systems [43]. Thus, the effects of Sipjeondaebo-tang on the immune system have been confirmed by clinical trials and animal experiments, providing experimental evidence in support of the traditional use of Sipjeondaebo-tang.

Bojungikki-tang (補中益氣湯, Bu-zhong-yi-qi-tang in Chinese or Hochu-ekki-to in Japanese) has been widely used in China, Japan, and Korea for chronic fatigue syndrome and is composed of 10 species of medicinal herbs. In particular, in Bojungikki-tang, Ginseng Radix and Astragali Radix are used in higher proportions. Several clinical trials were conducted to examine whether this formulation alleviates cancer-related fatigue and improves immunological capacity in elderly patients. The results of these trials suggested that Bojungikki-tang could help to improve age- or disease-related impairment in immune function [55,62]. Animal studies also showed that Bojungikki-tang exhibits immunopharmacological activity against microbial infections, and positive results were obtained in a murine model of chronic fatigue syndrome [57,82,145]. Although the main active ingredient in Bojungikki-tang has not been elucidated, Ginseng Radix and Astragali Radix could contribute to the effects of Bojungikki-tang [62]. Insamyangyoung-tang (人蔘養營湯, Ren-shen-yang-rong-tang in Chinese or Ninjin-youei-to in Japanese) is another prescription for the modulation of physiological immunity [85].

Several ginseng-containing prescriptions, including Daegeonjung-tang (大建中湯, Da Jian Zhong Tang in Chinese or Dai-kenchu-to in Japanese), Insam-tang (人蔘湯, Ninjin-to in Japanese or Ren Shen Tang in Chinese), and Banhasasim-tang, have been used to treat gastrointestinal problems, such as gastric atony, vomiting and anorexia. Substantial effort has been made to elucidate the pharmacological activities of these formulations. In a human study, Daegeonjung-tang increased gastrointestinal motility and improved ileal function by increasing motilin and vasoactive intestinal peptide levels in the plasma [146,147]. Postoperative ileus is an adverse consequence of abdominal surgery and leads to prolonged periods of

hospitalization and increased healthcare costs [148]. Itoh et al. [148] reported the effectiveness of Daegeonjung-tang on postoperative ileus, and this prescription has attracted attention for the treatment of postoperative ileus in Japan [149,150]. Insam-tang, which has been used for the treatment of gastroenteritis, gastric atony, gastrectasis, vomiting, and anorexia, is also useful for the treatment of postoperative ileus [151]. Because ginseng is not the main ingredient of either of these prescriptions, the active compound of Insam-tang may be 6-gingerol or 6-shogaol from Zingiberis Rhizome [104,151]. However, ginseng cannot be excluded as a contributor to gastrointestinal motility. Recently, Banhasasim-tang was reported to be effective against irinotecan-induced diarrhea [5]. Kase et al. [6] suggested that Ginseng Radix and Zingiberis Rhizome in Banhasasim-tang accelerate gastrointestinal motility.

Alzheimer's disease is the most common type of degenerative dementia. Cholinergic hypofunction and inflammatory responses induced by amyloid- β protein are the main causes of this disease. Consequently, acetylcholinesterase inhibitors are clinically used for the treatment of Alzheimer's disease, and anti-oxidative or anti-inflammatory agents may also be applicable because a redox imbalance is observed in the brains of Alzheimer's disease sufferers [152]. In addition, degenerative changes in the forebrain cholinergic system are reportedly linked to oxidative stress [153]. Ginseng is a well-known, anti-aging herb, and cognitive functions decrease gradually with age. Several traditional herbal prescriptions containing ginseng have been demonstrated to enhance cognitive activities. Saengmaek-san (生脈散, Shengmai-san in Chinese), which is composed of 3 different kinds of herbs (Ginseng Radix, Ophiopogon Rhizome, and Schisandrae Fructus), has been used to treat symptoms related to cardiovascular diseases, such as heart failure and stroke. This formulation has protective qualities against oxidative damage *in vitro* and *in vivo* [154,155]. Recently, Saengmaek-san, which possesses anti-oxidative properties, was reported to ameliorate scopolamine-induced cognitive dysfunctions via acetylcholinesterase inhibition [106]. In addition, DX-9386, which consists of Ginseng Radix, Polygalae Radix, Acorus Radix and Hoelen and is identical to Jeongji-whan, has anti-aging and memory-ameliorating effects [156,157]. Egashira et al. [84] reported that Insamyangyoung-tang may ameliorate memory dysfunction by enhancing the cholinergic system. Guibi-tang was described in historical documents as an effective prescription for psychotic problems such as insomnia, amnesia, depression, and neurosis. Recently, the administration of Guibi-tang for 3 consecu-

tive days was shown to ameliorate spatial and object-recognition memories in amyloid β protein-injected mice [35], suggesting that this formulation is an attractive candidate for anti-dementia drugs. Similar activities were also observed in Kyungok-Ko [158]. In these formulae, ginseng likely exerts its pharmacological effects on the central nervous system.

Diabetes is another serious disease, and its symptoms include severe polydipsia and polyuria. Baekho-ga-Insam-tang is a herbal medicine used for the relief of diuresis, thirst and dermal pruritus, which are associated with diabetes [124]. This result has been confirmed by experiments performed on, KKA^y mice, which are genetic animal models of diabetes mellitus [159]. The administration of Baekho-ga-Insam-tang relieves diuresis, thirst, and dermal pruritus by increasing kidney aquaporin 2 and skin aquaporin expression. In addition, Baekho-ga-Insam-tang enhances salivary secretion by increasing aquaporin 5 in a rat thirst model [126], suggesting that this formulation could be useful for xerostomia. Thus, the functions and efficacies of the aforementioned ginseng-containing prescriptions have been confirmed by modern experimental pharmacology. We summarized the results of *in vivo* animal or human studies on ginseng-containing prescriptions in Table 1, which includes the prescriptions mentioned in the present review.

THE VARIETY OF SPECIES IN THE PLANT GENUS PANAX

There are 13 species of ginseng in the Araliaceae Family, including [1] 1) *P. ginseng* Meyer, 2) *P. quinquefolius* L., 3) *P. japonicus* L., 4) *P. notoginseng* (Burk.) FH Chen, 5) *P. pseudoginseng* Wallich, 6) *P. vietnamensis* Ha et Grushv, 7) *P. omeiensis* J. Wen, 8) *P. trifolius* L., 9) *P. sinensis* J. Wen, 10) *P. stipuleanatus* HT Tsai & KM Feng, 11) *P. wangianus* Sun, 12) *P. zingiberensis* CY Wu & KM Feng, and 13) *P. major* Ting. The most commonly used *Panax* species include plants 1) to 6) in the list above [160]. *P. vietnamensis* was found in the mountainous regions of central Vietnam in the 1970s, and *P. pseudoginseng* has been used as a folk medicine in the Himalayas [161].

Since the pioneering work of Dr. Israel I. Brekhman, a Russian scientist, *P. ginseng* has been extensively studied [162,163]. For example, in 1964, Wood et al. [164] reported the vasodilatory effect of *P. ginseng* obtained from Keumsan, Korea, and in 1971, Lee and Huemer [165] reported the antitumor activity of ginseng obtained from Kangwhado, Korea. The Shibata group in Japan

has studied the chemistry of the saponins and sapogenins of the white ginseng, *P. ginseng*, which is cultivated in Japan [161].

Hsu [166] reported the pharmacological activities of *P. shinseng* Nies, var. *notoginseng* Burkill and published a picture of *P. shinseng* var. *notoginseng*, which has a different morphology than *P. ginseng*. According to Hsu's studies, *P. shinseng* var. *notoginseng* was first employed as a medicine not much earlier than the time of Shizhen Li's first report in the Bencao Gangmu. Therefore, this species of ginseng was not mentioned in texts on Chinese medicine produced before this period [166]. Thus, although other species of ginseng are also active, *P. ginseng* is the most popular and active species.

The therapeutic potency of ginseng is dependent on its geographical locality, dosage, and processing. Red ginseng and sun ginseng refer to processed ginseng [167,168]. Several studies have been conducted to compare the effects of different species of ginseng. For wound healing and hypoglycemic effects, *P. ginseng* is superior to *P. quinquefolius*, whereas *P. quinquefolius* displays better anticancer effects [169]. Similarly, *P. ginseng* (ginseng in Korea) has the highest therapeutic potency for the treatment of diabetes. *P. quinquefolius* (American ginseng) is a medium-potency-grade ginseng, and *P. japonicus* (Japanese ginseng) is considered a low-potency-grade ginseng [170].

PERSPECTIVES

In the future, a comprehensive and objective evaluation of ginseng should be conducted using evidence-based medicine to further elucidate the intriguing properties of ginseng in terms of treatment of various diseases shown in recent review articles [171,172].

CONCLUSION

In the present review, ethnopharmacological accounts of *P. ginseng* were discussed. Since the description of ginseng from the Korean Peninsula was first published in the Bencao Gangmu, *P. ginseng* has become the most commonly used therapeutic ginseng. Modern chemical and biological drugs are suitable for the treatment of diseases with specific causes and pathologies but are not suitable for diseases with multiple factors, such as diabetes, Alzheimer's disease, and chronic fatigue. Based on historical accounts and recent experimental or clinical studies, ginseng and ginseng-containing herbal prescriptions are useful for the treatment of chronic diseases.

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