



Short Review

Ancient herbal therapy: A brief history of *Panax ginseng*

Maria Assunta Potenza^a, Monica Montagnani^a, Luigi Santacroce^{b, c, *},
Ioannis Alexandros Charitos^{c, d}, Lucrezia Bottalico^c



^a Department of Biomedical Sciences and Human Oncology - Section of Pharmacology, School of Medicine, University of Bari "Aldo Moro," Policlinico University Hospital of Bari, Bari, Italy

^b Interdisciplinary Department of Medicine, Microbiology and Virology Unit, School of Medicine, University of Bari "Aldo Moro," Policlinico University Hospital of Bari, Bari, Italy

^c Interdepartmental Research Center for Pre-Latin, Latin and Oriental Rights and Culture Studies (CEDICLO), University of Bari "Aldo Moro," Policlinico University Hospital of Bari, Bari, Italy

^d Emergency/Urgent Department, National Poisoning Center, Riuniti University Hospital of Foggia, Foggia, Italy

ARTICLE INFO

Article history:

Received 7 January 2022

Received in revised form

7 March 2022

Accepted 17 March 2022

Available online 23 March 2022

Keywords:

History of medicine

History of pharmacology

Ethnopharmacology

Panax genus

Korean Red Ginseng

ABSTRACT

Ginseng was the most revered of the herbs in ancient times in China, Korea, Japan, America. Ginseng was discovered over 5000 years ago in the mountains of Manchuria, China. References to ginseng are found in books dating back more than two millennia. It is revered by the Chinese people as it is considered a herb for everything use and therefore for a wide range of diseases (currently its Latin name derived from the Greek *panacea*, meanings, that is, for everything). So, it was used exclusively by the Chinese Emperor's, and they were willing to pay the price without problems. Increasing its fame, ginseng brought a flourishing international trade that allowed Korea to supply China with silk and medicines in exchange for wild ginseng and later along with what grows in America.

© 2022 The Korean Society of Ginseng. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Herbs have played a key role in human health with their beneficial effects and their use to treat various types of ailments or diseases has been around since ancient times. In most cultures they were often used in rituals due to their magical and healing properties. The ancients used a wide range of medicinal plants and had a thorough understanding not only of the healing powers but also of the toxicity of plants [1,2]. In fact, first the physician Dioskouridis Pedanios (Πεδάνιος Διοσκουρίδης, 40–90 AD) will say that the quantity introduced (dose) can cause cure or it can cause damage (toxicity) to the living being if we don't know how to manage the drug. In the ancient civilizations of Egypt, Europe, the Middle East, India, Korea, China, and Japan, around 3000 BC, the use of herbs became more sophisticated where the first written descriptions of medicinal plants were attempted. Ginseng thrives in the mountain

forests of the northern temperate zone of the Far East and is therefore cultivated and/or harvested in Korea, China, Japan, America, and Russia [3,4]. Cultivated oriental ginseng has two varieties, white and red. The one that circulates throughout Europe is of Korean origin, it is mainly of the red variety is from that of China. Its name ginseng refers to many species of the genus *Panax*. Today around the world, commercially the plant Ginseng is present in thirty five countries [5]. The two most used species are the Asian ginseng (*Panax ginseng* C.A. Meyer), which includes China ginseng (White variety), Korean ginseng (Red variety), and American ginseng (*P. quinquefolium*). On the other hand, *P. ginseng* should not be confused with Siberian "ginseng" the *Eleutherococcus senticosus* which is an alternative to ginseng and is believed to have identical properties [6,7].

Genus *Panax* belonging to family Araliaceae contains eleven species (three varieties) namely *P. trifolius*, *P. notoginseng*, *P. quinquefolius*, *P. ginseng*, *P. pseudoginseng*, *P. zingiberensis*, *P. stipuleanatus*, *P. japonicus*, *P. japonicus* var. *angustifolius*, *P. japonicus* var. *major*, and *P. japonicus* var. *bipinnatifidus* (which are mainly distributed in the Eastern Asia and Northern America). Among them, most of the investigations have been conducted on *P.*

* Corresponding author. Interdepartmental Research Center for Pre-Latin, Latin and Oriental Rights and Culture Studies (CEDICLO), University of Bari, 70123 Bari, Italy.

E-mail address: luigi.santacroce@uniba.it (L. Santacroce).

notoginseng, *P. quinquefolius*, and *P. ginseng* for their pharmacological activity [8–10]. For its extensive use Charles Linnaeus gave to the genus the name *Panax* (Πάνωξ), that derives from the Greek which means “total healing”, such as the ancient healing resin obtained from *Opopanax chironium*, genus of the Apiaceae, a mythical plant for universal remedy such as the goddess Panàkia (Πανάκεια), daughter of the god of medicine Asklepios [11,12]].

In traditional Chinese medicine, it has been used for more than 2000 years and many peoples, considered it a cure for all ailments. There are some differences between raw (fresh) ginseng, Korean White ginseng, and Korean Red Ginseng. Raw ginseng is that extracted from the soil and its moisture content is at least 75%, (not suitable for long-term storage). White ginseng is a thinly peeled and sun-dried 4-year-old raw ginseng and must have a humidity of less than 15% without altering its original form which can be of three forms: straight ginseng, semi-curved ginseng, and curved ginseng. Finally, the red ginseng (pink-brownish color) is steamed with water and then dried for long-term storage up to 20 years. It has a humidity of 15% and has a solid and compact consistency (Fig. 1) [13–15].

2. Chemical composition and active ingredients

The most widely used ginseng species worldwide are Korean ginseng (*P. ginseng*), which is native to the Korean Peninsula and northern China, and American ginseng (*P. quinquefolius*), which is native to the United States and Canada. In general, only *P. ginseng* is called “Korean ginseng” or “ginseng.” Korean ginseng and American ginseng are plants of disparate species that differ in saponins called ginsenosides [15–18]. The red ginseng is produced from fresh ginseng by steaming it without peeling the roots and subsequently drying it and so the quality and quantity of ginsenosides content is different if this procedure varies. The functions of red ginseng as a functional food for health were certified with the application of the Korean law on functional foods for health in 2004 [19]. The type and composition of ginseng is that they confer different qualities as some are common in some species of ginseng

albeit in different quantities, while others are unique in a single species. Ginseng, contains powerful antioxidants which fight the effects of aging. They have also been shown to have a powerful function as adaptive, invaluable substances, helping the body adapt and recover from the effects of stress, illness, and fatigue. Also, ginseng contains vitamins (such as B1, B2, B3, B5, B12, choline), minerals (trace elements zinc, copper, magnesium, calcium, iron, manganese, vanadium, potassium, sodium, phosphorus), volatile oil polysaccharides starch, pectin and sterols [20]. About 50 kinds of ginsenosides have been identified with two major groups *protopanaxadiol* (PPD) and the *protopanaxatriol* (PPT). Most of them, are converted (such as those of red ginseng) thanks to the heat process during the production. Ginsenosides Rg2, Rg6, F4, 20(E)-F4, Rh1, Rh4, Rk3, Rg3, Rg5, Rz1, Rk1, Rg9, and Rg10 were found in red ginseng, and these are converted from the major ginsenosides Rb1, Rb2, Rc, Rd, Rg1, and Re, and their mechanism of action appears to be like that of steroid hormones [13,21]. It is the type and composition of ginseng that gives the different qualities as some ginsengs are common in some types of ginsengs although in different quantities, while others are unique to a single species [13,19]. Studies have shown that Ginseng has a stimulating effect on the central nervous system and helps the body metabolize harmful substances produced by the metabolism such as lactic and pyruvic acid (which are released in stressful situations), is an adaptogen while producing more efficient energy [13,22]. Ginseng, improves physical and mental performance at work for people who work in stressful environments, i.e., noisy, very hot, feverish environments. In addition, Siberian “ginseng”, eleuthero which contains the eleutherosides B (syringin) and E (syringaresinol), has also been shown to improve muscle oxygen consumption and help the body's defenses of unwanted bacteria, fungi and viruses and regulate the intestinal microbiota [23,24]. Additionally, preliminary studies have shown that ginseng can help treat chronic immune diseases such as the acquired immunodeficiency syndrome from HIV and chronic fatigue syndrome. It maintains the homeostasis of the functions of the organism and thus increases the body's resistance to physical stress [24–26]. The washed fresh ginseng root



Fig. 1. The various forms and color of the genus *Panax* according to the preparation and species (such as red or white).

ginsenosides Rh2/Rg3, seems to be beneficial with immune diseases, liver diseases, and cancer [27–30]. Chinese herbal combinations such as Ginseng and Dang can for potential ability to restore immunity in cancer patients, potentiate the therapeutic effect such as mitomycin, cisplatin and other) and avoid part of the adverse toxicity of anticancer agents. Long-term intake of ginseng extracts facilitates the growth of probiotics in the gut microbiota of rats and inhibits the colonization of some pathogenic bacteria including the *Helicobacter pylori* [31–35]. Finally, ginseng has been reported that reduce blood viscosity (reduce clot formation) and normalize blood pressure [34]. However, excessive and chronic use can lead to toxic effects such as blood hypertension, CNS hyperactivation (such as irritability, sleeplessness, dizziness, headache, hypoglycemia, gestational diabetes, vaginal bleeding, intermenstrual bleeding, amenorrhea, diarrhea, nephropathy and others [36–38].

3. The discovery as beneficial plant in the ancient far East

3.1. Korean knowledge on *P. ginseng*

The ancient Koreans called ginseng *shim* term that appeared in the “Guguepganyibangeanhae” text, published during the reign of King Seongjong in 1489. The term “Red” for Ginseng (*Hongsam* in Korean) was reported in the Annals of King Jeongjo of Joseon (1776–1800 AD, 22nd ruler of the Joseon dynasty of Korea) and was introduced in the record of “GoRyeoDoGyeong” (written in 1123 AD) by Seo-Gung (1091–1153 AD, Song Dynasty). In the text “Do Hong-Gyeong” written in 1123 by Seo-Gung (1091–1153 AD), under Song dynasty, the steaming process of ginseng was introduced. In this book 365 kinds of herbs are classified into three types of quality namely high, mediocre and low during the Yuan dynasty and classified ginseng as a high quality medicine. Ginseng is said to strengthen the body’s five digestive organs, bring peace to the mind and remove bad energies [15]. In the early 13th century during the Goryeo’s dynasty developed metal movable type for printing books, 200 years before Johannes Gutenberg in Europe helped to also preserve texts about the *P. ginseng*. There is also a legend (there are no documents) that ginseng cultivation began in the of Punggi (town in the outer regions of Yeongju City). There is only a legend about how the governor Joo Sae-bung of Punggi started the Ginseng cultivation. There is no literature that accurately records the origin of ginseng cultivation in Geumsan. In Korea, *Red ginseng*, there have been attempts to the cultivation of ginseng begun in the late 14th century or early 15th century and the subsequent cultivation was known to professional ginseng growers (only they can produce ginseng) from the 17th and 18th centuries [15,41,42]. In fact, trade with China and Japan was one of the largest markets until the 18th century. Before 1200 AD we are not able to describe exactly the preparation method for red ginseng (steaming time, number of repetitions and drying process) because there are no detailed records. At the end of the 1200s, the process began to be better described and the text by Taekyoung Kim (1850–1927 AD) in the SohoDang miscellany and the method of preparation of red ginseng currently used is described in the Samjung-Yolam (*A Bulletin of Ginseng Policy, 1908, Ministry of Strategy and Finance, The Greater Korean Empire*). Cultivation of *P. ginseng* in Korea began around 11 B.C. with the transplantation of wild ginseng. In 1122 AD, cultivation of ginseng by transplanting ginseng propagated from seeds was begun. Finally, in the 20th century, Kim Taek-yeong wrote about the origin of ginseng cultivation in the work “Hongsamji” (“Sohodang collection”) based on testimony from his parents and government documents [15,41].

3.2. Chinese knowledge about *P. ginseng*

The name Ginseng is Chinese and has origins from the term *Hokkien jîn-sim* and etymologically means “human root”, due to the characteristic forked shape of its root, which resembles human feet. It is still one of the most widespread herbs in the world and its tonic and healing properties make it one of the most important natural aids for toning the human body. Later, the pronounce ‘renschén’ and subsequently *Xiangshen* and *Sangsam* turns into *Shinseng*, and later to *Ginseng*. In fact, due to its human form it represented man in his transmigration of matter and spiritual energy according to Asian tradition [15,39–41].

Many Chinese governors dealt with these medicinal plants as did many herbalists who described their therapeutic utility. In fact, the *Chuan-di-neizsin*, written by the Emperor Chuan-di (2698–2599 BC) is one of the oldest texts of Chinese medicine. Subsequently, medicine in China was influenced by the philosophy of Confucius (552–479 BC). Thus, man is composed of 5 elements (wood, fire, earth, metal, and water) which corresponded to five plants, five senses, etc. [43–45]. For Chinese doctors the balance between the elements: yang (positive masculine), which represented heat and dryness, yin (negative female), which represented liquid and cold derived from the imbalance of these elements [46,47]. Notable for Chinese medicine is the doctrine of the vital force of life, called Qi, that surges through the body, on which not only the diagnosis but also the treatment depends. Chinese doctors were skilled pharmacologists. They used *Punica granatum* and *Allium sativum* root preparations for anthelmintics, arsenic for skin diseases and fever, mercury for syphilis, and rhubarb as a laxative [46,48]. They knew the use of iron for anemia, *Papaver somniferum* (opium) as an analgesic, *Ephedra* for asthma and bronchial diseases. Among these preparations, a drug widely used today is the root of the *Panax ginseng* plant (which means human root) with tonic properties. One of the earliest written texts covering the use of ginseng as a medicinal herb was “Shen Nong’s Pharmacopoeia”, written in China in 196 AD. Subsequently, Li Shizhen wrote in 1596 AD the “Compendium of Herbal Materia Medica”, which reports that Ginseng is a “superior tonic” for patients with chronic diseases and those who were convalescing [49,50]. Ginseng can be mixed with other herbs such as *Safflower* petals, *Angelica sinensis*, *Cinnamon*, *Salvia miltiorrhiza* and other. In 618 AD, the Tang dynasty of China ginseng becomes an important medicine. However, about 400 years ago, the pharmacology text “Pents Kaug-mu”, the first major publication by Li Wen-Yen and his son, describing in detail the effects of ginseng, was written. Ginseng becomes a concept of esoteric interaction between man and nature due to its age and shape [51]. From the animal kingdom they used beetles, snakes (bile of a boa as an antidote to rabies), cobwebs (as gauze), lizard blood, gallstone dust, mouse dung, and other. Mineral medicines include nitro, borax, alum, copper and mercury salts, cinnabar, etc. However, it should be noted that Chinese doctors, to treat smallpox, pulverized the blisters and introduced the powder into the nose (a type of vaccine). For internal use they had juices, infusions, decoctions, wines, powders, swallows, sweets and for external use ointments etc. [52]. In total there are 52 books on Chinese medicine, called “Pen-Tsao” (which means collector of herbs) which mention 1069 plants and 1892 therapeutic preparations. Their information dates to 2500 BC in the botanical studies of the then emperor Chin Nong and the first systematic writing took place in the 16th century BC, and from then dynasty to dynasty were completed. Superstition prevailed in all social classes and doctors were obliged not only to collect herbs, but also to prepare magic medicines. Initially, they made the medicines themselves, but gradually there was a separation of professions, but in the big cities there were doctors, pharmacy owners [53]. The practice of healing



Fig. 2. Illustration and description of mandrake plant (to the right) in Greek (the title in capital letters ΜΑΝΔΡΑΓΟΡΑ (MANDRAGORA) from the manuscript of Dioskouridis Pedanios *Περὶ ὅλης ἰατρικῆς* (De Materia Medica, Folio 90, Dioskouridis di Napoli, National Library, Cod. Gr.1, Naples, source: <https://www.wdl.org/en/item/10690/view/1/181/>).

was free and there were doctors from all walks of life. Anyone who wanted to study pharmacy (Kai-jo-p'outi) had to attend the small school (elementary education, learning to read and write) and the large school (Ta-hio), where science was taught. Then they learned prescription from the book “Yo-sing-fou”, and pharmacology from the “Pen-tsao” [46,54].

4. Early knowledge of *P. Ginseng* in the Western world

4.1. The middle ages

Ginseng when it becomes famous in the Western world is difficult to determine, but most likely through the Arabs, who were familiar with China, they brought its existence to European doctors during the Middle Ages. Ginseng was introduced in Europe in the early Middle Ages by Arabian merchants and Arab navigators such

as Ibn Cordoba that is credited with bringing ginseng back from China in the middle of 9th century AD [55,56]. Arabs were excellent pharmacists, and they combined mixing herbs to improve their healing effects but also the organoleptic properties such as taste and smell for those who were administered. They had their cultural contacts first with the Indian and Chinese medical tradition and then with that of the Roman Christian Empire (now also called Byzantium) and therefore possessed a considerable range of medical and botanical knowledge to create and develop not only herbal therapies. Avicenna (980–1037 AD) was the most famous doctor of the 10th century and author of the “Rule of Medicine” that reported the properties of Ginseng plants [57]. However, the superstitions of the time against a root that has a human form has banned it, contrary to the pharmacological success (since Hippocratic medicine’s age), of the *mandrake* plant, whose root also has an anthropomorphic aspect (Fig. 2). In fact, it seems to have no description about ginseng among eminent doctors and pharmacists of Christian Roman Empire such as Nikolaos Myrepsos (Νικόλαος Μυρεψός, 1240–1280 AD), who wrote at the capital Nova Roma a vast compendium on medical science together with the pharmacopoeia knowledge in that era called “Δυναμερόν” (Dynameron) and was the teaching text on Europe Medicine’s Universities until the 17th century [58]. Most likely they confuse it with mandraka as a similar plant resembling it and with some effects. In fact, in the text of Theophrastus (Θεόφραστος, 370–285 BC) “Περὶ Φυτῶν Ἱστορία” (De Causis Plantarum), among the aphrodisiac drugs is reported the *Mandrake* spp. root which has the partly similar use as *P. ginseng* which was widely used in herbal medicine in Asia for the treatment of erectile dysfunction [1,59]. Finally, Marco Polo (1254–1324), at the end of the 13th century AD wrote and brings in Europe the ginseng such as miraculous herb and that it was an essential food for the life of nomads, and of the Tartars [59,60].

4.2. Renaissance and modern era

Don Vasco da Gama, (1469–1524) begins the trade from the Far East and so everything that existed or grew in China became fashionable in Europe. Subsequently, in 1610 ginseng was brought back from Japan to Europe by the Dutch settlers [59–61]. Another testimony that the Dutch settlers knew and sold ginseng also comes from a newspaper set up by them the “Dagregister” of the Cape of Good Hope (South Africa) which will subsequently be published under the name of the newspaper of Van Riebeeck. In fact, Johan Anthonis zoon van Riebeeck (1619–1677) founder of the Cape Town reports in the newspaper the use by a local tribe, the Hamcumquar, of a herb called dacha, which drugs their brains making the comparison with opium and ginseng. Later, when a delegation from King Siam visited Louis XIV (1638–1715), they gave him a ginseng root ever since, it has spread among wealthy Europeans. Indeed, at the court of Louis XVI, a tincture obtained from the plant was used to cure his sexual weakness [62–64].

In the 18th century it was also popular in America, especially when the native *P. quinquefolium* was discovered to be used by various Native American tribes in North America. In fact, it is estimated that American colonists discovered it in the mid-1700s in New England. Meanwhile, the discovery of wild ginseng in Canada was published by French Jesuit father Joseph-François Lafitau (1681–1746) in the “*Mémoire concernant la précieuse plante du ginseng de Tartarie*” in 1718 [65]. An attempt was made to experimentally cultivate ginseng around 1878 in the botanical gardens in Jamaica, but without success then it was successfully cultivated in the town of Fabius (NY, USA) in 1897 by George Stanton thanks to a Korean technique. In 1900, the demand for ginseng exceeded its available supply and Korea began growing it commercially. The wild type of ginseng is considered the best type. Indeed, in the first

half of 20th century wild-growing ginseng plants could be found on the large forestlands of China, Korea and Russian Primorye, but nowadays its original distribution area has shrunk to few habitats in Russia and China [66]. It became a high-yielding crop for both American growers and European traders, who were now more interested in exporting it to China than importing it. Then, after being undermined by some negative clinical trials, ginseng was suddenly discredited.

The first European to point out the power of ginseng was Nikolai Gavrilovich Spathari (1636–1708) who was ambassador of the Russian Empire to Beijing (the capital of Qing dynasty) in China. He wrote that the root of the plant is boiled and then given to those who are weak from a long disability because they are a great help [67]. Later, the medicinal properties of ginseng root became known in the 17th century, especially when the Dutch made major forays into the Iberian monopoly on foreign trade thanks to missionaries operating in the West. Willem Piso (1611–1678) realizes the first monograph for ginseng with the title “Ninzin”. This was soon followed by various expert opinions, but the skepticism of most of the European medical community slowed its diffusion until the 1800s [68]. In 1754, the botanist Carl von Linnè (Carl Nilsson Linnaeus) called ginseng *Panax* and in 1843 another botanist, Carl Anton von Meyer (1795–1855), registered the ginseng as *Panax ginseng* C. A Meyer. Later, in 1833, Christian Gottfried Daniel Nees von Esenbeck (1776–1858) called Korean ginseng as *Panax shinseng* var. *coraiensis* Nees. Since 1972, various research groups studying the properties of the plant such as the “Ginseng Research Institute” in New York, have made a more in-depth investigation on its beneficial components, thus making its use increased over time until today. Today, in the international market we not only find an adulteration of a species of *Panax* but also plant preparations not of the genus *Panax* erroneously labeled “ginseng”, such as *Codonopsis pilosula* [45,69–71].

5. Conclusions

Herbs were used in different ways and for different purposes each time. They have been used as medicine against diseases, as poisons for the destruction and annihilation of their enemies, as love potions for people's desire and passion for a person, but they have also been used in cooking, bestowing on food pleasant smells and taste. In ancient times, Ginseng was used as an aphrodisiac, anti-aging and energy-boosting tonic to increase “energy levels” and is used as an antioxidant. In addition it has been used for the treatment of cardiovascular, kidney, and reproductive diseases and it was no coincidence that they called it *P. ginseng*, that is, a herb for all ills. Ginseng passed sporadically in the Western Middle Ages but with the Renaissance onwards it began to assert itself both in Europe and in America and then in all the world. In Asian countries the control of ginseng fields was as important as in China and Korea and also became a subject of contention as early as the 16th century. Since 1900, commercial demand has outstripped supply due to the availability of wild ginseng and therefore the commercial cultivation of Red ginseng in Korea which continues today.

Funding

No funds or grants available for this study.

Declaration of competing interest

The authors declare no conflict of interest.

References

- [1] Santacroce L, Topi S, Haxhiresha K, Hidri S, Charitos IA, Bottalico L. Medicine and healing in the pre-socratic thought - a brief analysis of magic and rationalism in ancient herbal therapy. *Endocr Metab Immune Disord - Drug Targets* 2021;21:282–7.
- [2] Petrovska BB. Historical review of medicinal plants' usage. *Pharm Rev* 2012;6:1–5.
- [3] Santacroce L, Bottalico L, Haxhiresha K, Topi S, Charitos IA. Pre-chemistry concepts and medical therapy among ancient physicians through the pre-socratic philosophers. *Endocr Metab Immune Disord - Drug Targets* 2020;20:1470–7.
- [4] Zhang H, Abid S, Ahn JC, Mathiyalagan R, Kim YJ, Yang DC, Wang Y. Characteristics of *Panax ginseng* cultivars in Korea and China. *Molecules* 2020;25:2635.
- [5] Baeg IH, So SH. The world ginseng market and the ginseng (Korea). *J Ginseng Res* 2013;37:1–7.
- [6] Yang JP, Yeo IS. [A study on the origins of 'Korean ginseng']. *Uisahak* 2004;13:1–19.
- [7] Park EY, Kim MH, Kim EH, Lee EK, Park IS, Yang DC, Jun HS. Efficacy comparison of Korean ginseng and American ginseng on body temperature and metabolic parameters. *Am J Chin Med* 2014;42:173–87.
- [8] Zhang H, Abid S, Ahn JC, Mathiyalagan R, Kim YJ, Yang DC, Wang Y. Characteristics of *Panax ginseng* cultivars in Korea and China. *Molecules* 2020;25:2635.
- [9] Hu SY. A contribution to our knowledge of ginseng. *Am J Chin Med* 1977;5:1–23.
- [10] Li G, Cui Y, Wang H, Kwon WS, Yang DC. Molecular differentiation of Russian wild ginseng using mitochondrial *nad7* intron 3 regions. *J Ginseng Res* 2017;41:326–9.
- [11] Müller-Wille S. Linnaeus' herbarium cabinet: a piece of furniture and its function. *Endeavour* 2006;30:60–4.
- [12] Skaltsa E. History of pharmacy. Association of Greek academic libraries. Athens, Greece: Kallipos editor; 2015.
- [13] Lee SM, Bae BS, Park HW, Ahn NG, Cho BG, Cho YL, Kwak YS. Characterization of Korean red ginseng (*Panax ginseng* meyer): history, preparation method, and chemical composition. *J Ginseng Res* 2015;39:384–91.
- [14] Nair R, Sellaturay S, Sriprasad S. The history of ginseng in the management of erectile dysfunction in ancient China (3500–2600 BCE). *Indian J Urol* 2012;28:15–20.
- [15] Park Jeonghill, Heasim Sul, Soonjongvine Ock. Divine herb grown by wind, water & people. GOD GIVEN Korean GINSENG. Korea. In: Ministry of agriculture, food & rural affairs. Korea Agro-Fisheries & Food Trade Corporation; 2016.
- [16] Qi LW, Wang CZ, Yuan CS. Ginsenosides from American ginseng: chemical and pharmacological diversity. *Phytochemistry* 2011;72:689–99.
- [17] Park EY, Kim MH, Kim EH, Lee EK, Park IS, Yang DC, Jun HS. Efficacy comparison of Korean ginseng and American ginseng on body temperature and metabolic parameters. *Am J Chin Med* 2014;42:173–87.
- [18] Shin BK, Kwon SW, Park JH. Chemical diversity of ginseng saponins from *Panax ginseng*. *J Ginseng Res* 2015;39:287–98.
- [19] So SH, Lee JW, Kim YS, Hyun SH, Han CK. Red ginseng monograph. *J Ginseng Res* 2018;42:549–61.
- [20] Yang Y, Ju Z, Yang Y, Zhang Y, Yang L, Wang Z. Phytochemical analysis of *Panax* species: a review. *J Ginseng Res* 2021;45:1–21.
- [21] Wee JJ, Mee Park K, Chung AS. Biological activities of ginseng and its application to human health. In: Benzie IFF, Wachtel-Galor S, editors. *Herbal medicine: biomolecular and clinical aspects*. second ed. Boca Raton (FL): CRC Press/Taylor & Francis (Boca Raton, Florida); 2011 [Chapter 8].
- [22] Panossian A, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals* 2010;3:188–224.
- [23] *Panax Ginseng*. European Medicines Agency. Assessment report on *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. radix, EMA/HMPC/680615/2013 Committee on Herbal Medicinal Products (HMPC); 2014. Available from: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-eleutherococcus-senticosus-rupr-et-maxim-maxim-radix_en.pdf.
- [24] Santacroce L, Man A, Charitos IA, Haxhiresha K, Topi S. Current knowledge about the connection between health status and gut microbiota from birth to elderly. A narrative review. *Front Biosci* 2021;26:135–48.
- [25] Kang S, Min H. Ginseng, the 'immunity boost': the effects of *Panax ginseng* on immune system. *J Ginseng Res* 2012;36:354–68.
- [26] Lu G, Liu Z, Wang X, Wang C. Recent advances in *Panax ginseng* C.A. Meyer as an herb for anti-fatigue: an effects and mechanisms review. *Foods* 2021;105:1030.
- [27] Sun M, Ye Y, Xiao L, Duan X, Zhang Y, Zhang H. Anticancer effects of ginsenoside Rg3 (review). *Int J Mol Med* 2017;39:507–18.
- [28] Kim HS, Lee EH, Ko SR, Choi KJ, Park JH, Im DS. Effects of ginsenosides Rg3 and Rh2 on the proliferation of prostate cancer cells. *Arch Pharm Res* 2004;27:429–35.
- [29] Lee HU, Bae EA, Han MJ, Kim DH. Hepatoprotective effect of 20(S)-ginsenosides Rg3 and its metabolite 20(S)-ginsenoside Rh2 on tert-butyl hydroperoxide-induced liver injury. *Biol Pharm Bull* 2005;28:1992–4.
- [30] Im DS. Pro-resolving effect of ginsenosides as an anti-inflammatory mechanism of *Panax ginseng*. *Biomolecules* 2020;10:444.
- [31] Zee-Cheng RK, Shi-quan-da-bu-tang (ten significant tonic decoction), SQT. A potent Chinese biological response modifier in cancer immunotherapy, potentiation and detoxification of anticancer drugs. *Methods Find Exp Clin Pharmacol* 1992;14:725–36.
- [32] Huang GC, Chen SY, Tsai PW, Ganzon JG, Lee CJ, Shiah HS, Wang CC. Effects of Dang-Gui-Bu-Xue-Tang, an herbal decoction, on iron uptake in iron-deficient anemia. *Drug Des Dev Ther* 2016;10:949–57.
- [33] Fu B, Wang N, Tan HY, Li S, Cheung F, Feng Y. Multi-component herbal products in the prevention and treatment of chemotherapy-associated toxicity and side effects: a review on experimental and clinical evidence. *Front Pharmacol* 2018;9:1394.
- [34] Charitos IA, D'Agostino D, Topi S, Bottalico L. 140 Years of *Helicobacter pylori*: a revolution in biomedical thought. *Gastroenterol Insights* 2021;12:111–35.
- [35] Bae M, Jang S, Lim JW, Kang J, Bak EJ, Cha JH, Kim H. Protective effect of Korean Red Ginseng extract against *Helicobacter pylori*-induced gastric inflammation in Mongolian gerbils. *J Ginseng Res* 2014;38:8–15.
- [36] Kim JH. Cardiovascular diseases and *Panax ginseng*: a review on molecular mechanisms and medical applications. *J Ginseng Res* 2012;36:16–26.
- [37] Coon JT, Ernst E. *Panax ginseng*: a systematic review of adverse effects and drug interactions. *Drug Saf* 2002;25:323–44.
- [38] Cho SK, Kim D, Yoo D, Jang EJ, Jun JB, Sung YK. Korean Red Ginseng exhibits no significant adverse effect on disease activity in patients with rheumatoid arthritis: a randomized, double-blind, crossover study. *J Ginseng Res* 2018;42:144–8.
- [39] Kim JK, Tabassum N, Uddin MR, et al. Ginseng: a miracle sources of herbal and pharmacological uses. *Orient Pharm Exp Med* 2016;6:243–50.
- [40] Lee SM, Bae BS, Park HW, Ahn NG, Cho BG, Cho YL, Kwak YS. Characterization of Korean red ginseng (*Panax ginseng* meyer): history, preparation method, and chemical composition. *J Ginseng Res* 2015;39:384–91.
- [41] Harding AR. In: Harding AR, editor. *Ginseng and other medicinal plants: a book of valuable information for growers as well as collectors of medicinal roots, barks, leaves*. Cambridge: Publishing Company: Harvard University; 1908.
- [42] Yun TK. Brief introduction of *Panax ginseng* C.A. Meyer. *J Korean Med Sci* 2001;16(Suppl):S3–5 (Suppl).
- [43] Bottalico L, Charitos IA, Potenza MA, Montagnani M, Santacroce L. The war against bacteria, from the past to present and beyond. *Expert Rev Anti Infect Ther* 2021 Dec 22:1–26 [Epub ahead of print].
- [44] Guo Z. Chinese Confucian culture and the medical ethical tradition. *J Med Ethics* 1995;21:239–46.
- [45] Huang Kee C. *The pharmacology of Chinese herbs*. second ed. USA: CRC Press; 1998.
- [46] Fulder S. *The book of ginseng: and other Chinese herbs for vitality*. Rochester, USA: Inner Traditions/Bear & Co editor; 1993.
- [47] Goetz P, Stoltz P, Delaporte D. *Il Ginseng: virtù terapeutiche di una droga adattogena*. Berlin: Springer Science & Business Media editor; 2012.
- [48] Xiang YZ, Shang HC, Gao XM, Zhang BL. A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials. *Phytother Res* 2008;22:851–8.
- [49] Santacroce L, Bottalico L, Topi S, Castellana F, Charitos IA. The "scourge of the renaissance". A short review about *Treponema pallidum* infection. *Endocr Metab Immune Disord - Drug Targets* 2020;20:335–43.
- [50] Shizhen L, Xiwen L. *Compendium of Materia Medica: bencao gangmu*. first ed. Beijing, China: Foreign Languages Press editor; 2003.
- [51] Wang J, Mei QX. [Literature research of *Compendium of materia medica* quoted from *bencao tujing*]. *Zhonghua Yi Shi Za Zhi* 2021;51:34–42.
- [52] DeFilippis RA, Krupnick GA. The medicinal plants of Myanmar. *PhytoKeys* 2018 28;102:1–341.
- [53] Zhao Z, Guo P, Brand E. A concise classification of *bencao (materia medica)*. *Chin Med* 2018;13:18.
- [54] Britannica, the editors of encyclopaedia. "traditional Chinese medicine. *Encyclopedia Britannica*; 2021. Available from: <https://www.britannica.com/science/traditional-Chinese-medicine>.
- [55] Masic I, Skrbo A, Naser N, Tandir S, Zunic L, Medjedovic S, Sukalo A. Contribution of Arabic medicine and pharmacy to the development of health care protection in Bosnia and Herzegovina - the first part. *Med Arch* 2017;71:364–72.
- [56] Winder M Paul, Unschuld U. *Medicine in China. A history of Pharmaceutics*. Berkeley, Los Angeles and London, University of California press, 1986, 4to, pp. Xiii, 366, illus., £40.50. *Med Hist* 1988;32:345, 345.
- [57] Pioreschi P. *A history of medicine: byzantine and islamic medicine*, vol. 4. Nebraska: Horatius Press editor; 1996.
- [58] Topi S, Santacroce L, Bottalico L, Ballini A, Inchingolo AD, Divalpa G, Charitos IA, Inchingolo F. Gastric cancer in history: a perspective interdisciplinary study. *Cancers* 2020;12:264.
- [59] Murray H, Wallace W, Jameson R, Hooker WJ, Swainson W, Bradford TG. In: *The encyclopaedia of geography: comprising a complete description of the earth, physical, statistical, civil, and political*, vol. 2. Philadelphia: Lea and Blanchard; 1848.
- [60] Huang Kee C. *The pharmacology of Chinese herbs*. second ed. Boca Raton, Florida: CRC Press; 1998.
- [61] Prance G, Nesbitt M. *The cultural history of plants*. London: Routledge editor; 2012.

- [62] Pooley Simon. Jan van Riebeeck as pioneering explorer and conservator of natural resources at the Cape of Good Hope (1652-62). *Environ Hist* 2009;15(1):3–33.
- [63] Appleby JH. Ginseng and the royal society. *Notes Rec R Soc Lond* 1983;37(2): 121–45.
- [64] Taylor DA. *Ginseng, the divine root: the curious history of the plant that captivated the world*. NY: Algonquin Books editor; 2006.
- [65] König T. On ginseng and Iroquois. *Neohelicon* 2020;47:417–32.
- [66] Zhuravlev YN, Koren OG, Reunova GD, Muzarok TI, Gorpenchenko TY, Kats IL, Khrolenko YA. *Panax ginseng* natural populations: their past, current state and perspectives. *Acta Pharmacol Sin* 2008;29:1127–36.
- [67] Ames GJ, Love RS. *Distant lands and diverse cultures: the French experience in Asia, 1600-1700*. Westport, USA: Greenwood Publishing Group; 2003. Praeger Publishers.
- [68] Bruchhausen Walter. Global health in the colonial era: the expansion of European medicine. In: *European history online (EGO)*. Mainz (Germany): published by the Leibniz Institute of European History (IEG); 2020. Available from: <http://www.ieg-ego.eu/bruchhausenw-2019-enURN:urn:nbn:de:0159-2019120917>.
- [69] Hu SY. The genus *Panax* (Ginseng) in Chinese medicine. *Econ Bot* 1976;30: 11–28.
- [70] Jia L, Zhao Y. Current evaluation of the millennium phytomedicine–ginseng (I): etymology, pharmacognosy, phytochemistry, market and regulations. *Curr Med Chem* 2009;1619:2475–84.
- [71] Foster Steven. Towards an understanding of ginseng adulteration: the tangled web of names, history, trade, and perception. *HerbalGram* 2017;111:36–57.