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Ginseng: Pharmacological Action and Phytochemistry Prospective

Shuchi Dave Mehta, Priyanka Rathore and Gopal Rai

Abstract

Ginseng, the root of *Panax* species is a well-known conventional and perennial herb belonging to Araliaceae of various countries China, Korea, and Japan that is also known as the king of all herbs and famous for many years worldwide. It is a short underground rhizome that is associated with the fleshy root. Pharmacognostic details of cultivation and collection with different morphological characters are discussed. Phytocontent present is saponins glycosides, carbohydrates, polyacetylenes, phytosterols, nitrogenous substances, amino acids, peptides, vitamins, volatile oil, minerals, and enzymes details are discussed. The main focusing of the bioactive constituent of ginseng is ginsenosides are triterpenoid saponin glycosides having multifunctional pharmacological activities including anticancer, anti-inflammatory, antimicrobial, antioxidant and many more will be discussed. Ginseng is helpful in the treatment of microbial infection, inflammation, oxidative stress, diabetes, and obesity. Nanoparticles and nanocomposite film technologies had developed in it as novel drug delivery for cancer, inflammation, and neurological disorder. Multifaceted ginseng will be crucial for future development. This chapter review pharmacological, phytochemical, and pharmacognostic studies of this plant.

Keywords: Ginseng, ginsenosides, pharmacological, phytochemistry

1. Introduction

About 3.3 billion people in communities of less developed and even developed countries employ medicinal plants for the treatment and prevention of various diseases in their daily routine. Medicinal plant can be defined as the plant which contains metabolites that can be utilized for therapeutic indications or can be utilized for the synthesis of synthetic drugs. These plants are used in the indigenous system of medicine having no sufficient scientific predictions to confirm their therapeutic efficacy. Every medicinal plant consists of a variety of constituents that are involved in the synthesis and development of new and different kinds of the drug in the medicinal field.

Over 2000 years, China, Korea, and Siberia are major countries where ginseng was used as traditional medicine and commercial cultivation on a minor scale was in Germany, France, Holland, and England. the word ginseng i.e. Jen Sheng is originated from a Chinese word meaning 'man-herb' whereas the word *Panax* means 'all heal' in Greek which is a powerful plant that can all and any type of disease. **Figure 1** showing Ginseng a man root. It is commonly named as 'man root' due to the likeness of a man showing pharmacological uses of the whole body. In 1596, the Compendium of Materia Medica founded by Li Shizen discussed Ginseng as a "superior tonic" as compared to other herbal remedies. The usage of ginseng



Figure 1.
Ginseng a man root.

is worldwide which is entitled as the most popular herbal remedy. It belongs to the genus *Panax*, the various species include *Panax quinquefolius*, *Panax ginseng*, and *Panax notoginseng* where their common names are American ginseng, Korean ginseng, and South China ginseng. The other species include *Panax japonicas*, *Panax vietnamensis*, *Panax pseudoginseng*. All the species are regarded as wild where *Panax ginseng* is mostly cultivated.

2. Cultivation, collection, and preparation with morphological characters

These plants are cultivated in Northern Hemisphere countries mostly in China, Japan, Korea, United States, and Canada which requires a relatively cooler climate with temperatures between 0 and 25°C with loamy rich soil, well-drained land, and no direct sunlight, the shades are preferred. The height of the plant is 6 to 18 inches with greenish-yellow corollas with 15–30 flowers where light red, pear-shaped, globular fruits having 2 seeds.

Roots are thickened subcylindrical fleshy after drying the size is 25 cm long having 0.7–2.5 cm diameter, with 2–5 big branches where the outer surface is spirally wrinkled longitudinally with root scars.

The outer surface color differs in various varieties i.e., yellowish-white for Chinese and *Panax quinquefolius* and *Panax notoginseng* whereas yellowish-brown color for *Panax ginseng*. The taste is sweetish, mucilaginous and bitter sometimes where odor is slightly aromatic. The number of leaf scar in rhizome gives sign of age of plant. The yellowish-brown internal surface which is scattered with bark and wood containing brownish-red resin and oil [1, 2].

2.1 Plantation of ginseng seeds

After 3–6 years, either in autumn or summer season the roots are separated very carefully from plants due to presence of pest. For the purpose of avoidance of pest infection, the roots are sterilized and prepared. **Figure 2** showing plantation of ginseng.



Figure 2.
Plantation of ginseng.

The method of preparation is different for white ginseng and red ginseng. In China, white ginseng's surface skin is removed by peeling and then dried and stored carefully for 12–15 months with less decrease of ginsenoside contents whereas in Korea, red ginseng is sterilized by steam sterilization method at a temperature of 120–130°C for about 3 hours which as a result saponin content is increased and can be stored for 2–3 years with no decrease of photo content.

2.2 Plants parts used

Root, Rhizomes, Leaves, Stem [3], flower bud [4].

2.3 Traditional uses

For more than a thousand years, ginseng was used as traditional herbal medicine as a healer of every type of disease. It was considered the best medicine for main fatigue and spiritlessness [5]. In traditional Chinese medicine, it was used for the treatment of heart and blood vessel disorder and also to make people feel calmer. In the ayurvedic system of medicine, traditionally ginseng was utilized as a cardioprotective, anticancer, and also as antioxidant.

3. Ginseng phytoconstituents

The classification of ginseng's phytochemistry consists of more than 200 chemical entities from ginseng species. The various groups of phytoconstituents include saponins glycosides, carbohydrates, polyacetylenes, phytosterols, nitrogenous substances, amino acids, peptides, vitamins, volatile oil, minerals, and enzymes.

3.1 Saponins

Saponins are the bioorganic glycoside having at least one glycosidic linkage at C3 between aglycone and sugar chain. On hydrolysis of saponin, molecule converts to

glycone moiety i.e. glucose, pentose, galactose, maltose, fructose, or methyl pentose and aglycone moiety (sapogenin). The sapogenin can be classified as triterpenoid, steroid, alkaloid glycosides. Ginseng's saponins are usually known as ginsenosides which were named by Japanese workers whereas panxosides were named by Russian workers.

The ginsenosides are considered as the main constituents of ginseng having different pharmacological activities such as anti-fatigue, anti-cancer, anti-aging, anti-oxidant, anti-hyperglycemic, anti-obesity, and many more in ginseng root, berry, leaf, and stem. The basic structure of ginsenosides consists of a steroid nucleus with seventeen carbon atoms arranged in four rings. On the position of the hydroxyl group on carbon-20 shows are stereoisomers where every ginsenoside have at least 2 (carbon-3 and -20) or 3 (carbon-3, -6, and -20) hydroxyl groups, which are free or bound to monomeric, dimeric, or trimeric sugars. Total ginsenosides can be classified as oleanane, dammarane and ocotillol types. Ginsenoside Ro is an oleanane type whereas Ginsenoside-Ra-3, G-Rb1-2, and G-Rh2 are dammarane type are subclassified into two types i.e., protopanaxadiols and protopanaxatriols. Pseudoginsenosides F11 and its derivatives such as makonoside-Rs are representative of ocotillol type ginsenosides [6]. Ginsenosides Rb2, Rb3, and Rg1 are showed on root hair, root and leaf whereas ginsenosides Rb3 and Rh1 were present in large amounts, and ginsenosides Rb1 and Rc were found in large amount main roots [4]. **Figure 3** showing various examples of ginsenosides. The pharmacological response of each ginsenoside is dependent on the type, position, and glycone moieties attached by the glycosidic bond at C-3, C-6, and C-20 positions. Among *Panax* species, more than 100 ginsenosides are isolated. More than 200 ginsenosides have been isolated and identified. The pharmacological effects include anti-electroconvulsive, memory enhancer, cardiac cell protector, coronary vascular dysfunction, antioxidant, antidiabetic, antiobesity, anti-foot and mouth disease, antiaging, antiulcer, antifatigue, and many more.

The bioavailability of ginsenosides is very poor. The absorption of ginsenosides in the intestinal mucosa is energy-dependent. The biliary excretion in active transport results in a shortage of its biological half-life and lower systemic exposure level [3, 7–9].

3.2 Carbohydrates

Among carbohydrates, the polysaccharides have considered highest content in the ginseng, which are classified into two parts according to their monosaccharide's structure i.e. ginseng starch like glucans and ginseng pectin. Neutral and acid polysaccharides are present in ginseng. These polysaccharides attribute pharmacological activity as immunomodulating, antioxidant, anti-depressant anticancer, anti-inflammatory, and antiproliferative activities by playing a vital role on nervous system disorders through regulation of signaling pathway, immune system and inflammatory response [10]. Two bioactive ginseng polysaccharides named GP50-dHR and GP50eHR showed antidiarrheal effects [11].

3.3 Amino acid

Organic compounds containing carboxyl and amine groups are known as amino acids. The concentration of amino acid in ginseng is large which is useful in human health that is applied in pharmaceutical and food applications. All the basic, acidic, and neutral amino acid including histidine, lysine, arginine, aspartic acid, glutamic acid, serine, alanine, glycine, proline, valine, tyrosine, leucine, and threonine plays as the major content of ginseng [12].

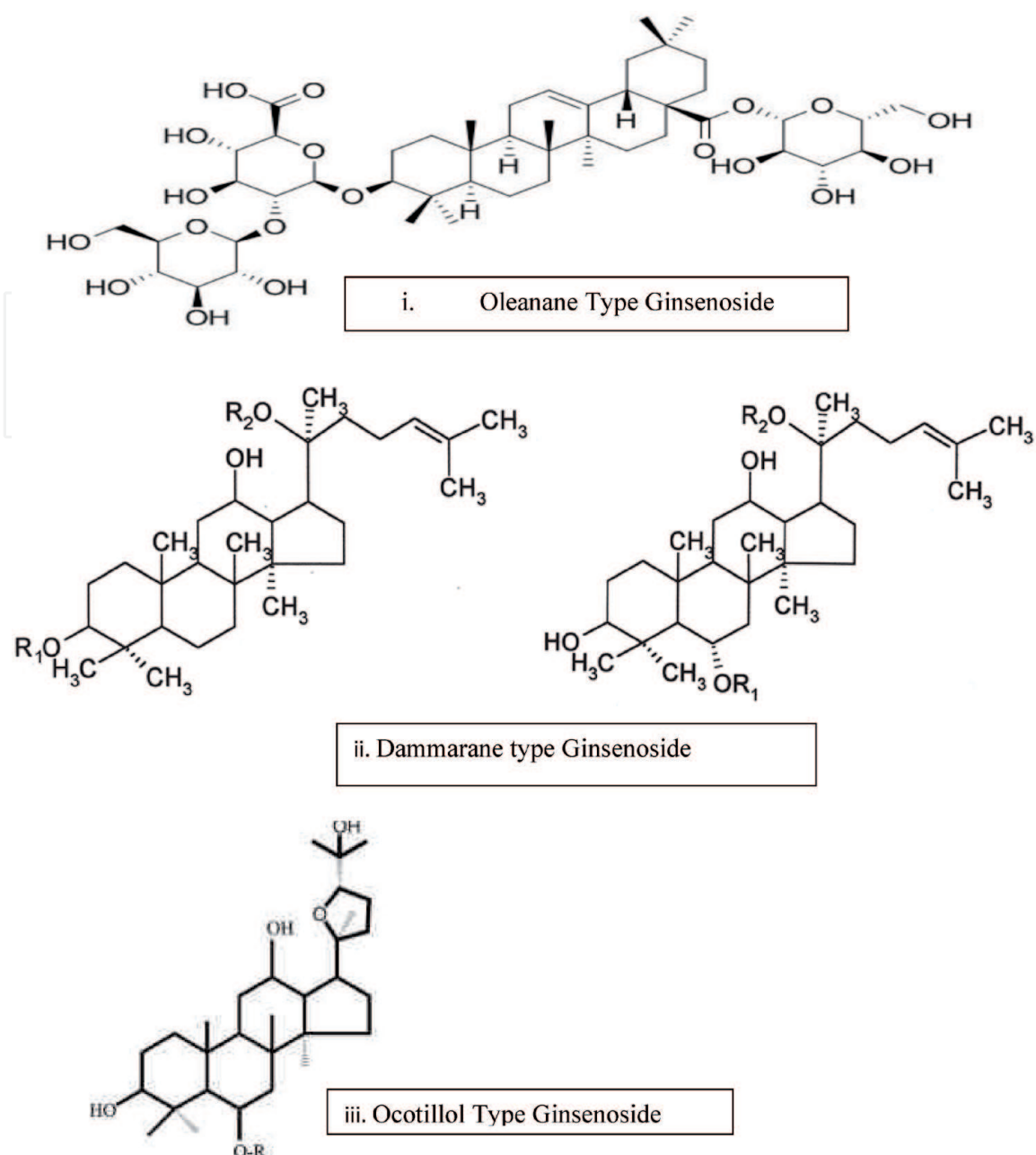


Figure 3.
 Examples of Ginsenosides.

3.4 Polyacetylenes

The organic polymer with the repeating unit of polymerization of acetylene is known as polyacetylene. The total amount of polyacetylene in ginseng was reported as 0.020–0.073%. The anti-proliferative effect was reported in bioactive panaxynol and panaxydol, major polyacetylene in *Panax ginseng* Meyer roots using MTT assay viability method [13]. Ginsenoyne C is polyacetylene in *Panax Ginseng* showed anti-inflammatory through regulating phosphorylation of extracellular regulated kinases signaling [14].

3.5 Volatile oil

The pharmacological effects, qualities, and chemical content of volatile oil are varied to species to species of ginseng. More than 369 volatile oil compounds are identified in the ginseng species. Heterocycles, aldehydes, fatty acids, sesquiterpenoids, sesquiterpene hydrocarbon, alkane hydrocarbons, and fatty acid

ester. Reported sesquiterpenoid includes bicyclogermacrene, calarene, (E)- β -farnesene, β -phellandrene, α -humulene where sesquiterpene hydrocarbon includes (E)-caryophyllene, aromadendrene, β -farnesene, α -neoclovene, β -neoclovene, bicyclogeracrene, α -panasinsene, β -panasinsene, ginsenol, panasinsenol A, panasinsenol B [15–17].

4. Pharmacological potential

Ginseng is considered a miracle source of multifaceted pharmacological activities such as anti-inflammatory, anticancer, antifungal, antibacterial, antiviral, immune-booster, antidiabetic, and antioxidant activities. **Figure 2** is showing various pharmacological uses of ginseng. The bioactive of ginseng has the power of interaction with membrane-bound ion channels, cell membranes, and extracellular and intracellular receptors which as consequences causes alteration at the transcriptional level. The extracts of Ginseng had shown protective effects on hepatocytes and liver injury. **Figure 4** showing Ginseng Pharmacological Potential. Previously demonstrated that both neurotrophic effects in learning and memory enhancement and also cause neuroprotective action for prevention of neuron degeneration [18–20].

4.1 Anti-inflammatory activity

Inflammation is an uncontrolled response that is the result of disorders including metabolic disorder, autoimmune diseases, cardiovascular disorder, or allergies; on the other hand, it is a response of our body to hazardous stimuli such as injury to tissues. For the treatment of suppressing and controlling inflammatory crisis various steroids, nonsteroids anti-inflammatory, and immunosuppressant are utilized. The inflammatory responses are classified as acute inflammation and chronic inflammation. Acute inflammation is for 7 days or a week whereas chronic inflammation extends for the past four weeks. During inflammation, cytokines are produced by Th1 cells (IL-2, interferon [IFN]- γ , TNF- α , and so on) will be decreased by Th2 cells releasing IL-4, IL-6, IL-10 and transforming growth factor- β . The mutual balance between Th1 and Th2 responses in inflammation immediately attenuate acute inflammation conditions back to normal whereas various conditions with imbalanced Th1/Th2 responses result in chronic inflammation [21].

Ginseng has suggested anti-inflammatory activity which was proven by various in vivo, in vitro, and clinical studies. Gensenosides Rb1, Rg1, Rg3, Re, Rd., Rh1, Rc, Rf, Rg5, Rg6, Rh3, Rk1, Ro, and Rz1 have been reported as anti-inflammatory responses due to negative regulation of pro-inflammatory cytokine expressions (TNF- α , IL-1 β , and IL-6) and enzyme expressions in M1-polarized macrophages and microglia [22]. Ginsenosides Re and Rp1 can suppress the NF- κ B signaling pathway whereas ginsenosides Rc inhibits macrophage-derived cytokines. Clinical studies concluded a 38% higher more survival rate for patients who took ginseng as compared to patients who had not taken ginseng [21]. Extract of *P. ginseng* berry calyx (Pg-C-EE) reported an anti-inflammatory mechanism through the expression of TNF- α , iNOS, COX-2 in lipopolysaccharide-activated macrophages and through NO production [23].

4.2 Anti-cancer activity

According to the world health organization, cancer is considered the second leading cause of death globally an estimated 9.6 million deaths or one in six deaths, in 2018. Cervical, thyroid, lung, colorectal, and breast cancer are common cancer

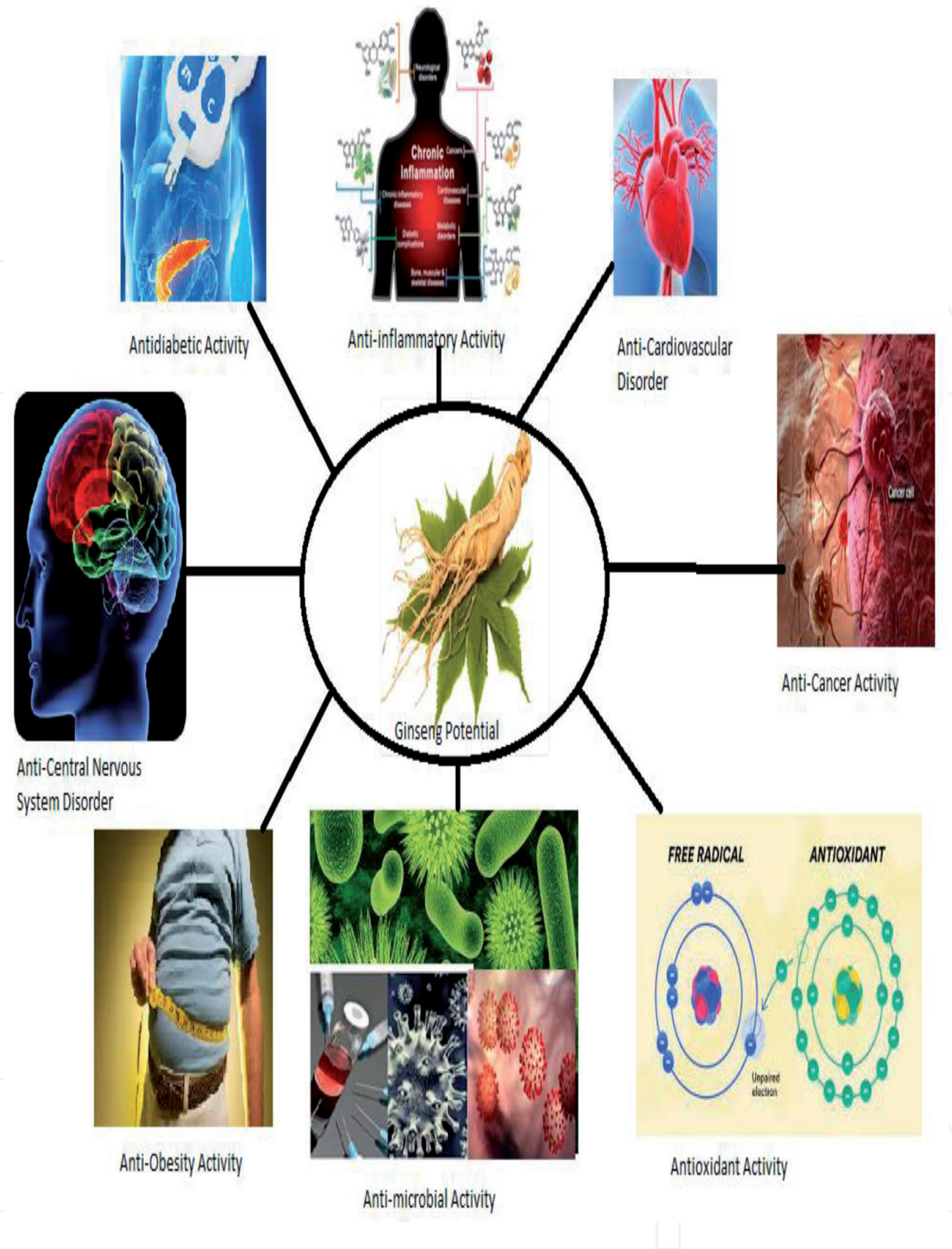


Figure 4.
Ginseng pharmacological potential.

diseases in women whereas stomach, liver, prostate, lung, and liver cancer are common cancer in men. Cancer can be defined as the growth of abnormal cells in uncontrolled conditions in almost any organ or tissue of the body, if beyond their usual boundaries then goes inside adjoining parts of the body and spread to other organs. At metastasizing process, results in cancer death. Cancer can be prevented by implementing evidence-based strategies by avoiding the risk factors use of tobacco, use of alcohol, less consumption of fruits and vegetables. For the treatment of cancer, chemotherapy is the most common therapy for treatment. Administration of chemotherapeutic agents as result gives a reduction in bone density and immunosuppression.

For many years, natural products have been a good source of agents for treating cancer and plants played a huge role in anti-cancer product development. Ginseng is a universal herb that is utilized for the prevention and treatment of cancer. It has been acting as a chemopreventive and also used to improve the quality of life among patients with cancer [24, 25]. Ginseng as an herbal drug is consumed and mentioned in the Pharmacopieas formulation in various countries like United Kingdom, China, Japan, France, Austria, and Germany. In Western Europe and Asian countries, it is commonly utilized as a combinational drug to improve cancer chemotherapy. Ginseng is responsible for the inhibition of the growth of human cancer cells of prostate cancer, lung cancer, and colon cancer. **Figure 5** is showing Ginsenoside anticancer activity.

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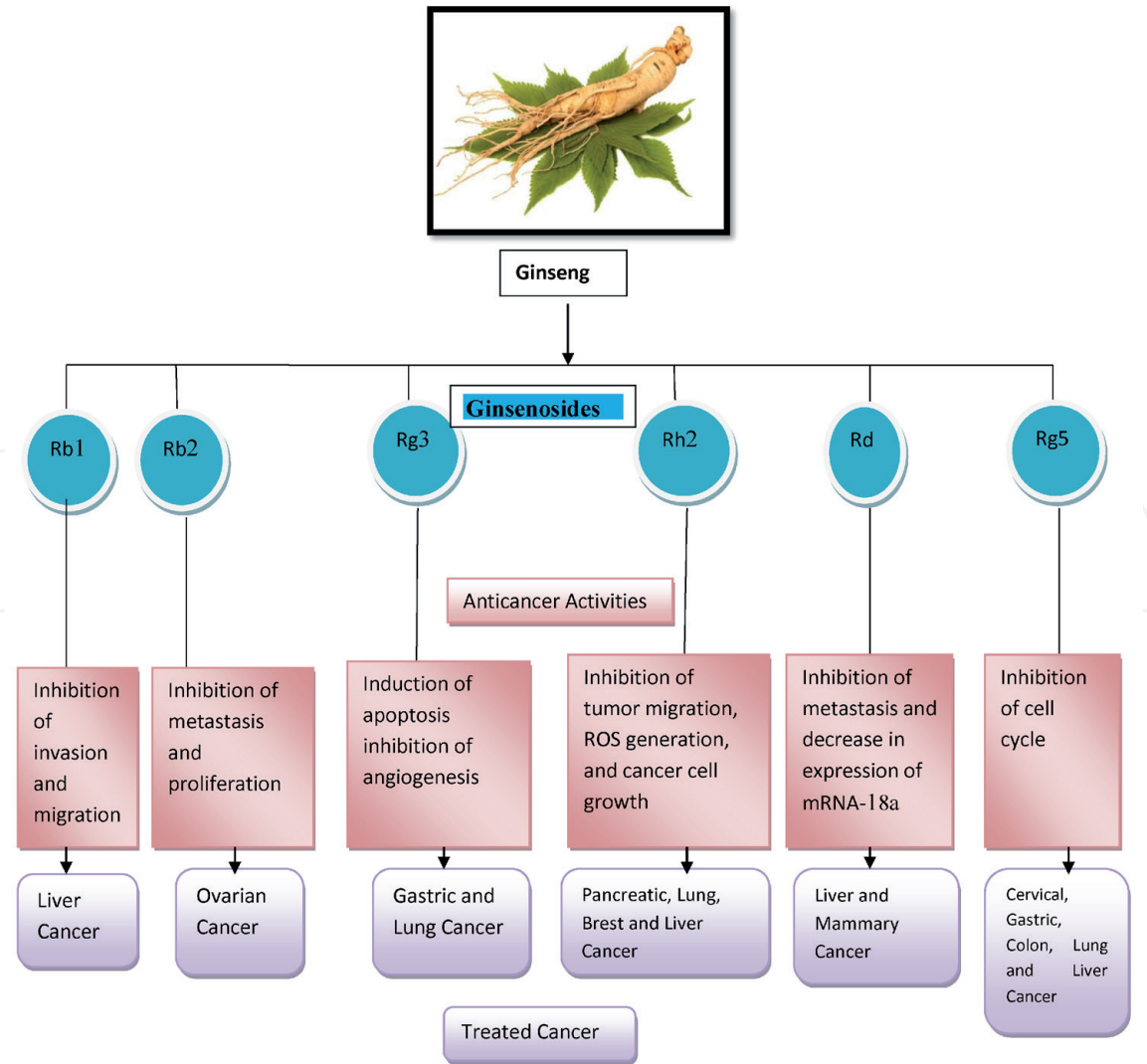


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The anticancer action is by modulation of diverse signaling pathways, including regulation of cell proliferation mediators (cyclins and CDKs), growth factors (c-myc, vascular endothelial growth factor, and EGFR), tumor suppressor (p53 and p21), cell mediators (Bcl-2, caspases, Bcl-xl, death receptors), inflammatory response molecules (COX-2 and NFκB), protein kinase (JNK, Akt, and AMP-activated protein kinase) It acts on its cellular and molecular targets through various pathways by inhibiting the tumor by regulation of the cell cycle and inhibition of angiogenesis and invasion [26].

Ginseng extract can induce chemosensitization of the conventional anticancer agent through multidrug resistance (MDR-1) associated protein. Ginseng had also shown a reduction of drug-induced toxicity when used in combination with anticancer drug for example ginsenosides Rh4 and Rk3 reduces the cisplatin-induced nephrotoxicity in dose dependant level where the reason and structure–activity relationship with other ginsenosides are remained to be studied by Baek *et al.* [27, 28].

In clinical studies, Ginseng is acting as a tonic in combination with chemotherapy which concluded that ginseng with the other anticancer drug, for example navebine, Vinorelbine, enhances the short term therapeutic efficiency of lung cancer where the study was conducted by 63 patients. The result showed an improvement in the patient's quality of life. Researchers are focusing on purified ginsenosides which gives the result to a rapid specific mechanism of action rather than using ginseng extract.

Ginseng polysaccharides are also reported as an anticancer agent which includes fractions such as WGPA-1-RG, WGPA-2-RG, WGPA-1-HG, WGPA-2-HG, WGPA-3-HG, and WGPA-4-HG that acts by regulating the immune response of host organisms whereas Ginseng pectin reported inhibiting the action of proteins linked with cancer progression [24].

4.4 Antimicrobial activity

Antimicrobial activity was derived from the Greek words anti-meaning against, mikros meaning little, and bios meaning life which can be defined as the activity against the growth of microorganisms or by their killing. The microorganisms include bacterial, fungi, parasites or viruses. Antiviral activity is defined as the action of killing a virus or suppression of its ability to replicate and inhibition of the

virus for multiplication and reproduction. It is used in the treatment of infectious disease caused by a virus where the virus responsible for the disease include influenza, herpes simplex type 1 and type 2, herpes zoster, viral hepatitis, encephalitis, infectious mononucleosis, HIV/AIDS, and many more. Viruses are nucleic acid i.e. DNA or RNA and a protein coat.

Novel antiviral formulation therapies and vaccines are in recent progress of research scientists which supported to prevent and shorten the duration of the extremity of viral infection. Due to the continuous growth of new infection of the Ebola virus and respiratory syndrome coronavirus, it is compulsory to develop advanced novel therapeutic approaches. The main problem in the development of novel antiviral agent is mutation process in the viral mutation that as result in drug resistance and immune evasion. Recently the development of novel antiviral formulation has the target to develop broad-spectrum antiviral and immunomodulators which improve and inhibit the host resistance to the viral infection. In large population infection, vaccination is the main measure of treatment of disease [29, 30].

In vitro and in vivo antiviral activity of Panax Korean red ginseng extract was determined on respiratory syncytial virus infection (RSV) which as a result showed improved the survival of human lung epithelial cells against RSV infection and also inhibited RSV replication by suppressing the expression of RSV-induced inflammatory cytokine genes and also enhanced level of interferon- γ producing dendritic cells which are subsequent to RSV infection [30].

Antiviral activity of fermented *Panax ginseng* extracts against a broad spectrum of Influenza viruses (H1N1, H3N2, H5N1, and H7N9) in genetically diverse mouse models was investigated. Antiviral protection was observed due to more components of saponins of fermented ginseng extracts against influenza viruses than nonfermented ginseng extract. For the development of a new vaccine and new antiviral drug against influenza viruses, the Panax notoginseng root was studied where both in vitro and in vivo analysis was investigated. The Panax notoginseng root decreased influenza A virus-induced mortality by 90% and also increased the NK cell activity of mouse splenocytes [31].

Antifungal is an agent for the treatment and prevention of fungal infections which selectively eliminates fungal pathogen from a host with minimal toxicity to the host. Fungi examples are yeast, *Candida albicans*, molds, *Xanthoriaparietina*, *Amanita phalloides*, *Polyphagus euglena*, *Gigaspora gigantean* and many more. Korean red ginseng containing saponin as ginsenosides were reported as having antifungal effects against *Candida albicans*. The result was concluded that ginsenosides antifungal activity by disrupting the structure of cell membrane were awaited for further clinical investigation [32].

The root of ginseng, Notoginseng was investigated antifungal activities against *Epidermophyton floccosum*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. The mechanism of antifungal activity was to find out which was due to interaction with the fungal cell membrane and damages the integrity of the membrane. The result concluded that notoginseng saponin can used for the treatment of ringworm [33].

Antibacterial and antifungal effect of ginseng powder on gram-positive, gram-negative, and *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecalis* and *Candida albicans* as fungus was investigated by disc diffusion method showed significant zone inhibition [34].

4.5 Antioxidant activity

Antioxidant activity is the limitation and inhibition of nutrient oxidation by restraining oxidative chain reactions. Herbal antioxidants prevent destructive

processes caused by oxidative stress by stabilizing or deactivate free radicals before they attack targets in a biological cell. Cancer, diabetes, inflammation, senile dementia, asthma, liver damage, and many other diseases are closely related to free radicals. Free radicals are originated from various sources such as pollution, alcohol, tobacco, smoking, pesticides, phagocytic cells etc. In vitro and in vivo antioxidant effect of *Panax ginseng* showed higher free radical scavenging activity power than white and red ginseng which was due to the presence of higher content of total saponin, phenolic, and flavonoids. The antioxidant activity analyzes by free radical scavenging activity assay and reducing power assay method, lipid peroxidation, antioxidant enzyme activity models [35].

The antioxidant effect of *Panax Ginseng* was studied on healthy volunteers of 82 participants of which 21 men and 61 women were investigated where Serum level of reactive oxygen species (ROS), malondialdehyde (MDA), total antioxidant capacity (TAC), the activities of catalase, superoxide dismutase (SOD), glutathione reductase (GSH-Rd), and peroxidase (GSH-Px), and total glutathione content were determined. The healthy volunteers confirmed the antioxidant potential of *P. ginseng*. *P. quinquefolius* containing ginsenosides analyzed affinity DPPH-stable free radical, metal chelation, and hydroxyl free radicals for characterization of antioxidant effect [36].

5. Novel formulation development

Ginseng as a supertonic herbal drug should be in novel approaches that get rid of the limitation of the conventional drug. Novel approaches will help in increase of bioavailability, minimize drug physical and chemical degradation and loss, prevention of harmful side-effects, protecting toxicity and enhancement stability. This will help to overcome problems associated with herbal medicine. Herbal Novel drug delivery includes nanoparticles, liposomes, phytosomes, nanoemulsion, microsphere, transferosomes, nanocapsules and ethosomes are reported using extract and marker Nanoparticles and nanocomposite technology of ginseng had reported previously [37, 38].

A novel multifunctional liposome system was developed in a combination of three ginsenosides with paclitaxel using the thin-film hydration method. Antitumor activity was analyzed by GC, MTT, cell cycle, and apoptosis assays method. The result concluded that ginseng liposome was acting as tumor-targeting therapy with dual effect as chemotherapy adjuvant and functional membrane material [39]. Nanoginseng showed better antitumor activity and high drug load efficiency and capacity, excellent biocompatibility with reduced damage to normal tissues [40]. Nanocapsulated red ginseng extract using bioactive coating materials chitosan enhanced antithrombotic activities by both in-vitro and ex vivo platelet aggregation assay method [41]. Phytosome *Panax ginseng* containing ginsenosides acting as nutraceutical and immunomodulator elevated superoxide dismutase, glutathione peroxidase, and glutathione reductase activities. Commercial product of phytosome as Ginseng Phytosome™ is in market.

6. Conclusion

The traditional system of medicine including the Chinese system of medicine and Ayurvedic system of medicine already mentioned ginseng as man herb acting as a supertonic which is used for the treatment of all type of disease cancer, cardiovascular disorder, impotence, diabetes, palpitation, insomnia, hyperdynamic, anorexia, and many more. Unique cultivation and collection techniques are

discussed. More than 200 phytochemical are reported where main classes include saponins glycosides, carbohydrates, polyacetylenes, phytosterols, nitrogenous substances, amino acids, peptides, vitamins, volatile oil, minerals, and enzymes. The miracle ginseng consist of anti-inflammatory, anticancer, antifungal, antibacterial, antiviral, immune- booster, antidiabetic, and antioxidant activities pharmacological actions of which latest anticancer, anti-inflammatory, antimicrobial, and antioxidant pharmacological activities is discussed where not only in vivo and in vitro studies is discussed but also clinical trial is highlighted. Novel formulation phytosome, nanocapsulated, nanoparticles for cancer, inflammation, and neurological disorder developed to enhance bioavailability and target delivery of drug. It can be concluded that focusing the herb in research and development of the pharmaceutical industry in private and government agencies in future development would be beneficial and helpful to eliminate the toxic effect of supertonic ginseng.

Author details


Shuchi Dave Mehta^{1*}, Priyanka Rathore² and Gopal Rai¹

1 Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy),
Jabalpur, MP, India

2 Sagar Institute of Research and Technology Pharmacy, Bhopal, MP, India

*Address all correspondence to: shuchi1801@gmail.com

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