Pharmacogn. Commn. 2021;11(4):177-181.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogcommn.org

Review Article

Ginsenosides and other Phytochemicals of *Panax* spp. Properties and Uses in the Pharmaceutical Field

Grettel Solís Vindas, Marianela Chavarría-Rojas, Rolando Vargas Zúñiga, Gustavo Carazo Berrocal, German Madrigal Redondo*
Instituto de Investigaciones Farmacéuticas (INIFAR), Facultad de Farmacia, Universidad de Costa Rica, San José, COSTA RICA.

ABSTRACT

Introduction: Ginseng has been used since ancient times, for its medicinal properties. This plant comes from the genus *Panax*, and the most representative species are *Panax quinquefolium*, *Panax ginseng*, and *Panax notoginseng*. **Methods:** In this research, database, books and scientific articles were reviewed from 1999 to 2019, using the following descriptors: *Panax*, ginsenosides and adaptogens. **Results:** These plants active components are saponins, known as ginsenosides, and can be classified according to their chemical structure. These are found in different proportions according to the different *Panax* species. **Conclusion:** Ginseng is used due to its adaptogenic properties. It also can be used to treat cardiovascular and neurological diseases and to counteract inflammation, cancer, and sexual impotence. Finally, some adverse effects are presented, and formulations containing ginseng are detailed.

Key words: Ginseng, Ginsenoside, *Panax*, Adaptogens, Species.

Correspondence:
Dr. German Madrigal Redondo
Rodrigo Facio Campus, San Jose, Costa Rica, Postal Code 11501-2060, San José, COSTA RICA.
Phone no: +506-25118349
E-mail: german.madrigal@ucr.ac.cr

DOI: 10.5530/pc.2021.4.36

INTRODUCTION

The ginseng plant has been known since prehistoric times. The first information reported was about 5,500 years ago by emperor Yan in China, who provided information on several medicinal plants. That information was passed verbally to subsequent generations, and ginseng was one of these plants. This information was later compiled during 502-557 A.D. by Tao Hongjing in the book Shennong Bencao Jing. Ginseng is also mentioned in the book Jijuzhang written by Shi You in 48 B.C. Different prescriptions for this plant are described in Treatise on Fevers between 196-200 B.C.[1]

The name *Panax* in Greek means "cure everything"; since pan refers to everything and axos medicine. On the other hand, ginseng comes from the Chinese *jen shen*, which means "sacred root of man"; Since it is shaped like a human. It is important to emphasize that this is the part of the plant with medicinal properties. Also, this plant is known as the king of all herbs.[2,3]

Ginseng has traditionally been known in the East as a miraculous medicinal plant. It has been classified as the most valuable medicinal herb. The eastern population has used this plant as a revitalizer for the body and mind to increase strength and prevent aging.[4]

Ginseng is a short and lively perennial herbaceous plant with branches that can reach 50 cm. The leaves are webbed with five leaflets, the flowers are white, and they are grouped in umbels. It has a fruit that is small and red that contains two seeds. The root is the most used part of the plant. It is cylindrical/fusiform and is divided into several branches that give a human appearance. The roots are fragile and break easily because of their large dimensions.[5]

Ginseng botanical classification is as follows: Phylum: Embryophyta Siphonogama, Subphylum: Angiospermae, Class: Dicotyledoneae, Subclass: Archichlamydeae, Order: Umbelliflorae, Family: Araliaceae, and Genus: *Panax*.[6] Siberian or Russian ginseng belongs to the same family, but not the same genus. The genus Eleutherococcus is considered a completely separate drug, and it is not possible to guarantee both species present the same pharmacological characteristics.[7]

Apart from being one of the most important agricultural products in Asian countries such as Korea, China, and Vietnam, ginseng has become a high-value product in places like Russia, Canada, and the United States.[8] The most representative species of this genus are *Panax quinquefolius*, a species native to North America, cultivated mainly in Wisconsin. *P. ginseng* is the original species from Korea, China, and Asia in general. *Panax pseudoginseng*, better known as *P. notoginseng*, is also found in Korea, China, and Japan. There is also the *P. japonicus* variety, also known as Japanese ginseng. The *Eleutherococcus senticosus*, mentioned above, is Siberian ginseng. It is not considered true ginseng since it does not come from the same genus. Furthermore, this plant does not contain ginsenosides (pharmacologically active compounds of ginseng) but instead contains eleutheroside substances.[9]

After a phylogenetic analysis, it was discovered *P. quinquefolius* is the one that differs the most from all the species since it has a higher nucleotide substitution rate. However, almost zero variation was identified between the *P. ginseng* and *P. japonicus* species. It was determined that the *P. notoginseng* variety diversified from the *P. ginseng* species more than 1.3 million years ago, while *P. quinquefolius* differed from this same species, thanks to the adaptation to the American continent, no more than 0.29 million years.[10]

METHODS

In this research, books and scientific articles were reviewed from 1999 to 2019, using the following descriptors: *Panax*, ginsenosides and adaptogens. The review was performed using EBSCO, Google Scholar, PubMed, Springer, JSTOR and Science Direct with both English a non-English references.

COMPONENTS

Approximately 200 components of *P. ginseng* have been isolated, and 100 of them from *P. quinquefolius* and *P. notoginseng*. Among all these components, are the carbohydrates (polysaccharides) polyacetylenes, peptides, amino acids, and saponins.[11]

Although carbohydrates are not the main active components of ginseng, they are the components with a higher proportion, accounting for 60-70% of the mass. The sucrose content, for example, can vary between 11-20% depending on the plant growth stage. Regardless, it has been seen that the *P. ginseng* and *P. quinquefolius* varieties have similar amounts, while *P.notoginseng* has a lower content. On the other hand, the glucose and maltose content is constant during the plant's growth process. The content of amino acids is qualitatively the same in all species. However, there is a variation in the number of free amino acids in *P. ginseng*, and the percentage is higher.[12]

The main active components of ginseng are saponins, which are also called ginsenosides. These are found mainly in the root and vary in percentage depending on the variety of ginseng; *P. ginseng* has 4.8-5.2%, *P. quinquefolius* 7.0-7.3%, and *P. notoginseng* has 9.8%.[12]

Ginsenosides are derived from three triterpenic genins; two of these, when cyclized, form a tetracycle and the other a pentacycle. Tetracycles are dammaran molecules and are divided into protopanaxadiol (PD) and protopanaxatriol (PT). Another way to classify dammaran-type saponins is by considering their chemical configuration in C20, dividing them into 20 (S) and 20 (R) types. It is relevant to note that most ginseng plant saponins are from type 20 (S).[13] The pentacycle derived from these genins is the oleanic acid.[14,15] Ginsenosides are mainly derived from PD and PT, except for Ro ginsenoside, which comes from oleanic acid.[7]

PHARMACOLOGICAL USES

Ginseng is widely used for its promising healing and restorative properties. The studies related to this plant are currently focused on individual and purified ginsenosides to study a possible action mechanism in different diseases and conditions.[16] The pharmacological activity of the ginsenosides depends on the diversity and the position of their sugar residues. For this reason, different ginsenosides have different effects, and each of them can cause several responses on the same tissue, evidencing the pharmacology of these compounds is complex.[17]

Adaptogenic property

Adaptogens are natural substances that help the body adapt to stress, support the body's metabolic functions, and restore systemic balance. These substances also increase the body's resistance to physical, chemical, biological, and environmental stressors. The adaptogens effects are achieved by maintaining the endocrine hormones in an adequate balance, modulating the immune and nervous system, and allowing the body to have adequate homeostasis.[18] The adaptogenic effect of ginseng becomes important when the body maintains a decreased resistance or encounters additional demands.[19]

The adrenal glands execute different responses to each type of stress, whether physical, biochemical, external, or mental. However, when adrenal hormones secretion is not enough for the physiological compensation, adrenal fatigue may appear, which quickly becomes metabolic syndrome, meaning that glands might still be working, but lose their ability to maintain homeostasis.[20]

In these cases, adaptogens, such as ginseng, can increase the adrenal glands' secretion efficiency. On the other hand, ginsenosides can inhibit compounds such as 11-beta hydroxysteroid-dehydrogenase-1, helping to catalyze stress hormones' degradation to active compounds. They also increase cellular energy levels and prevent oxidative damage, maintaining normal adrenal function.[20]

Cardiovascular diseases

One of the main uses of ginseng is to treat cardiovascular diseases. The National Health Interview Survey conducted in 2002 indicated ginseng is a herbal therapy commonly used by the general population to treat diseases such as hypertension, coronary heart disease, and vascular insufficiency. The survey results indicate an 80% of people using ginseng to the mentioned conditions saw beneficial effects.[21]

The cardioprotection of ginsenosides, such as the Re-type, is attributed to a toxicity reduction induced by hydrogen peroxide in myocardial cells, showing its antioxidant properties. Another mechanism of Re ginsenoside is the increase of nitric oxide (NO) endothelial production due to the activation of eNOS occurs. The NO release occurs by non-genomic routes and involves steroidal receptors, such as glucocorticoid receptors, which lead to the activation of potassium channels, activating cardiomyocytes, and preventing acute injuries, ischemia, and reperfusion.[16,22]

Since these saponins have a similar structure to cardiac glycosides, they can bind to the Na-K-ATPase α subunit, contributing to cardiac contractility. However, not all ginsenosides have cardiotonic activity. Those capable of influencing muscle contraction have sugar residues attached to carbons 3, 6, or 20. Inhibition of the Na-K-ATPase α subunit occurs when the sugar is linked to only the C3 position, but when it is attached to C6 or C20, the inhibitory effect over the Na-K-ATPase α subunit is suppressed.[23]

Another useful ginsenosides mechanism in heart disease is presented by Rg3, which inhibits platelet aggregation, modulating signaling components such as cyclic adenosine monophosphate and extracellular signal-regulated kinase.[16] Protopanaxatriol-type ginsenosides also affect hemin-induced hemolysis, and this effect depends on the interaction that occurs with the sugar residues in the different positions.[24] Another way platelet inhibition is contributed is by decreasing leukocyte adhesion to the vein wall, mast cell degranulation, and cytokine release.

Neurological diseases

Among the uses given to ginseng are neurological disorders. This plant has been used to treat both acute and chronic neurological diseases, and its foundation is the maintenance of homeostasis, the attenuation of inflammatory mediators, and the suppression of oxidative stress, among others.[25]

An ischemic brain injury leads to apoptosis and necrosis of nerve cells, leading to strokes. Currently, there are few therapeutic alternatives for patients with this condition. The ginsenosides are a promising alternative. Rb1 can increase neuronal cell survival and delay cell death caused by transient forebrain ischemia. This ginsenoside can also decrease cortical neurons' apoptosis since it negatively regulates the nuclear factor-kappa B / NO.[26,27]

Another ginsenoside that has been studied as a neuroprotective is Rd. After a stroke, Rd prolongs neural cells survival through several mechanisms, including protein tyrosine kinase activation, positive regulation of the endogenous antioxidant system, preservation of membrane potential, the cytochrome c expression factor reduction and, the apoptosis inducer factor reduction.[26]

The ginsenoside Rg1 is also efficient in neuroprotection due to the effects in the nervous expression improvement related to apoptosis reduction and the increase in both enolase-positive neuron cells and glial fibrillary acidic protein-positive cells. Rg1 increase also Bcl-2 levels and decrease Bax protein levels.[27] The Bcl-2 is a protein that controls apoptosis by inhibiting cytochrome c expression and reversing Bax protein effects, which is pro-apoptotic.[28]

Although ginseng extracts have been the target of study for multiple neurodegenerative diseases, Parkinson's disease has more evidence and information supporting its use. It has been shown that, for example, ginsenoside Rb1 confers cytoprotection to human dopamine cells against oxidative stress caused by 6-hydroxydopamine by increasing the expression of hemeoxygenase-1 through an estrogen receptor, it also significantly reduces caspase-3.[29]

Ginsenoside Rg1 also increases the dopamine content (and its metabolites) in the striatum by increasing TH expression. Besides, iron levels are decreased, which are high, by interrupting the divalent metal transporter 1 (DMT1) and increasing the expression of ferroportin 1. In addition, it has been seen that this ginsenoside blocks the signaling cascade c-Jun NH2 -terminal kinase (JNK).[29,30]

Inflammation

The alternatives to treat conditions associated with inflammation are generally accompanied by side effects such as stomach ulceration. For this reason, pharmacological alternatives have been evaluated and studied for inflammation-related diseases. Ginsenosides, such as Ro type, are considered a possible treatment due to their anti-inflammatory properties; for example, against edema induced by carrageenan (a harmful agent that produces inflammation).[31]

Ginsenosides have been used as adjuvants in vaccines due to their anti-inflammatory effects are associated with regulating cytokines, phagocytosis, and T and B lymphocytes activation.[32] The influenza vaccine is an example. In this case, ginsenosides are used to prevent the virus from binding to receptors on host cells, minimizing the virus's entry. Furthermore, when using these compounds as helpers, an antigenic cross-reaction with other influenza viruses is generated.[33]

Ginsenosides such as Rg1 have been shown to negatively regulate the release of pro-inflammatory cytokines by inhibiting nuclear translocation, DNA binding, and glucocorticoid receptor phosphorylation stability.[34] Other anti-inflammatory mechanisms that have been studied in the different ginsenosides are the inhibition of TNF-ALFA, IL-1, IL-6, IL-12, and the inhibition of the MAPK, JNK, and NF-kB pathways.[33]

Cancer

The relationship between inflammation and cancer is well known and can be explained since inflammation could generate genetic damage and oncogenes' activation could cause inflammation. A pro-inflammatory state is required for cancer development, which generates angiogenesis, metastasis, and immune system suppression.[35] Ginseng can prevent and reduce inflammation processes, and different authors indicate the possibility to used ginseng as a cancer treatment. Considering angiogenesis and inflammation are often related, ginseng is a promising target for new antiangiogenic therapies development, mainly due to its ability to modulate both processes.[36]

The ginseng chemopreventive effect has been demonstrated by different mechanisms, such as tumor inhibition by angiogenesis suppression, apoptosis induction, and cell cycle regulation. These mechanisms are related to specific signaling pathways, and the most common pathways are cell proliferation, growth factors, tumor suppressors (p53 and p21), and cell death mediators.[37]

The mechanism used by Rp1 to reach its antimetastatic effect is based on the cell cycle and apoptosis arrest. In contrast, this ginsenoside reduced the stability of the IGF-1R protein in breast cancer cells; IGF-1R protein plays an important role in cell proliferation and invasion signaling.[38]

Rg3 ginsenoside inhibits capillary proliferation and invasion, decreasing the microvasculature and neovasculature. This angiosuppression is regulated by 2 and 9 matrix metalloproteinases. However, Rg1 has been associated with promoting neovasculature and cell proliferation. The oxide-nitro-synthase expression and the phosphatidylinositol-3-kinase pathway mediate the opposite effect. Moreover, these effects may depend on ginsenosides proportion.[39]

These mechanisms and others have been observed in cancer progressions, including pharynx, stomach, liver, pancreas, and colon. Every day, more and more information is being obtained on how ginseng inhibits the sequence of inflammation to cancer.[40]

Sexual Impotence

The administration of ginseng in men has demonstrated an effect on the central nervous system and the gonads, facilitating erection by inducing corpora cavernosa vasodilation and relaxation. NO secretion also mediates these effects. On the other hand, ginsenosides increase the levels of testosterone, dihydrotestosterone (DHT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the synthesis of proteins in the testes (spermatogenesis enhancement); the mobility of these sperm is also facilitated by stimulating the spermatid (an effect achieved through estrogen and progesterone receptors).[41]

Ginsenosides have demonstrated an effect increasing testosterone levels directly and indirectly since the LH stimulates its secretion. FSH release is also influenced by ginsenosides administration. The stimulating effect is equal to the obtained effect when the gonadotropin releasing hormone (GnRH) stimulates the pituitary gland. However, whilst the stimulating mechanism is not well-understood, ginsenosides could directly stimulate the gland or have a mimetic effect.[41]

ADVERSE EFFECTS

Although ginseng is widely used because of its significant health benefits, there is no evidence to prove the long-term intake side effects.[42] However, the excessive consumption of ginseng roots causes effects in and out the central nervous system. Those effects are known as Ginseng Abuse Syndrome (GAS) and include, among others, insomnia, nervousness, skin eruptions, vasodilation or vasoconstriction that led to hypertension and palpitations.[43]

It has been seen that the number and position of the glucose molecules in the structures of PDs indicate their allergenicity degree. F2 has been shown to have a potent anaphylactoid and allergen present in ginseng. Also, Rd directly promotes degranulation, skin permeability and significantly increases the plasma histamine levels.[44]

Several *in-vivo* and *in-vitro* studies have shown that ginseng has beneficial effects for the liver, which is related to its anti-inflammatory, antioxidant, and anti-apoptotic capacity. However, a meta-analysis named Benefits and harms of ginseng supplementation on liver function? Presented contrary results.[45] This may be because these investigations used diseased hepatocytes that were treated until recovery, in contrast with the meta-analysis approach that used healthy hepatocytes for the investigation.[45]

In a preclinical study, hepatotoxicity and nephrotoxicity were evaluated after the administration of high doses of ginseng. It was observed an increase in liver and kidney weight, an increase in plasma enzymes. However, it occurred temporarily.[46]

FORMULATIONS

A method has been created to process ginseng and obtain an extract to treat erectile dysfunction, hypertension, atherosclerosis, and anti-thrombosis, improve blood circulation and brain functions, reduce fatigue, and prevent cerebral apoplexy.[47]

This product's preparation requires a ginseng extraction under high temperature. After the extraction, a mixture with ginseng, water, and methanol or ethanol is obtained. The water must be evaporated during 1 – 3 hr, then, 100 parts of ginseng (white ginseng, fresh ginseng, hairy root ginseng, red ginseng, ginseng leaves of *P. quinquefolium*, *P. ginseng*, *P. notoginseng*, *P. japonicus*) are mixed with 4-10 parts of water. The obtained mixture is heated until 70-120 °C for 1-6 hours, and then, it is cooled at room temperature and filtered. The filtrate is then concentrated to obtain a ginsenoside extract or concentrate powder.[48] The obtained extract may be used to formulate pharmaceutical products, such as liquids, tablets, granules, pills, hard and soft capsules, and food supplements.

A procedure to obtain a lyophilized product maintaining ginseng pharmacological components has also been described.[49] The method indicated that crude ginseng must be placed in a heat-resistant sealed bag to maintain the aromatic components and the active pharmacological ingredients. The product is heated to 60-100°C with hot water, steam or microwave until a soft product is obtained. Then the product is cooled to room temperature. The plant material softening temperature is a critical factor during the process since if it is below 60°C, there is a risk that the ginseng will not soften enough, and the quality of the obtained product may be low due to the enzymatic process of heat. On the other hand, if the temperature exceeds 100°C, the ginseng starch's gelatinization occurs, resulting in the trunk root and branch roots' breakage due to the swelling pressure generated internally.[48]

The softened ginseng is subsequently removed from the sealed bag, and the branch roots fiber-like roots are arranged to be put together orderly in the direction along the ginseng trunk root, which reduces the occupying space. The ordered arrangement of the ginseng roots improves the subsequent freezing and lyophilization steps' efficiency. The ginseng is then transferred to a closed pressure-resistant container filled with inert gas, such as methane, nitrogen, or air. The internal pressure of the container must be 20 kg / cm^2 or higher. The container is then frozen at -10 to -30°C, and after the container is degassed, a conventional lyophilization process is carried out under reduced pressure. Thus, a ginseng product is obtained, which maintains its shape, color, and active components during long storage periods.[49]

Additionally, an extract with pharmaceutical properties has been developed for preventing and treating obesity.[50] This extract is produced with any of the following ginseng genera: *P. ginseng*, *P. quinquefolius*, *P. notoginseng*, *P. japonicus*, *P. trifolius*, *P. pseudoginseng*, *P. vietnamensis*, *P. elegatior* outpost, *P. wangianus*, *P. bipinratifidus*. The parts of the plants that may be used are the roots, stems, or leaves.[50]

The procedure consists of obtaining dried ginseng plants and sterilizing them in an autoclave at 70-150°C for 2-6 hr. Then, with a reflux extractor, water, and some alcohol with a 1-4 carbon chain, the extraction is carried out over 3-6 hr. At the end of the filtration, the product is concentrated under reduced pressure and dried. The extract is finally heated between 40-80°C.[50]

In the following description, another ginseng extract obtaining procedure is described. The below procedure allows an extract obtention with high ginsenosides content using an inexpensive alternative.[51]

A suspension of root, stem, leaves, and fruits is prepared with some solvent, (water or alcohols with no more than four carbons in their chain). The ratio between the solvent and the ginseng should be 10-25 of solvent per 1 part of ginseng.[51]

A saccharide degradation enzyme (cellulase, amylase, pectinase, cellobiose, viscozyme) is added to the suspension and the enzyme is deactivated after 10-50 min at 70-100°C. This enzyme must be in 1-5 parts compared to the suspension, the reaction time of 5-80 hr, and the temperature of 20-60°C.[51]

The enzyme used to obtain the ginsenosides Rg1 and Rb1 may be amylase or pectinase. An extract with these compounds can be used as a functional drink. On the other hand, using cellulose enhances the Rd extraction, which could be useful for external skin application. The biscozyme and cellulose enzymes allow obtaining an extract rich in Rh1 that can treat cancer. Another extract that can be used for cancer contains compound K (metabolite of some ginsenosides), which is achieved using cellulose, amylase, and cellobiose.[51]

CONCLUSION

Ginseng is a medicinal plant used since ancient times. The active component that gives this plant its healing properties are ginsenosides, which are generally found in the roots of this plant. These are triterpenic structures that cycle to form either tetracycles or pentacycles. Although ginseng has been used since ancient times for its adaptogenic properties and for its ability to reduce sexual impotence, it has been discovered that it can also be beneficial in other conditions such as cardiovascular and neurological diseases, in the process of inflammation and cancer. Due to these and other uses, methods have been created to obtain extracts in a more efficient and purer way.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PD: Protopanaxadiol; **PT:** Protopanaxatriol; **NO:** Nitric oxide; **TH:** Thyroid hormone; **DHT:** Dihydrotestosterone; **FSH:** Follicle-stimulating hormone; **LH:** Luteinizing hormone; **GAS:** Ginseng abuse syndrome.

REFERENCES

1. Yun TK. Brief introduction of *Panax ginseng* CA Meyer. J Korean Med Sci. 2001;16;Suppl:S3-5. doi: 10.3346/jkms.2001.16.S.S3, PMID 11748372.
2. Yun T-K. *Panax ginseng*—a non-organ-specific cancer preventive? The Lancet Oncology. 2001;2(1):49-55. doi: 10.1016/S1470-2045(00)00196-0.
3. Sanders A. Descubra los poderes del ginseng: todo sobre esta raíz maravillosa para la salud y la belleza. Imaginador. 2002. 102 p.
4. Choi KT. Botanical characteristics, pharmacological effects and medicinal components of Korean *panax ginseng* C A Meyer. Acta Pharmacol Sin. 2008;29(9):1109-18. doi: 10.1111/j.1745-7254.2008.00869.x, PMID 18718180.
5. González Minero FJ, Bravo Díaz L, González Minero FJ, Bravo Díaz L. Estudio botánico y farmacéutico de productos con aplicación en cosmética y cuidado de la piel. Ars Pharm Internet Diciembre de. 2017;58(4):175-91.
6. Bhardwaj J. The therapeutic effects of the combined use of American ginseng (*panax quinquefolius* L.) extract and Korean red ginseng (*panax* ginseng C.A. Meyer) extract in the management of type 2 diabetes mellitus and cardiovascular risk factors. Vol. 150.
7. Villar AM, Naval MV, Gómez Serranillos MP. Ginseng [internet]; 2003 [citado 20 de julio de 2020]. Available from: https://www.elsevier.es/es-revista-farmacia-profesional-3-pdf-13054584 [cited 20/9/2021].
8. Nguyen VB, Linh Giang VN, Waminal NE, Park HS, Kim NH, Jang W, et al. Comprehensive comparative analysis of chloroplast genomes from seven *Panax* species and development of an authentication system based on species-unique single nucleotide polymorphism markers. J Ginseng Res 1 de enero de 2020;44(1). 2020;44(1):135-44. doi: 10.1016/j.jgr.2018.06.003, PMID 32148396.
9. Seervi C, Kirtawade R, Dhabale P. Ginseng- multipurpose herb. 2010;2:12.
10. Kim JH, Jung J-Y, Choi H-I, Kim N-H, Park JY, Lee Y, Yang T. Diversity and evolution of major *Panax* species revealed by scanning the entire chloroplast intergenic spacer sequences. Genet Resour Crop Evol. 2013;60(2):413-25. doi: 10.1007/s10722-012-9844-4.
11. Kim DH. Chemical Diversity of *Panax ginseng*, *Panax quinquifolium*, and *panax notoginseng*. J Ginseng Res. 2012;36(1):1-15. doi: 10.5142/jgr.2012.36.1.1, PMID 23717099.
12. Jee H-S, Chang K-H, Park S-H, Kim K-T, Paik H-D. Morphological Characterization, Chemical Components, and biofunctional Activities of *Panax ginseng*, *Panax quinquefolium*, and *Panax notoginseng* Roots: A Comparative Study. Food Rev Int Abril de. 2014;30(2):91-111. doi: 10.1080/87559129.2014.883631.
13. Yu L, Chen Y, Shi J, Wang R, Yang Y, Yang L, Zhao S, Wang Z. Biosynthesis of rare 20(R)-protopanaxadiol/protopanaxatriol type ginsenosides through Escherichia coli engineered with uridine diphosphate glycosyltransferase genes. J Ginseng Res 1 de enero de. 2019;43(1):116-24. doi: 10.1016/j.jgr.2017.09.005, PMID 30662300.
14. Marcial Méndez M, Determinanción PD A de saponinas triterpénicas en la pulpa y corteza de los frutos de mimusops sp. en diferentes estados de maduración [Internet]. [Citado 20 de julio de 2020]; 2018. Available from: http://repositorio.ug.edu.ec/bitstream/redug/33666/1/BCIEQ-T-0313%20Marcial%20M%C3%A9ndez%20Mario%20Michael%3B%20Pilla%20D%C3%ADaz%20Richard%20Andr%C3%A9s.pdf.
15. Moreno MP. Productos naturales como candidatos en enfermedades neurodegenerativas [internet]; 2015 [citado 20 de julio de 2020]. Available from: https://eprints.ucm.es/48639/1/MARIA%20DEL%20PILAR%20GARCIA%20

DEL%20VELLO%20MORENO%20%281%29.pdf [cited 20/9/2021].

16. Lee CH, Kim JH. A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. J Ginseng Res 1 de julio de. 2014;38(3):161-6. doi: 10.1016/j.jgr.2014.03.001, PMID 25378989.
17. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 1999;58(11):1685-93. doi: 10.1016/s0006-2952(99)00212-9, PMID 10571242.
18. Winston D. Adaptogens: herbs for strength, stamina, and stress relief. Simon & Schuster; 2019. 437 p.
19. Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia. 2000;71;Suppl 1:S1-5. doi: 10.1016/s0367-326x(00)00170-2, PMID 10930706.
20. Liao LY, He YF, Li L, Meng H, Dong YM, Yi F, et al. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. China Med 16 de noviembre de. 2018;13(1):57. doi: 10.1186/s13020-018-0214-9, PMID 30479654.
21. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. Am J Cardiol 1 de septiembre de. 2006;98(5):673-80. doi: 10.1016/j.amjcard.2006.03.051, PMID 16923460.
22. Gan XT, Karmazyn M. Cardioprotection by ginseng: experimental and clinical evidence and underlying mechanisms. Can J Physiol Pharmacol. 2018;96(9):859-68. doi: 10.1139/cjpp-2018-0192, PMID 29940129.
23. Zheng SD, Wu HJ, Wu DL. Roles and mechanisms of ginseng in protecting heart. Chin J Integr Med. 2012;18(7):548-55. doi: 10.1007/s11655-012-1148-1, PMID 22772919.
24. Li GX, Liu ZQ. The protective effects of ginsenosides on human erythrocytes against hemin-induced hemolysis. Food Chem Toxicol. 2008;46(3):886-92. doi: 10.1016/j.fct.2007.10.020, PMID 18069111.
25. Rastogi V, Santiago-Moreno J, Dor éS. Ginseng: a promising neuroprotective strategy in stroke. Front Cell Neurosci. 20 de enero de. 2015 [citado 21 de julio de 2020];8.
26. Rokot NT, Kairupan TS, Cheng K-C, Runtuwene J, Kapantow NH, Amitani M, et al. A role of ginseng and its constituents in the treatment of central nervous system disorders [internet]. Hindawi Publishing. Vol. 2016. p. e2614742; 2016 [citado 22 de julio de 2020]. Evidence-Based Complementary and Alternative Medicine. Available from: https://www.hindawi.com/journals/ecam/2016/2614742/ [cited 20/9/2021].
27. Zheng M, Xin Y, Li Y, Xu F, Xi X, Guo H, et al. Ginsenosides: A potential neuroprotective agent [internet]. Hindawi Publishing. Vol. 2018. p. e8174345; 2018 [citado 22 de julio de 2020]. BioMed Research International. Available from: https://www.hindawi.com/journals/bmri/2018/8174345/ [cited 20/9/2021].
28. Nivel de participación social, recreativa, deportiva e independencia de adolescentes y adultos jóvenes con osteogénesis imperfecta. Arch Argent Pediatr. 1 de junio de. 2016 [citado 22 de julio de 2020];114(3).
29. González-Burgos E, Fernandez-Moriano C, Gómez-Serranillos MP. Potential neuroprotective activity of ginseng in Parkinson's disease: a review. J Neuroimmune Pharmacol. 2015;10(1):14-29. doi: 10.1007/s11481-014-9569-6, PMID 25349145.
30. Cho IH. Effects of *Panax ginseng i*n Neurodegenerative Diseases. J Ginseng Res 15 de octubre de. 2012;36(4):342-53. doi: 10.5142/jgr.2012.36.4.342, PMID 23717136.
31. Paul S, Shin HS, Kang SC. Inhibition of inflammations and macrophage activation by ginsenoside-Re isolated from Korean ginseng (*Panax ginseng* CA Meyer). Food Chem Toxicol. 2012;50(5):1354-61. doi: 10.1016/j.fct.2012.02.035, PMID 22401937.
32. Lee DC, Lau AS. Effects of *Panax ginseng* on tumor necrosis factor-α-Mediated Inflammation: A Mini-Review. Molecules. 2011;16(4):2802-16. doi: 10.3390/molecules16042802, PMID 21455094.
33. Nguyen NH, Nguyen CT. Pharmacological effects of ginseng on infectious diseases. Inflammopharmacology. 2019;27(5):871-83. doi: 10.1007/s10787-019-00630-4, PMID 31407196.
34. Lim W, Shim MK, Kim S, Lee Y. Red ginseng represses hypoxia-induced cyclooxygenase-2 through sirtuin1 activation. Phytomedicine. 2015;22(6):597-604. doi: 10.1016/j.phymed.2015.03.005, PMID 26055124.
35. Wong AST, Che CM, Leung KW. Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview. Nat Prod Rep. 2015;32(2):256-72. doi: 10.1039/c4np00080c, PMID 25347695.
36. Dai D, Zhang CF, Williams S, Yuan CS, Wang CZ. Ginseng on cancer: potential role in modulating inflammation-mediated angiogenesis. Am J Chin Med. enero de. 2017;45(1):13-22. doi: 10.1142/S0192415X17500021, PMID 28068835.
37. Jin X, Che DB, Zhang ZH, Yan HM, Jia ZY, Jia XB. Ginseng consumption and risk of cancer: A meta-analysis. J Ginseng Res 1 de julio de. 2016;40(3):269-77. doi: 10.1016/j.jgr.2015.08.007, PMID 27616903.
38. Kang JH, Song KH, Woo JK, Park MH, Rhee MH, Choi C, Oh SH. Ginsenoside Rp1 from *Panax ginseng* Exhibits Anti-cancer Activity by Down-regulation of the IGF-1R/Akt Pathway in Breast Cancer Cells. Plant Foods Hum Nutr. 2011;66(3):298-305. doi: 10.1007/s11130-011-0242-4, PMID 21748437.
39. Qi LW, Wang CZ, Yuan CS. American ginseng: potential structure–function relationship in cancer chemoprevention. Biochem Pharmacol. 2010;80(7):947-54. doi: 10.1016/j.bcp.2010.06.023, PMID 20599804.
40. Hofseth LJ, Wargovich MJ. Inflammation, cancer, and targets of ginseng. J Nutr 1 de enero de. 2007;137(1);Suppl:183S-5S. doi: 10.1093/jn/137.1.183S, PMID 17182823.
41. Buhner SH. Remedios naturales para aumentar la testosterona: cómo mejorar la salud sexual y la energía masculina. Simon & Schuster; 2017. 275 p.
42. Sun Y, Chen S, Wei R, Xie X, Wang C, Fan S, Zhang X, Su J, Liu J, Jia W, Wang X. Metabolome and gut microbiota variation with long-term intake of *panax* ginseng extracts on rats. Food Funct. 2018;9(6):3547-56. doi: 10.1039/c8fo00025e, PMID 29896600.
43. Bucciarelli A, Moreno ML, Skliar MI. Efectos adversos de plantas medicinales Y sus IMPLICANCIAS. En: SALUD. Vol. 7; 2014.
44. Wang L, Zhang F, Cao Z, Xiao Y, Li S, Yu B, Qi J. Ginsenoside F2 induces the release of mediators associated with Anaphylactoid reactions. Fitoterapia. 2017;121:223-8. doi: 10.1016/j.fitote.2017.07.010, PMID 28734737.
45. Ghavami A, Ziaei R, Foshati S, Hojati Kermani MA, Zare M, Amani R. Benefits and harms of ginseng supplementation on liver function? A systematic review and meta-analysis. Complement Ther Clin Pract. mayo de 2020. Vol. 39. PMID 101173.
46. Gao Y, Wang T, Wang G, Li G, Sun C, Jiang Z, Yang J, Li Y, You Y, Wu X, Sun L, Wang H, Li C, Tian J, Zhu J, Wang K, Cho S. Preclinical safety of ginsenoside compound K: acute, and 26-week oral toxicity studies in mice and rats. Food Chem Toxicol. 2019;131:110578. doi: 10.1016/j.fct.2019.110578.
47. PARK MHE. Method for processing ginseng and the uses of extract of processed ginseng [internet]; 1710 TP. EP1467627A1, 2004 [citado 30 de julio de 2020]. Available from: https://patents.google.com/patent/EP1467627A1/en?oq=ginseng+root+tablets [cited 20/9/2021].
48. Hwan M. Method for processing ginseng and the uses of extract of processed ginseng [internet]. Vol. 2004. p. 2-23; 2003/056929. Seúl; Wo. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2003056929 [cited 20/9/2021].
49. Hachiya I, Mochizuki K, Kuwada Y. Method of preparing dried ginseng for drug [internet]. US4446130A, 1984 [citado 30 de julio de 2020]. Available from: https://patents.google.com/patent/US4446130/en?oq=ginseng+root+preparation [cited 20/9/2021].
50. 서주원, 양승환, 사시쿠마. 인삼 추출물의 제조방법 [internet]. KR20150130582A, 2015 [citado 30 de julio de 2020]. Available from: https://patents.google.com/patent/KR20150130582A/en?q=ginseng+extract+formulation&oq=ginseng+extract+formulation&page=4 [cited 20/9/2021].

Cite this article: Vindas GS, Rojas MC, Zúñiga RV, Berrocal GC, Redondo GM. Ginsenosides and other Phytochemicals of *Panax* spp. Properties and uses in the Pharmaceutical Field. Pharmacognosy Communications. 2021;11(4):177-81.