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Review

Ginseng: A dietary supplement as immune-modulator in various diseases

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ABSTRACT

Background: Mechanistic studies suggest that ginseng, as dietary supplement, plays a key role in disease prevention by modulating the immune function of human body. The root of *Panax ginseng* and *Panax quinquefolius* (Family: Araliaceae) are commonly known as 'ginseng'. Ginseng roots are well known for their high content of saponins, ginsenosides, phenolic compounds, including carbohydrates and carotenoids. In recent years, there is a growing interest in the role of ginseng as a nutraceutical or functional food with increasing market value. Extracts and bioactive compounds isolated from ginseng are studied for their various health promoting activities such as antioxidant, antitumor, antihyperglycemic, skin protecting, anti-osteoporotic anticancer, anti-infective and respiratory problems.

Scope and approach: The present review reports structural and functional diversity of ginseng, key bioactive compounds, their immunity boosting potential and studies related to cell mediated and humoral immunity of ginseng. Immunity-boosting power of ginseng against cancer, autoimmune diseases and viral and bacterial infections has been compiled. The vaccine adjuvant role, safety profile and drug interactions ginseng and derived products are also discussed. Nano-ginseng as immune modulators has been a unit of article. The clinical trials carried out and patent portfolio of ginseng against immune disorders is the important section of this article. Patent search was performed by using The Patent Lens search engine and results included under heading "Ginseng based Patents for immunomodulation". Key isolated compounds have been mentioned along with their structures to give a quick overview of the chemical constituents.

Key findings and conclusions: After critically reviewing the immune potential of ginseng both *in vitro* and *in vivo* and even describing the clinical data in humans we reached at conclusion that ginseng can be considered as good candidates for the development of novel functional foods that has natural potential to modulate immunity against various diseases. Future work will have to focus on the identification of the relevant compounds from ginseng, the thorough preclinical characterization and selection of the candidate bioactives, and the rational design of immunotherapy studies involving objective as well as subjective parameters for measuring clinical efficacy. We believe that this review will be a valuable resource for more studies on ginseng as a dietary supplement in relevance to immune-modulation.

1. Background

Immunotherapy is a treatment strategy used to activate or suppress the immune system (Fig. 1) by drugs (natural or synthetic), and microorganisms (partly or wholly or prepared antibodies) to combat disorders. The successful treatment of various types of infections, cancers, allergies and allogenic problems are difficult without using immunotherapy. Intake of immune modulators is the key component of immunotherapy. These are natural and synthetic agents used to adapt the response of the immune system. Natural agents comprising of botanicals and dietary supplements are comparatively safe, but less explored, while synthetic one have characteristic side effects manifested as fatigue, hair loss, blood disorders, constipation, infection, anemia, nausea, and vomiting (Bascones-Martinez, Mattila, Gomez-Font, &

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Abbreviations

BALB/c mice Albino, laboratory-bred strain of the house mouse
AGRP American ginseng root polysaccharides extract
β Beta
BMP-2 Bone morphogenetic protein 2
C57BL6 C57 black 6″, is a common inbred strain of laboratory mouse
CD4 or CD8 Cluster of differentiation, a glycoprotein found on the surface of immune cells
CAGR Compound annual growth rate
GLTα Germ-line alpha transcripts
GRb1 Ginsenosides-Rb1
Ig Immunoglobulin
ICR Institute of Cancer Research
INF Interferon
IFN-γ Interferon gamma
IL Interlukin
PI3K/AKT Intracellular signaling pathway
LLC Lewis Lung Carcinoma cells
LPS Lipopolysaccharides
MAPKs Mitogen-Activated Protein Kinases
MC3T3-E1 cells musculus (mouse) calvaria or Mouse osteoblastic cells
NK Natural killer
NO Nitric oxide
NF-κB Nuclear factor-kappa B
PO Per oral
PKD/AMPK Protein kinase D/AMP-activated protein kinase
RANKLE Receptor activator of nuclear factor-κB
RANTES Regulated upon activation normal T-cell expressed and secreted
R&D Research and development
TLR Toll like receptor
TGFβ1 Transforming Growth Factor-Beta 1
TNF Tumor necrosis factor
TNFα Tumor necrosis factor alpha

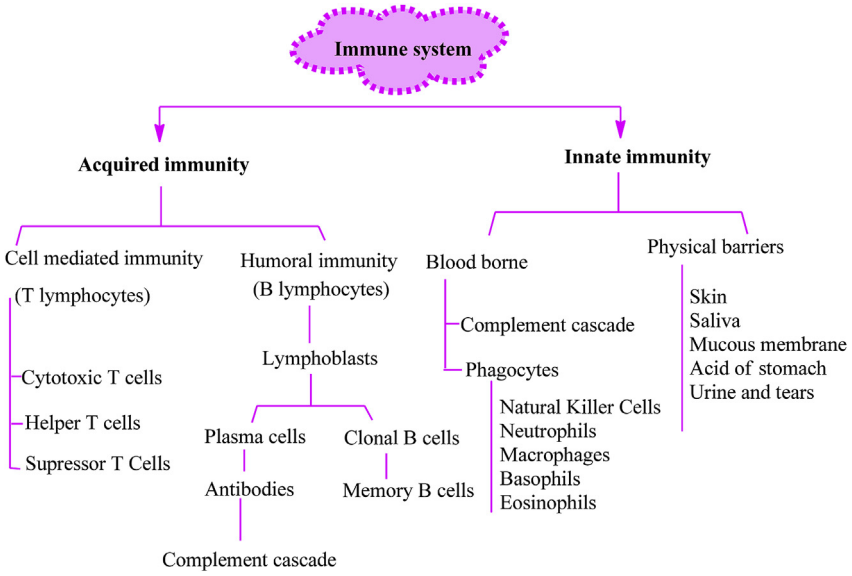


Fig. 1. Overview of the immune system.

Meurman, 2014). The present review is an effort to bring the attention of health professionals to a dietary supplement, i.e. ginseng to be explored as useful immune modulator in the management of life threatening diseases. Ginseng like other supplements, strengthens the resistance of the body to illness through effects on immune system components. The use of herbs and botanicals as alternative remedy to conventional therapy has attracted health professionals especially where immune system is partially compromised or selective immune therapy is required with the objective of minimizing the adverse events (Ganju et al., 2003).

According to the American Dietary Supplement Health and Education Act (1994) ginseng is included in dietary supplement that defines a dietary supplement as "*a product* (other than tobacco), intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb or other botanical; or a dietary substance for use to supplement the diet by

Table 1
Types of ginseng (based on occurrence and botany) (Keville, 2004).

Botanical name	Synonyms	Geographical distribution
Panax ginseng	Oriental, Chinese or Korean ginseng (most explored) most common	Asia and North America
Panax quinquefolius	American Ginseng	Quebec, Manitoba, Canada, Alabama, Oklahoma and Florida
Panax trifolius	Dwarf ginseng (American ginseng) not very common	Southern Appalachians, although its range extends from Nova Scotia to Georgia
Panax notoginseng, or *Panax pseudoginseng*	Sanchi ginseng (Asian)	China
Panax pseudoginseng subsp. *Himalaicus*	Himalayan ginseng	Tibet and western Bhutan
Panax japonicas	Japanese ginseng (native ginseng of Japan)	Japan
Eleutherococcus senticosus	Siberian ginseng	Siberia

increasing the total dietary intake; or a concentrate, metabolite, constituent, extract or combination of any ingredient described above". American council for responsible nutrition's reported in 2015 that 31% of the consumers, use herbal supplements to cope various health problems and ginseng ranks as the 4th leading dietary supplement.

Ginseng belongs to Araliaceae family, which is also known as the ginseng family. There are several different species, all bearing the common name ginseng shown in Table 1. The two major genus of ginseng are Chinese/Korean/American or Asian ginseng (genus *Panax*), and Siberian/Russian ginseng (genus *Eleutherococcus)*. However we, focus here mainly Asian ginseng and American ginseng. The *Panax,* is a Greek word meaning "all-cure", and reflects the ancient belief of panacea. The name ginseng means "essence of the earth in the form of a man." (In Chinese, *gin* is "man" and *seng* is a fleshy root used as a tonic). Ginseng, being a rich source of useful secondary metabolites, has been used in Asia for more than 5000 years ago and is known as a king of the tonic herbs (Keville, 2004). The *Panax ginseng* has different types/forms based on their processing methods e.g. **Fresh** (less than 4 years, eaten as fresh), **white ginseng** (4–6 years, peeled and dried in oven or air), **Red ginseng** (6 years old, unpeeled, steamed), and **Sun ginseng** (steamed white ginseng at high temperature and pressure) (Chen et al., 2014; Yun, 2001) while its cataloguing based on occurrence and botany is given in Table 1.

Among various segments of global ginseng market dietary supplements is the leading segment in terms of revenues. Ginseng sales in the United States have been reported to be over $300 million annually (Melvin, 2006). The global dietary supplement market was valued at over US$ 123 billion in 2015, and is poised to increase at 7.4% CAGR through 2025. Ginseng Demand as dietary supplements will continue to increase during the forecast period 2016–2025. On the basis of distribution channels, pharmacies/drugstore account for bulk of ginseng sales, followed by health/beauty stores and online retail. North America, Europe and China are expected to be the major market for ginseng products. China Health Ministry approved its use in food products in 2012 so the demand for ginseng will increase exponentially during the forecast period (https://www.futuremarketinsights.com/reports/ginseng-market). Like sales, research on ginseng increases exponentially as shown by the reports from PubMed/Medline database till 2018 (Graph 1). In 1944, there were very few articles about ginseng but exponential rise in publication is observed with the passage of time until 2018 as Graph 1 clearly shows the whole story.

Extensive *in vitro* studies on ginseng extracts, fractions and isolated compounds have been reported with valuable results. In these studies, researchers have used various cell lines and reported direct cytotoxic effects and indirect effects like nuclear factor-kappa (nf-κB) inhibition, apoptosis induction, cell cycle arrest, and increased cellular drug accumulation (Yun, 2001). The *in vitro* studies provide useful guideline for novel lead in cancer immunotherapy.

Ginseng has been reported for extra-ordinary adaptogenic potential, and evidence-based on antioxidant, anticancer and anti-diabetic properties, the details of immunotherapeutic uses are given in Fig. 2. The structural and functional similarities of isolated compounds to steroids are reflected in its immune modulatory role (He et al., 2018). It will be further particularized in this review as most of the biological actions of ginseng previously reviewed are due to their direct actions while the biological actions via indirect way of modulating immune response in host have not been studied comprehensively in animals and humans. This review will bridge this gap by highlighting meandering effect of ginseng.

2. The effect of ginseng on cellular and humoral immunity

Ginseng has been reported for altering both cellular and humoral immunity. Ginsenosides isolated from flowers and leaves namely floralginsenoside Kc, floralginsenoside J, and ginsenoside I exert inhibitory effects on LPS-induced IL-12 production. In addition, floralginsenoside

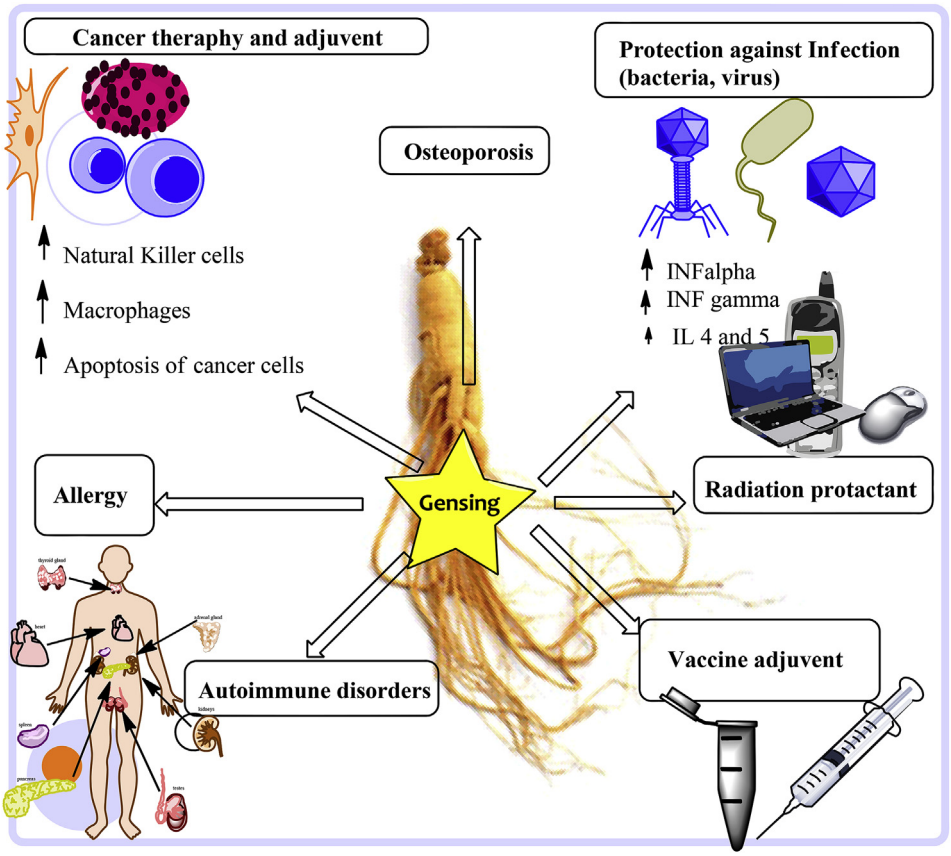


Fig. 2. The immunotherapeutic uses of ginseng, The role of ginseng via immune modulation of the host immune functions in various disorders like autoimmune disorders, allergy, cancer, infectious diseases, radiation protactant and as vaccine adjuvant are the key components of the manuscript. (IL, interlukin; INF, interferon; TNF, tumor necrosis factor).

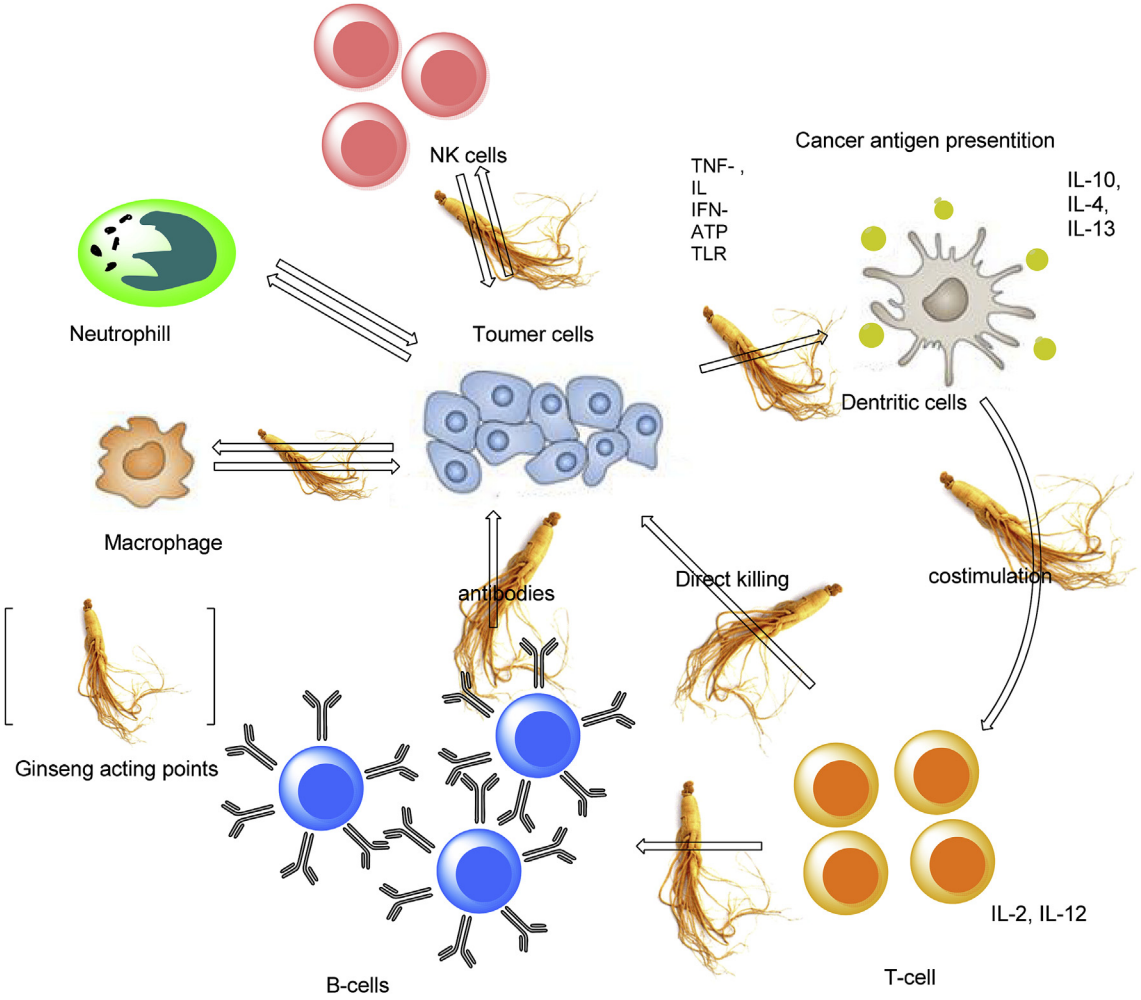


Fig. 3. Ginseng modulates cancer immunity, Various point of actions have been highlighted in figure where ginseng or its components play its active role in immune modulation; cancer antigen presentation via mediators like TNFα, INF, TLR, ATP: Co-stimulation of T Cells, via IL-2, IL-12 by dendritic cells that may either directly kill tumor cells or by indirect way of B Cells; Antibody production stimulation step: Macrophage activation step; NK cells activation step **Abbreviations**: (IL, interlukin; INF, interferon; TNF, tumor necrosis factor; TLR, toll like receptor; NK, natural killer).

Kc suppresses significantly LPS-stimulated IL-6 and tumor necrosis factor-α (TNF-α) production (Tung et al., 2010). Fatty acid esterification of 20 (*S*) -protopanaxadiol 20-*O*-β-D-glucopyranoside potentiates the antitumor activity through immunostimulation (Hasegawa & Saiki, 2000). More details about the role of ginseng in immune mediation, both at cellular and humoral level are given in Table 2.

Hot water extract of ginseng have been reported for mitogenic activity on lymphocytes *in vitro*, besides significantly increasing the population of lymphocytes in mice administered wild ginseng hot water fraction (Mizuno et al., 1994). Ginseng treated leukocytes from bovine blood and milk, has enhanced oxidative and phagocytic activities compared to untreated cells (Hu, Concha, Cooray, & Holmberg, 1995). Administration of Shenzau Cha i.e., a mixture of ginseng and Chinese Jujube, in ICR mice improved both the humoral and cell mediated immunity (Yu, Xu, Lu, Zheng, & Chen, 2016). Pidotimod, a synthetic immune regulator in combination with ginseng acidic polysaccharide synergistically enhanced the humoral immune response in immunosuppressed mice (Du, Jiang, Wu, Won, & Choung, 2008a; 2008b). The role of ginseng extracts and their isolated compounds in TNFα mediated inflammation was reviewed by Lee and Lau and reader can consult for the details results (Lee & Lau, 2011).

3. Cancer

Ginseng in various forms has been studied to elaborate the immunizing role against cancer as shown in Fig. 3. The studies were performed using ginseng root as powder, extract, decoction, fractions and isolated compounds. A meta-analysis report of ginseng use, in about 214 cancer studies, comprising of 7436 cases and 334,544 participants, confirmed an inversely proportional relationship between ginseng consumption and a significantly decreased overall risk of almost all types of body cancers (7,32). It is well-known now that anticancer effects of ginseng or its derivatives are due to the activation of the immune regulatory pathways in human body (Byeon et al., 2012). It is well-established through *in vitro* and *in vivo* studies that anti-carcinogenic effects of ginseng are due to the increase in natural killer cells both numbers and action (Kim, Germolec, & Luster, 1990).

3.1. Polysaccharides fraction of ginseng and cancer immunity

Polysaccharides usually present up to 15% in ginseng root, 75% of them are neutral while the remaining 25% are acidic. They exert antitumor effect through modulation of innate immunity. The antitumor action of these polysaccharides has been attributed to the regulation of the immune response, specifically both neutral and acidic polysaccharides are potent stimulator of B and T cells in proliferation assays

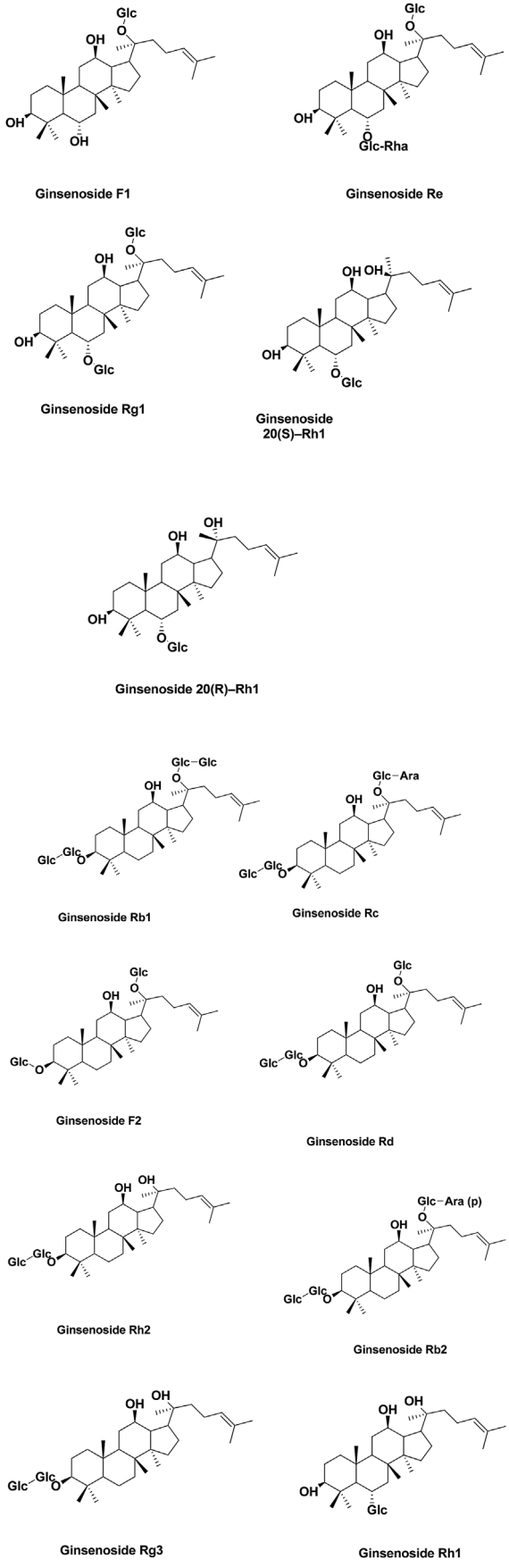


Fig. 4. Potential novel immune modulator drug candidate isolated from ginseng, these compounds have been reported for immune modulating action in various *in vitro* and *in vivo* studies.

(Kim, Kang, & Kim, 1990). Water soluble acidic polysaccharides (10,000 to 150,000Da molecular weight) are considered to be more active than neutral polysaccharides (Du, Jiang, Wu, Won, & Choung, 2008b, 2008a; Shim, Han, Ahn, Yun, & Song, 2007; Shin, Kim, Kwak, Song, & Park, 2004). Pectin has been reported to inhibit the cancer progression associated protein bound to galectin-3, α β-galactoside (Gao et al., 2013). A polysaccharide GFP1, isolated from ginseng fruit showed antitumor immune response against Lewis lung carcinoma mouse model via regulation of innate immunity and interlukins (Wang, Huang, Sun, & Pan, 2015). D-glucose based oligosaccharides isolated from *P. ginseng* C.A produced antitumor action via immunity-boosting effect (Jiao et al., 2014). Immunostimulating polysaccharides isolated from gel filtered sub fraction named PBGA12 of ginseng were found more active fraction in immune modulation than others (Gao, Wang, Lien, & Trousdale, 1996).

Ginseng root polysaccharides were investigated for the immune action in murine macrophages, it was observed that nitric oxide synthesis was stimulated dose dependently that ultimately led to improved nuclear factor κB DNA binding activity (Friedl, Moeslinger, Kopp, & Spieckermann, 2001). Ginseng polysaccharides increased the production of interlukin 1β, 6, 12, tumor necrosis factor α and NO and besides being useful immune modulator, it has direct anti-tumor activity in peritoneal mice macrophages (Rhee, 2016; Wang et al., 2010).

A polysaccharide named **Ginsan,** has been reported for enhancing macrophage tumoricidal action and modulating immune response (Song et al., 2002). Several researchers reported ginsan for immune mediated anticancer effect (Choi et al., 2008; Kim et al., 1998; Lee et al., 1996; Shin et al., 2002). Neutral polysaccharide fraction was found to have antitumor immune function in sarcoma S-180 tumor model (Ni et al., 2010). Ginseng polysaccharide fraction from leaves that consist of 15 different monosaccharide of 10.2 kDa showed *in vitro* and *in vivo* anti-metastatic activity (Shin, Hwang, Yoon, Kim, & Shin, 2017). Ginseng polysaccharide improves radio-sensitivity of osteosarcoma cells via increasing apoptosis and autophagy (Zhang, Sun, Zhu, Song, & Liu, 2017).

3.2. Ginseng extracts/preparations and cancer immunity

Panax ginseng derived products are well-known for immunity dependent antitumor effects in various animal tumors (Bespalov et al., 2001). Ginsenoside Rg3 enriched ginseng preparations exhibited immunity mediated antitumor effects *in vitro* and *in vivo* (Park et al., 2011). A recent study (Hwang et al., 2015) showed the importance of the enzymatically modified ginseng extract that has stronger anti-growth and proapoptotic effect in human gastric cancer cell lines (KATO3) than simple butanolic extract. The effect seems to be linked with the up-regulation of Bax and IκBα proteolysis-mediated activation of NF-κB, and the inhibition of mTOR and PKB signals (Hwang et al., 2015). MMP-2 and MMP-9 are useful pathways for the prevention of cancer. Anti-cancer effects of ginseng extracts may be due to immunity-boosting action against colon cancer cells following MMP-2 and 9 pathways (Seo & Kim, 2011). Red ginseng based fermented preparation of the Korean company Woong-Jin Foods R&D Center (Seoul, Korea) was evaluated for immune modulatory action both *in vitro* (macrophage) and *in vivo* (mice model). Amplification of immunity related functionalities like NO, IL-6 and TNF-α was observed confirming the immunity-enhancing properties of extract (Park et al., 2014). A proprietary extract of ginseng, CVT-E002, from Canadian company Afexa Life Sciences, Inc., significantly enhanced the absolute levels of natural killer cells and increased the survival of a leukemic adult mice significantly (Miller, Delorme, & Shan, 2011).

Ginseng and its products have been investigated using *in vivo* studies to evaluate its efficacy and bioavailability. Rats, ferret, BALB/c mice, c57bl/6 mice, athymic mice and several others *in vivo* cancer models were used in these studies. The use of ginseng or its products have also been reported for decreasing the development of multiple resistance

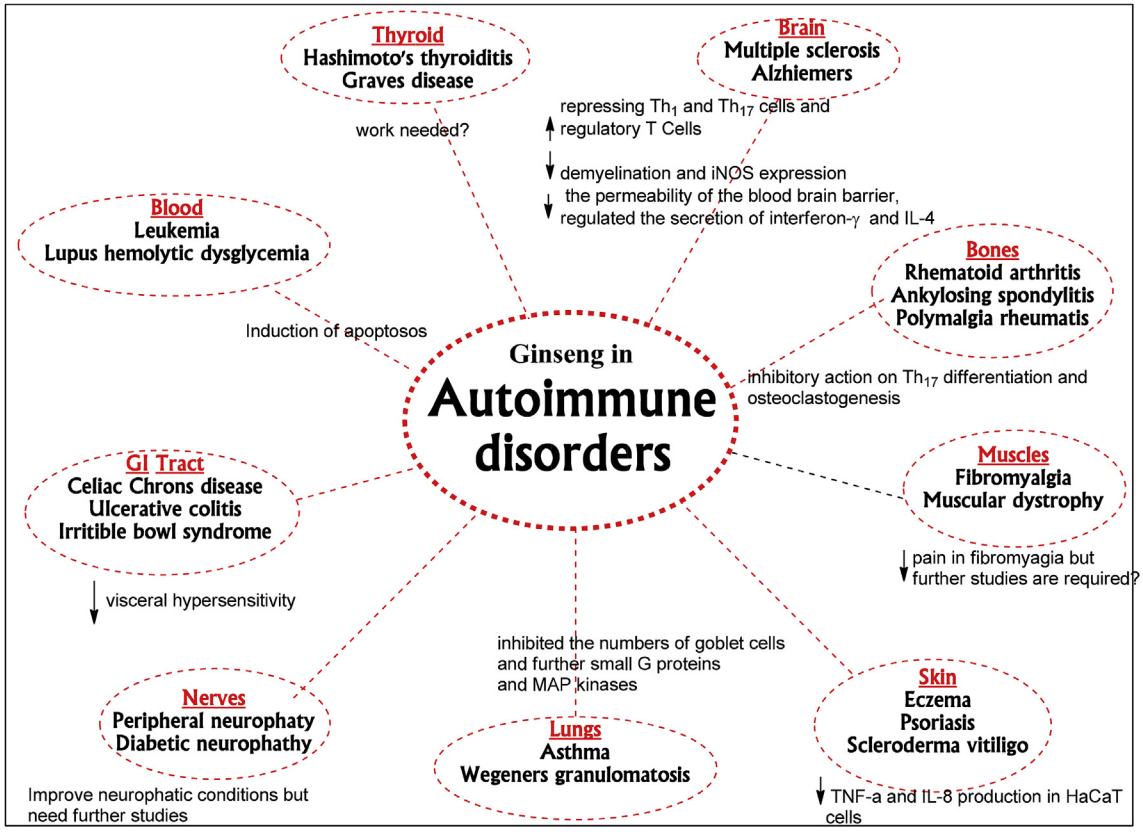


Fig. 5. Ginseng and autoimmune disorders. Ginseng or its preparations have been reported to have immune modulation in eczema, psoriasis via decreasing TNf α and IL-8 production in HaCaT cells, in asthma the number of goblet cells are inhibited that further inhibit small G proteins and MAP kinases, in leukemia the apoptosis is induced, In multiple sclerosis and alziemers, Th1 and Th17 cells are suppressed, regulatory T cells are activated, in rheumatoid arthritis it has inhibitory action on Th17 differentiation and osteoclastogenesis, however the work need to be expansively investigated in autoimmune diseases mentioned already and ulcerative colitis, irritable bowel syndrome diabetic neuropathy, peripheral neuropathy and wegeners granulomatosis etc **Abbreviations:** (IL, interlukin; INF, interferon; TNF, tumor necrosis factor).

against anticancer drugs, promoting synergistic immunostimulating effects and reduction of the toxicities associated with treatment (Du et al., 2008b; Yun, 2001). The *in vivo* studies showed reduced toxicities like drug-induced immunosuppression, renal & diaphragm muscle toxicity, drug-induced weight loss, decrease in cancer chemotherapy related fatigue, nausea and vomiting, and increased immune response by increasing both cell immunity and humoral immunity leading to increased survival time (Park et al., 2015; Takeda & Okumura, 2015; Yun, 2001). Microwave-irradiated processed ginseng has a higher content of ginsenosides Rg3, Rg5, and Rk1, and thus has significant suppressive action on the growth of human prostate cancer cells both *in vitro* and *in vivo* by inducing apoptotic cell death and autophagy (Park, Choi, Kim, Kang, & Ham, 2016). Long-term administration of ginseng decreases the incidence of cancer (Wang & Yuan, 2008). The humoral immunity of BALB/c mice against ovalbumin increased eight-fold when mice were fed ginseng extract (Liou, Huang, & Tseng, 2005). *In vitro* and *in vivo* (in mice models of primary liver tumors) investigations pointed out the immune modulating effects of ginseng (Durairaj & Miller, 2012). Boiled extract of ginseng exhibited anti-tumor effects against H22 tumor by immune-potentiating effect (Lin & Bao, 2013). Ginseng stimulated the suppressive function of myeloid-derived suppressor cells that lead to immune activating events such as T-cell proliferation and the secretion of IFNγ and IL-2 (Jeon et al., 2011).

3.3. Ginsenosides as immune modulator

More than 100 ginsenosides have been isolated from ginseng and evaluated for their biological effects. Cancer cells release antigens when they die, either by necrotic or apoptotic mode. There are several mediators that stimulate necrotic mode while others that inhibit the apoptotic mode of death. The anticancer properties of ginseng are due to compound K, ginsenoside Rh1, F2, Rg3, and Rp1 that induce apoptosis of cancer cells (Choi & Choi, 2009). **20-S-protopanaxatriol**, an intestinal metabolite of steroidal ginseng saponins, may be a useful vaccine adjuvant as it helps in maturing dentritic cells *in vitro* by naïve T cells to Th1 response (Takei, Tachikawa, Hasegawa, & Lee, 2004). **Ginsenoside Rh2** has been reported in a number of studies for anticancer potentials. It induces apoptosis through caspase-like proteases activation by the use of Bcl-2-insensitive signaling pathway (Kim, Oh, Lee, & Oh, 1999; Park, Lee, Oh, Kim, & Lee, 1997). **20(R) - and 20(S)-ginsenoside-Rg3** isolated from ginseng at a dose of 10 μg/mouse (intravenously) and 100–1000 μg/mouse (orally) inhibited lung metastasis by anti-angiogenesis and tumor cells invasion/adhesion inhibition mechanism (Mochizuki et al., 1995). **Ginsenoside Rh1 and Rh2** isolated from the root of ginseng showed anti-proliferative action in the NIH 3T3 mouse fibroblast cell lines through the inhibition of phospholipase C (Byun, Shin, Yoon, Kim, & Joe, 1997). In natural antitumor agents heat processed ginseng is found to possess potent antitumor properties.Surh et al., 2001 found that **ginsenoside Rg3** isolated from heat processed ginseng markedly suppressed 12-*O*-tetradecanoylphorbol-13-acetateinduced ornithine decarboxylase, tumor promotion and cyclooxygenase-2 expression in mouse skin (Surh et al., 2001). Ginsenoside **Rg1** activated the human lymphocytes proliferation and increase the fluidity of its membrane (Liu, Wang, Liu, Yang, & Nan, 1995). Administration of ginsenoside Rg1developed immunity in mice against circulated candidiasis through the induction of Th1 type differentiation of CD4(+) T cells (Lee & Han, 2006). Structures of the ginsenosides are given in Fig. 4 that may be future immunetherapeutic

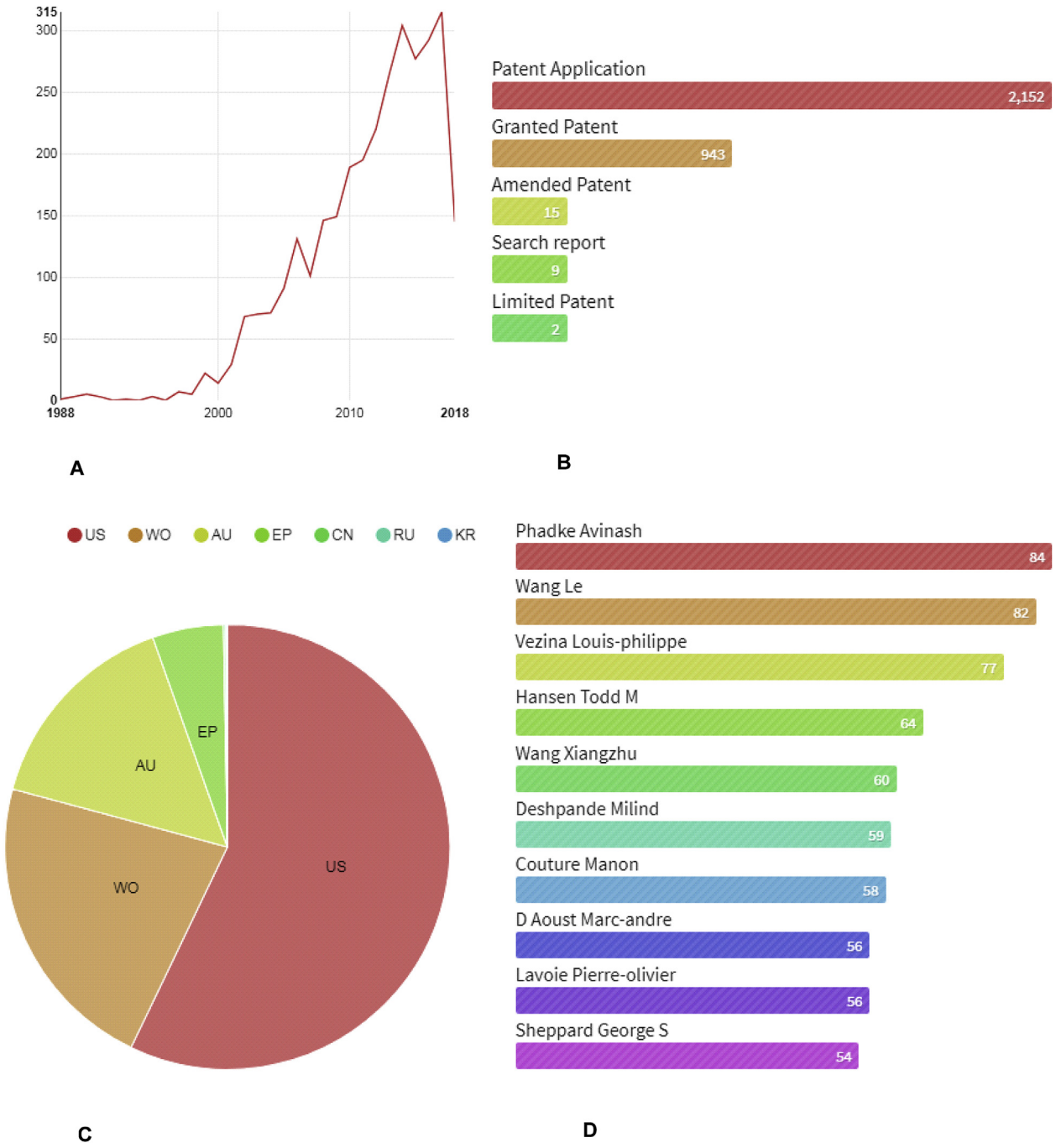


Fig. 6. Analysis 3121 patent that were browsed using search term Ginseng, immune modulator until 2018, A: shows patent applications per year **B**: document type **C**: Jurisdictions, US United States; AU Australia; WIPO World Intellectual property organization; EP European patent; CN China **D**: Represent inventors of the patents (https://www.lens.org/lens/search?preview=true&q=ginseng,%20immunity%20modulator).

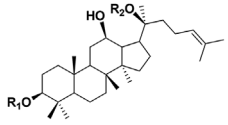
drug candidates.

3.4. Chemo or radiotherapy induced side effects reduction

The use of ginseng during chemotherapy and radiotherapy enhances immune functions, prevents the recurrence of cancer, decreases the side effects and promotes overall survival of patients (Suh, Kroh, Kim, Joh, & Cho, 2002). Li et al., emphasized that use of ginseng during chemotherapy reduces the side effects via immune modulation as ginseng based injection reduced side effect in GI cancer patient during chemotherapy (Li, 1992).

4. Immunotherapeutic agent against virus, bacteria and other parasites

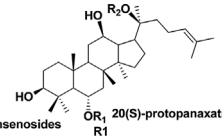
Im et al., in his review on the effect of ginseng on human pathogenic viruses concluded that ginseng can exert direct antiviral effects but the foremost antiviral actions of ginseng are due to the enhancement of host immunity (Im, Kim, & Min, 2016). The ginseng extract is a good immune modulator for both natural and acquired immunity associated with the virus (Wang et al., 2004). The study carried out by Park *et el.*, using mice and ferrets models supports the use of ginseng as a dietary component to enhance immunity in the form of interferon alpha and gamma against H5N1 influenza virus. It suggests the use of ginseng in



20(S)-protapanaxadiol

Protopanaxadiol ginsenosides	R1	R2
20S-ginsengoside Ra1	-glc(2-1)glc	-glc(6-1) ara(p) (4-1) xyl
20S-ginsengoside Ra2	-glc(2-1)glc	-glc(6-1) ara(f) (2-1) xyl
20S-ginsengoside Ra3	-glc(2-1)glc	-glc(6-1) glc(f) (3-1) xyl
20S-ginsengoside Ra4	-glc(2-1)glc(6)Bu	-glc(6-1) ara(p) (4-1) xyl
20S-ginsengoside Ra5	-glc(2-1)glc(6)Ac	-glc(6-1) ara(p) (4-1) xyl
20S-ginsengoside Ra6	-glc(2-1)glc(6)Bu	-glc(6-1) glc
20S-ginsengoside Ra7	-glc(2-1)glc(6)Bu	-glc(6-1) ara(p)
20S-ginsengoside Ra8	-glc(2-1)glc(4)Bu	-glc(6-1) ara(f)
20S-ginsengoside Ra9	-glc(2-1)glc(6)Bu	-glc(6-1) ara(f)
20S-ginsengoside Rb1	-glc(2-1)glc	-glc(6-1) glc)
20S-ginsengoside Rb2	-glc(2-1)glc	-glc(6-1) ara(p)
20S-ginsengoside Rb3	-glc(2-1)glc	-glc(6-1) xyl
20S-ginsengoside Rc	-glc(2-1)glc	-glc(6-1) ara (f)
20S-ginsengoside Rd	-glc(2-1)glc	-glc
20S-ginsengoside Rg3	-glc(2-1)glc	-H
20S-ginsengoside Rh2	-glc	-H
20S-ginsengoside Rs1	-glc(2-1)glc(6) Ac	-glc(6-1) ara(p)
20S-ginsengoside Rs2	-glc(2-1)glc(6) Ac	-glc(6-1) ara (f)
20S-ginsengoside Rs3	-glc(2-1)glc(6) Ac	-glc(6-1) ara (f)
malonyl-20S-ginsengosideRa3	-glc(2-1)glc(6) mal	-glc(6-1) glc(f) (3-1) xyl
malonyl-20S-ginsengosideRb1	-glc(2-1)glc(6) mal	-glc(6-1) glc
malonyl-20S-ginsengosideRb2	-glc(2-1)glc(6) mal	-glc(6-1) ara(p)
malonyl-20S-ginsengosideRc	-glc(2-1)glc(6) mal	-glc(6-1) ara (f)

Name	R1	R2
malonyl-20S-ginsengosideRd	-glc(2-1)glc(6) mal	-glc
malonyl-20S-notoginsengosideR4	-glc(2-1)glc(6) mal	-glc(6-1) glc (6-1) xyl
20S-gypenosideXVII	-glc	-glc(6-1) glc
20S-notoginsenoside-Fe	-glc	-glc(6-1) ara(f)
20S-notoginsenoside R4	-glc(2-1)glc	-glc(6-1) glc (6-1) xyl
20S-pseudo-ginsenoside RC1	-glc(2-1)glc(6) Ac	-glc
20S-quinquenoside R1	-glc(2-1)glc(6) Ac	-glc(6-1) glc
20S-vinaginsenoside R16	-glc(2-1)xyl	-glc



20(S)-protopanaxatriol

Protopanaxatriol ginsenosides	R1	R2
20S-ginsenoside Re	-glc(2-1)rha	-glc
20S-ginsenoside Re1	-glc	-glc(3-1) glc
20S-ginsenoside Re2	-glc(3-1)glc	-glc
20S-ginsenoside Re3	-glc	-glc(4-1) glc
20S-ginsenoside Re4	-glc	-glc(6-1) ara (f)
20S-ginsenoside Re6	-glc	-glc(6) Bu
20S-ginsenoside Rf	-glc(2-1)glc	-H
20S-ginsenoside Rg1	-glc	- glc
20S-ginsenoside Rg2	-glc(2-1) rha	-H
20-gluco-20S-ginsenoside Rf	-glc(2-1)glc	- glc
20S-ginsenoside Rh1	-glc	- H
20S-koryoginsenoside R1	-glc(6-1) Bu	-glc
20S-notoginsenoside N	-glc(6-1) glc	-glc
20S-notoginsenoside R1	-glc(2-1) xyl	- glc
20S-notoginsenoside R2	-glc(2-1) xyl	-H
20S-yesanchinoside D	-glc(6) Ac	-glc

Fig. 7. An overview of various compounds isolated from ginseng.

diet especially in influenza pandemic in humans. As the influenza virus develops resistance with time, against antiviral drugs, so ginseng may be used as an alternative to immunize the population under attack (Park et al., 2014). Oral administered of ginseng extract boosts immunity more than ginseng saponins against influenza virus (Xu, Kim,

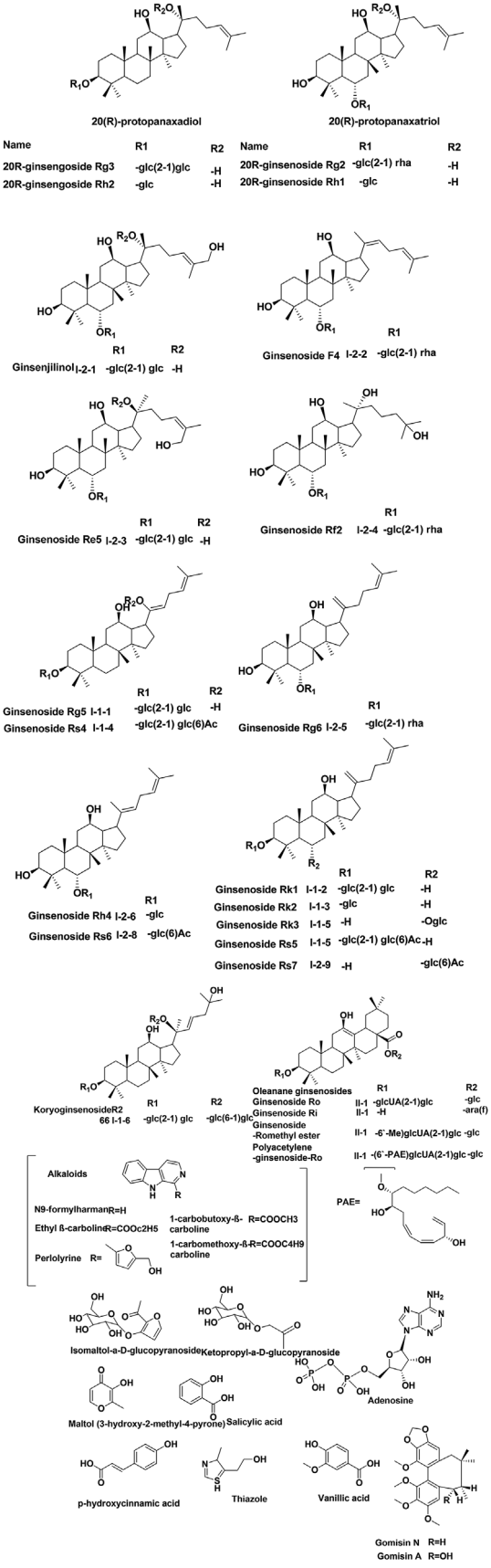
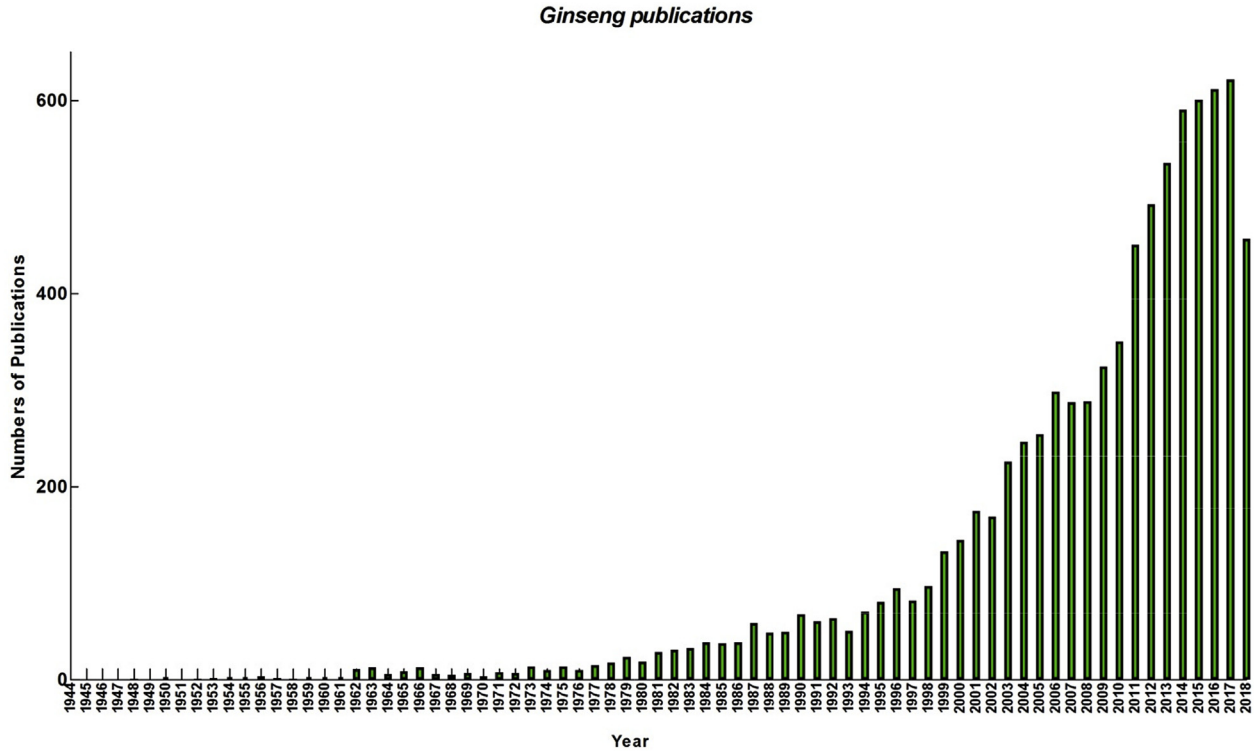


Fig. 7. (*continued*)



Graph 1. The trend in number of publications related to ginseng until August 2018, The pubmed/medline database search term (MEsH) "Ginseng" year 1944 to Aug 2018, a quick overview of the graph depicts that interest of researchers increase year wise.

Choi, & Kim, 2012). Oral administration of ginseng polysaccharides ameliorates symptoms of influenza virus infection (Yin, Kim, & Kim, 2013). Daily intra-nasal administration of ginseng polysaccharide to mice prior to be infected with influenza H1N1 and H3N2 viruses led to improvement against infections. Ginseng polysaccharide treated mice was observed for hetro subtypic protection i.e. immunized for one influenza strain but protected against other strains also (Yoo et al., 2012). Ginseng extracts were found useful immune-modulator against influenza viral infection and more pronounced effect were produced when extract was co-administered with attenuated influenza virus A (Shi et al., 2007). The use of ginseng extract in influenza virus infected human lung epithelial cells increased the life of these cells besides increasing the level of cytokines like interferon γ in influenza infected mice (Lee et al., 2014). Ginseng plus vitamin C synergistically improved the both types of immune cells like T and natural killer cells, oppressed the growth of viral lytic cycle and decreased the survival of influenza A virus infection (Kim et al., 2016). *In vitro* studies with ginseng extract on peripheral blood mononuclear cells obtained from healthy and AIDS or chronic fatigue syndrome individuals exhibited significantly increased NK activity and the antibody-dependent cell-mediated cytotoxicity (See, Broumand, Sahl, & Tilles, 1997). Ginseng extract improved immunity in respiratory syncytial virus mice model and also suppressed the growth of virus in human lung cells *in vitro* study (Lee et al., 2015). Ginsenoside Rg3 isomers were found to inhibit lytic replication and gamma herps viral proliferation via p38 and JNK associated pathways. S isomer is more active than R isomer (Kang, Song, & Min, 2018).

Ginseng extract (@ 25 mg/kg/day) for 14 days in rats with chronic *Pseudomonas aeruginosa* lung infection activated the phagocytes in blood (Song et al., 1999). Ginseng extract induced cellular immune response in chronic *P. aeruginosa* lung infected mice. The survival time of the infected mice was increased besides modulation of production of cytokines (Song et al., 2003). Similar results were obtained with chronic *P. aeruginosa* lung infected rat model and it was observed that the overall pathology of lung and bacterial clearance was improved. The results suggest the use of ginseng in cystic fibrosis patients (Song, Johansen, & Faber, 1998; Song et al., 1997; Song, Johansen, Faber, Hiby, & Hoiby, 1997). Subcutaneous administration of Gerimax, ginseng based product of a Danish Company (@ 150 mg/kg) showed the same therapeutic response as discussed in previous lines about chronic *P. aeruginosa* lung infection rats model (Song, Wu, Mathee, Høiby, & Kharazmi, 2002). It is also established in, *in vivo* and *in vitro* studies that the use of ginseng polysaccharides and ginsenosides increased the phagocytosis, activities of natural killer cells and TNF-α production (Lim et al., 2002; Song et al., 1999; Yang & Yang, 1993).

Ginsenosides and ginseng polysaccharides have also been reported for anti-malarial action. They inhibit the growth of *Plasmodium yoelii* in mice by boosting the immune system (Han et al., 2011).

5. Ginseng in autoimmune disorders

Ginseng has received attention as a promising preventive and therapeutic agent for autoimmune disorders as depicted in Fig. 5. Ginsenoside Rd of *P. ginseng* results differentiation of regulatory T cells by up-regulating Foxp3 expression and increased the generation of TGF-β1, IL-10 and IL-35 suggesting the use of ginseng as immune modulator in transplantation and autoimmune diseases (Kim, Byeon, Im, & Min, 2018).

The effect of ginseng extracts in cell-mediated immune functions in 60 healthy volunteers (divided in 3 groups) was investigated. Chemotaxis, phagocytosis index and phagocytosis fraction enhanced at 4th week in ginseng extract as well as in standardized ginseng extract treated group; the increase became more marked at the 8th week in subjects treated with standardized extracts (Scaglione et al., 1990). Ginseng extract (@3 μg and 10 μg/ml) decreased the immune-suppression in transplant patients receiving cyclosporine by mutual regulation of Th17 and T reg cells (Heo et al., 2016).

Rheumatoid arthritis is an autoimmune chronic disorder of knee joint that leads to its destruction and disability. Ginseng extract inhibited Th17 differentiation and osteoclastogenesis, thus ameliorating

Table 2
The effect of Ginseng or derivatives on cellular and humoral immunity.

Form of Ginseng used	Animal Model	Immune action and reference
ginseng root water extract	10, 50 and 250 mg per Kg body weight for 6 days in mice	modulation in humoral and cellular immunity the effect at dose dependent manner (Jie, Cammisuli, & Baggiolini, 1984)
Ginseng leaves saponins	Aged rats intraperotinally, 12.5–50 mg/kg	Enhance immunity both celluar and humoral (Kejian & Gengtao, 1999)
Fermented ginseng extract	PO, BALB/c mice, lung metastasis of colon 26 carcinoma cells, Macrophage assay, cytokine assay	enhancement of systemic as well as mucosal immune systems (Kang et al., 2010)
American ginseng root polysaccharides (AGRP)	Rats, culturing of alveolar macrophages from AGRP fed rats PO 125 mg/kg	Increase TNFα in blood, suppress LPS induce TNFα level, both suppression and stimulation of immune response, ex vivo and *in vivo* (Azike, Charpentier, & Lui, 2015).
American ginseng root polysaccharides extract, (active agent is acid polysaccharide ≥100 kDa and 50–100 kDa)	Orally, adult rats by measuring cultured alveolar macrophage production of NO and changes of plasma cytokine level, LPS induced elevation of plasma TNF-α *in vivo*	Stimulate basal innate immunity and suppress lipopolysaccharide induced proinflammatory response (Azike et al., 2015).
Fermented red ginseng extract	500 μg/mouse, lung metasis, macrophage stimulatory assay	Inhibitory effect on lung metastasis in mice activate macrophages and enhance TNFα production (Kim et al., 2011)
ginseng polysaccharide	50, 100, and 200 mg/kg, C57BL/6 mice bearing with Lewis lung carcinoma	splenocytes proliferation, and the ratio of CD4 + /CD8 + T lymphocyte in peripheral blood, IL-2 and IFN-γ production and NK cytolytic activity (Zhou, Shi, Jiang, Zhou, & Xu, 2014)
Ginseng extracts, ginsenoside Rg1 and 20(S)-Rg3	mouse B cells *in vitro*	slightly reduced B cell proliferation, but increased IgA production by LPS-stimulated B cells, ginsenoside Rg1 and 20(S)-Rg3 selectively induced IgA production and expression of GLTα transcripts by LPS-stimulated B cells (Park et al., 2015)
Ginsenoside Rg3	both immunogenic (B16F10 melanoma cells) and non-immunogenic (LLC: Lewis Lung Carcinoma cells)	Killed tumor cells by inducing apoptosis (Son, Lee, & Lee, 2016)
Wild *panax ginseng* extract	RAW264.7 macrophages proliferation assay	interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor-α and granulocyte-macrophage colonystimulating factor, and chemokines such as macrophage chemotactic protein-1 and regulated upon activation, normal T-cell expressed and secreted (RANTES), induce NO production (Jang & Shin, 2010)
Panax ginseng root or its polysaccharides	0.4 g/kg over a period of 84 days, white shrimp	increase immune enzyme activity and modify expression of immune genes (Liu et al., 2011)
CVT E002, a proprietary extract of North American ginseng, *Panax quinquefolius*	Mice	An Extract from North American Ginseng Stimulates Spontaneous Immunity in Infant Mice: Sustained, Augmented Immunity in Adulthood Long after Withdrawal of the Extract (Miller, Delorme, Miller, & Delorme, 2008)
lower-molecular weight oligosaccharide of ginseng	(100–500 μg/ml), RAW264.7 cells, B16F10 melanoma cells were co-cultured with the GOS-activated Macrophages	dose-dependently enhanced the production of TNF-α, IL-6, and NO, cell viability of melanoma cells was dose-dependently decreased through the induction of apoptotic cell death (Seo et al., 2015)
50% ethanol extract of ginseng root	Male BALB/c mice with 2 g/kg, orally for 30 days	potentiate humoral immune suppress spleen cell functions (Liou et al., 2005)
Ginseng total saponins	lipopolysaccharide (LPS)-stimulated mouse RAW 264.7 macrophages	Anti-inflammatory effect via LPS-induced nitric oxide (NO) production and LPS-induced tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (Jang et al., 2016)
Korean red ginseng extract	Type 1 Diabetic mice	Immunomodulatory effect via T and NK cells recovery in the secondary lymphoid organs and hypoglycemic effect (Joo et al., 2012)
Ginsenosides-Rb1	rats at dose (25, 50 and 100 mg/kg) during strenuous physical exercise	Immune function changes via GRb1 also increased the levels of serum IgA, IgG and IgM, and decreased the levels of serum IL-1β, IL-6 and TNF-α (Qi & Huang, 2015)
North American Ginseng proprietary extract (CVT-E002)	As Dietary Supplement for Adult and Juvenile Mice (injection)	Augment NK cell-mediated immunity long after withdrawing (Miller, Ti, & Shan, 2012)
Ginseng oligopeptide	Mice model 0.3–0.6 g/kg	Improved cell and humoral immunity (He et al., 2017)
Heat Processed Ginseng containing Rg3, Rg5, and Rk1	RAW264.7 cells	increased macrophage activation via ERK/c-Jun pathway (Shin et al., 2018)
Enzyme-assisted extracted functional polysaccharide	cyclophosphamide-induced immunosuppressed mice 100–200 mg/kg	Potential immune-stimulatory agent (Song et al., 2018)
oleanolic acid β-D-glucopyranosyl ester	Cell proliferation assay, 2.5, 5, 10 μM	activates T cell function via the regulation of NF-AT-mediated IL-2 production (Vinh et al., 2018)
Korean red ginseng extract	cyclophosphamide-induced immunosuppressed mice, 500 mg/kg	Activate both cell immunity and humoral immunity(Saba, Lee, Kim, Kim, & Rhee, 2018)
Ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, and Rh2	Mouse lung inflammation model 20 mg/kg each	Reduction of total cell numbers in bronchoalveolar lavage fluid, Ginsenoside Rc, Re, Rg1, and Rh2 exhibited significant inhibitory action (Lee et al., 2018)

collagen induced arthritis in mice (Jhun et al., 2014).

Pre- and onset treatment with red ginseng extract decreases experimental autoimmune encephalomyelitis in rats and mouse models by repressing Th1 and Th17 cells and increasing regulatory T Cells. It suggests its use as preventive and therapeutic remedy in autoimmune disorders like multiple sclerosis (Lee et al., 2016). Aqueous extract of ginseng (@ 150 mg/kg) decreased demyelination and iNOS expression in the spinal cord, decreased TNF − α levels in the blood, and reduced clinical signs of disease in experimental autoimmune encephalomyelitis mice model (Bowie, Roscoe, Lui, Smith, & Karlik, 2012). Ginsenoside Rd (@40 mg/kg/day) intraperitoneally in mice model of multiple sclerosis, decreased the permeability of the blood brain barrier,

regulated the secretion of interferon-γ and IL-4, and decreased the severity of autoimmune encephalomyelitis (Ong, Farooqui, Koh, Farooqui, & Ling, 2015). Ginsenoside Rg2 protects against cognitive impairment in vascular dementic rat model, via anti-apoptosis mechanism (Zhang et al., 2008). Prolonged oral administration of the ginseng extract in Parkinson's disease (Rat and mouse model) decreased the progression of disease by minimizing the dopaminergic cell loss (Van Kampen, Robertson, Hagg, & Drobitch, 2003). The neuroprotective effects of ginseng were further confirmed during a study of the same research group in more accurate Parkinson's disease animal model (Van Kampen, Baranowski, Shaw, & Kay, 2014). Parkinson's disease and other neurodegenerative disorders share common features of cell pathogenesis thus neuroprotective benefits of the ginseng may be extended to other disorders such as amyotrophic lateral sclerosis, Huntington disease, and Alzheimer's disease (Van Kampen et al., 2014). Ginsenoside protopanaxatriol significantly lowered the experimentally-induced visceral hypersensitivity, suggesting its use as alternative treatment remedy for irritable bowel syndrome (Kim et al., 2005).

Systemic lupus erythematosus is a human autoimmune disease with diverse clinical manifestations including organ damage. Ginsinoside Rb1, Rh1, Rg1 and Rg3 inhibit the humoral immunity of Systemic lupus erythematosus, among which Rh1 exhibited the most obvious inhibitory effect (Yu et al., 2018).

6. Ginseng and allergies

Various scientists have studied the role of ginseng in combating the untoward response of immune system. The role of ginseng in regulating both humoral and cellular immunity (discussed above) is closely related to the allergic immune response. Saponins from ginseng in a chronic inflammation rat model inhibited the IL-1β and IL-6 gene expression (Yu & Li, 2000). Aqueous ginseng extract decreased the production of TNFα, IL-1β, and IL-6 and expression of chemokines through the mitogen-activated protein kinases nuclear factor kappa B pathway in allergic inflammatory atopic dermatitis and anaphylactic shock mice models (Kee et al., 2016). An intestinal ginseng metabolite, 20(S)-Protopanaxatriol, showed anti-allergic effects in guinea pig lungs and mouse bone marrow derived mast cells by suppressing various allergic mediators (Kim, Ro, & Lee, 2015). Ginseng saponins and isolated ginsenosides, Rg3, Rf, and Rh2 produced anti-allergic action in atopic and contact dermatitis mouse models by regulating cytokines production during the allergic response (Bae, Han, Shin, & Kim, 2006). A polysaccharide of ginseng, Cvt-e002, can be a useful immune-therapeutic agent for asthma as it showed anti-allergic action in hypersensitive mouse model of lungs and airways (Adamko, Ebeling, & Wu, 2009).

Ginsenoside Rg1 exhibited anti-inflammatory potential via its intestinal metabolite, 20(S)-protopanaxtriol, which inhibited the lipopolysaccharide binding to toll like receptors 4 and thus blocked the inflammatory signals produced during trinitrobenzene-sulfonic acid-induced colitis in mice. The nuclear factor kappa B was also inactivated. Ginsenoside Rb1 and its metabolite compound K produced similar effect in trinitrobenzene-sulfonic acid induced-colitis model (Joh, Lee, Jung, & Kim, 2011; Lee, Jeong, Eun, & Kim, 2015). Ginsenoside Rb1 and its metabolite compound K showed anti-inflammatory effect by inhibiting the activation of interleukin-1 receptor-associated kinase-1without interacting toll like receptor 4 (Joh et al., 2011). Ginseng extract acts as a potential modulator of the inflammasome complex as it inhibited the IL-1β maturation (Kim et al., 2014). Panaxynol, a polyacetylenes, from ginseng suppressed the production of Nrf2 mediated cytokines that are responsible for hypertrophy of cardiomyocytes (Qu et al., 2015). Ginsan, a ginseng polysaccharide, increased the survival of infected mice by down-regulating the cytokines via toll like receptors (Ahn et al., 2006). Ginseng extract increased the survival of macrophages in *S. pneumonia* infected mice via modulation of the PI3K/AKT signaling pathway. It indicates that ginseng may be a useful alternative to handle bacterial sepsis and the resulting inflammation (Nguyen et al., 2015). Ginsenoside Rh1 showed anti-allergic effect by inhibiting histamine release in rat peritoneal mast cells and IgE-induced passive cutaneous anaphylaxis in mice. Cyclooxygenase-2 expression and nuclear factor-κB activation was also inhibited (Park, Choo, Han, & Kim, 2004). Interestingly Korean red ginseng is anti-genically safe as there was no systemic anaphylactic shock or local cutaneous anaphylaxis in guinea pigs even at 12 times higher dose than human (Hyun, Kyung, Song, So, & Kim, 2018).

7. Ginseng as radioprotectant via immunomodulation

Ginsan, an acidic polysaccharide, may be a potential radioprotective agent against gamma radiation. Ginsan was reported to increase the level of cytokines and improve Th1 immune response and other immune mediators in gamma irradiated mice (Han, Song, Yun, & Yi, 2005; Kim et al., 2007). Song et al., also reported ginsan for hematopoietic recovery (Song et al., 2003). Kim et al. found that ginseng water extract (@ 500 μg/ml) had radioprotective effects against γ-ray-induced DNA double strand breaks in cultured murine spleen lymphocytes (Kim et al., 1996). A traditional Chinese formulation Si-Jun-Zi-Tang, containing ginseng as the main ingredient, was found to enhance the leukocytes and thrombocytes in x-ray irradiated mice (Hsu, Yang, Lian, Ho, & Lin, 1996).

8. Role in hepatic disorders

Various hepatic models have been used to assess the role of ginseng in liver disorders. Researchers associated the pathology of liver disorders with toll like receptor-4 and immune cascades (Bang et al., 2014). The study carried out by Bang and his group using alcoholic liver disease mouse model, showed that ginseng down-regulated the over expression of toll like receptor-4 (Bang et al., 2014). The Ginsenoside Re, may be responsible for the reduction of alcohol induced hepatic injury through toll like receptor down regulatory mechanism (Lee, Hyam, Jang, Han, & Kim, 2012). Ginsan, exhibited hepatoprotective action via multiple mechanisms, like strong antioxidant effects of ginsan and reducing the level of total hepatic cytochrome P-450 (Song et al., 2004).

9. Immunoadjuvant or vaccine adjuvant

Immunoadjuvant modulate host immune response via both cellular and humoral ways. Currently only aluminum compounds are approved as adjuvants for clinical use, however these have side effects like allergy (Gupta & Siber, 1995) so effective and safe natural adjuvants need to be explored. Ginseng as a useful vaccine adjuvant was confirmed by investigations in pigeons that were vaccinated against *Salmonella typhi*. The strain plus ginseng produced double cellular and humoral immune response as compared to the commercial vaccine (Majer-Dziedzic et al., 2015). Recent studies on vaccine for bovine viral cattle diarrhea showed that glycoprotein Erns of the said diarrhea can be effectively expressed in transgenic ginseng hairy roots. Thus ginseng may be used as an antigen source for a possible vaccine against this viral infection (Y. Gao et al., 2015). Ginseng saponins (stems and leave) exhibited synergistic immune response when used in combination with vaccine against foot and mouth disease of pigs. The sole administration of vaccine manifested low or decreased immunogenicity (Li et al., 2012). Ginseng saponins with rapeseed oil may be a good veterinary vaccine adjuvant in foot and mouth disease, as they synergistically enhance the host immunity via Th1 and Th2 immune response (Zhang et al., 2014). The synergistic immune adjuvant effect was also reported for saponins from ginseng leaves and stems in combination with mineral oil against foot and mouth viral disease (Song, Bao, Wu, & Hu, 2009). In another study using BULB/c mice, the Rb1 containing a fraction of ginseng as an adjuvant in porcine parvovirus vaccines stimulated antigen specific immunity via balanced Thi and Th2 immune response (Rivera,

Pettersson, Inganäs, Paulie, & Grönvik, 2005).

Ginseng enhanced virus specific immunity synergistically as IgA antibody in lungs against influenza virus mouse model when co-administered through nasal route with inactivated influenza virus A (PR8) (Shi et al., 2007). Ginseng saponins Rg1, Re, Rg2, Rg3, and Rb1 showed potent adjuvant effects when co-administered in oval albumin antibody response assay in BALB/c mice (Sun, Hu, & Song, 2007). Ginsomes, Rb2, Rc, Rb1, and Rd ginsenoside-based spherical nano-particles acted as a novel adjuvant and up-regulated specific antibodies when co-administered with concanavalin A, LPS, and OVA in imprinting control region mice. They increased Th1 and Th2 immune response and T and B lymphocyte proliferation was also observed (Song, Zang, & Hu, 2009). Ginseng leaves polysaccharides have been reported for immunoadjuvant role in mice model (Hwang, Shin, Yoon, & Shin, 2018).

Saponins from ginseng leaf and stems produced enhanced adjuvant immune response when used with live bursa disease vaccine in chickens. A pronounced immune response was reported for immune suppressed chickens during another study of the same research group (Yu, Shi, & Hu, 2015; Zhai, Wang, Yu, & Hu, 2014). Orally administered saponins obtained from stem and leaves of ginseng were reported for adjuvant role in vaccine against Newcastle disease and avian influenza in chickens (Zhai, Li, Wang, & Hu, 2011). Gensinoside Rd may be a useful adjuvant to improve the immunity via Th1 and Th2 pathway (Yang, Chen, Sun, Ye, & Fang, 2007).

Ginseng berry extract was found more potent than ginseng root extract for up-regulating the molecules responsible for immune response. It activated the dendritic cells in tumor bearing mice so ginseng berry or its derivatives may be a new anticancer vaccine adjuvant (Zhang et al., 2015). Ginseng extract and Ginsenoside Rb1 is a safe and effective vaccine adjuvant against *Staphylococcus aureus* caused mastitis in cattle (Hu, Concha, Lin, & Waller, 2003). During another study in pigs ginseng extract was found to be a safe and cheap alternative adjuvant in conventional vaccine against porcine parvovirus and *Erysipelothrix rhusiopathiae* infections (Rivera, Daggfeldt, & Hu, 2003). Ginseng and aluminium hydroxide synergistically enhanced the immunity of host organism when given with vaccine of pocine parvovirus (Rivera, Hu, & Concha, 2003).

10. Immunity modulation in stress

Ginseng has been reported to immunize the body to cope with various types of internal and external stress, for example, work-space oriented fatigue, or environmental stress like cold weather (Kaneko & Nakanishi, 2004). The physiological stress of the human body is properly managed by the use of ginseng e.g., a study in postmenopausal women showed that ginseng helped to alleviate climacteric syndromes, mainly weakness, sleeplessness, and despair (Tode et al., 1999). Ginseng root saponins and gensenoside Rb1 enhanced anti-stress immunity in stressed mice and rats (Yun-Man, Xiu-Juan, & Wen-Xue, 1993). Clinical trials in healthy individuals confirmed the use of ginseng in decreasing stress and maintaining and modulating homeostasis via the autonomic endocrine route (Kaneko & Nakanishi, 2004). The dietary supplementation of ginseng in animals during pregnancy not only improved mother immunity related bio-molecular level in serum and milk, but are also beneficial for the growth and health of their piglets (Xi et al., 2017).

11. Anti-osteoporosis effect of ginseng

Osteoporosis is a skeletal disorder characterized by bone tissue deterioration and loss of bone mass. Ginsenosides have been reported for anti-osteoporotic effect in ovarictomized rats (Cui, Wu, Li, Lin, & Liang, 2001). Ginsenoside Rb1 showed anti-osteoporotic action via suppressing RANKL-induced activation of both JNK and p38 MAPKs and NF-κB pathways (Cheng et al., 2012). 20(R)-Rh2 showed selective osteoclastgenesis inhibitory activity without any cytotoxicity using RAW264 cells *in vitro* (Liu et al., 2009). Ginsenoside Rh2(S) induces differentiation and mineralization of MC3T3-E1 cells through activation of PKD/AMPK signaling pathways (Kim et al., 2011). Ginsenoside Rd stimulates the differentiation and mineralization of osteoblastic MC3T3-E1 cells by activating AMP-activated protein kinase via the BMP-2 signaling pathway (Park, Quan, Kim, Jung, & Chung, 2012). Ginsenoside Rh2(S) induces the differentiation and mineralization of osteoblastic MC3T3-E1 cells through activation of PKD and p38 MAPK pathways (Kim et al., 2011). Korean red ginseng causes delay in osteoporosis (Kim, Lee, Kang, Chun, & Hwang, 2015). In another study in overectomized rats, the Korean red ginseng mixture produced anti-osteoporotic effect (Kim et al., 2008). Ginseng aqueous extract showed anti-osteoporotic activity *in vitro* and *in vivo* (Lee et al., 2015). Korean red ginseng can prevent radiation-induced bone loss in mice (Lee et al., 2013). Fermented red ginseng extract enriched with Ginsenoside Rg3 improved effects on bone formation and differentiation of pre-osteoblastic MC3T3-E1 cells (Siddiqi et al., 2015). Ginseng extract exhibited prevention and treatment of age-induced osteoporosis in old Wistar rats (Kim et al., 2018).

12. Nano-ginseng and immunity

Nanotechnology is an emerging field of science that mainly focuses on production of nano-dimensioned substances of intended modified physiochemical properties. In case of dietary supplements and functional foods, drug bioavailability has been tremendously improved via using nanotechnology. The improved safety, effectiveness and bioavailability have been reported for ginseng nano-particles (Ganesan, Ko, Kim, & Choi, 2015). In this section we will emphasize those ginseng nano-particles studies that have been reported for improved immune function. Spherical shaped (70–107 nm) ginsenoside Rb2, Rc, Rb1 and Rd nanoparticles have been reported for the amplified immune response in mice model (Song, Zang, and Hu, 2009). The polysaccharides of ginseng possess immune modulaltory potentials but a significant amount of these molecules are not absorbed in the small intestine. This problem was successfully addressed by Akhtar et al., by preparing nanoparticles of these polysaccharides via micro-fluidic synthesis, thus enhancing bioavailability and ultimately immune modulation (Akhter, Mumin, Lui, & Charpentier, 2015). The gold nanoparticles of extracts of ginseng leaves have been reported for anti-inflammatory action by activation of NF-κB signaling pathway (Ahn et al., 2017). The role of ginseng nanoparticles in various disorders like diabetes, cancer, toxicity, thrombosis and CNS disorders, is usually limited to its direct effect (Kim, Lee, & Lee, 2016), very few studies have been reported for its immune modulatory role. The oral bioavailability of Ginsenoside Rh2 is low which can be improved when co-administered with bio-enhancer piperine or another possible solution is incorporating nano-particle technology (Zhao-Hui, Wen, Hui, Jiang, & Ling, 2018). The ginseng extracts, ginsenosides and polysaccharides nano-particles can be prepared and their expected amplified immune potentials, improved bioavailability and reduction in toxicity can be explored. However the choice of materials, charge, size, shape, stiffness, fluidity of nano-particles and route of administration must be considered for targeted and amplified immune modulation.

13. Clinical trials in relation to ginseng immune modulation

Currently, dietary supplements have been reported in different clinical trials for immune modulation and overall health improvement. Several clinical trials of ginseng and/or derived preparations have been performed. Until 1999, no clear and valid use was established; it was recommended that in depth research is required to elaborate the position of ginseng (Vogler, Pittler, & Ernst, 1999). However, as ginseng is the most renowned herb of the world so afterward various scientists have carried out extensive studies to clear the position of ginseng for its diverse functionalities.

Thirty randomized clinical trials have been reported related to the use of ginseng in various ailments up to 2013, in Korean literature, and four of these clinical studies are related to the immune modulator function of ginseng (Choi, Kim, Choi, & Lee, 2013). Healthy individuals (72; @age of 50–75 years) were given ginsan, a ginseng polysaccharide, in randomized double blind, placebo controlled study, to evaluate the immune modulatory action. Before and after 8–14 weeks, assessment showed significant results in terms of increasing TNFα and peripheral blood cells with no unwanted effects on blood chemistry (Cho, Son, & Kim, 2014). In 2011, Lee and Son published a systematic review to evaluate the clinical efficacy and clinical safety of Ginseng. They confirmed that ginseng has good safety profile, after reviewing 411 related studies and 57 clinical trials (Lee & Son, 2011).

Bespalov et al., carried out preliminary clinical trials for 3 months with *Panax ginseng* based panaxel and bioginseng in 64 volunteer patients (aged 36–41 years; men 41; women 23), with precancerous lesions of the esophagus and endometrium. The panaxel and bioginseng produced strong therapeutic effect in patients. The authors recommend ginseng based drugs for long term clinical trials in chemoprevention (Bespalov et al., 2001). A ginseng based product CVT-E002, was found very effective in preventing the upper respiratory tract infection, while testing in 783 healthy adults living in influenza vaccinated community (@400 mg–800 mg/day for 6 months) (McElhaney, Simor, McNeil, & Predy, 2011). A multicenter, double blind, placebo controlled study in 227 volunteers, receiving ginseng standard extract (Ginsana G115) @ 100 mg for 12 weeks increased the immune response of influenza polyvalent vaccine by increasing higher antibody titers and activity level of natural killer cells (Scaglione et al., 1996). In another study involving 60 individuals, ginseng standard extract (Ginsana G115) @ 100 mg for 8 weeks was modulated immunity by enhancing chemotaxis, phagocytosis, the number of lymphocytes, and increasing T helper cells (Scaglione et al., 1990).

A study was performed on 75 patients suffering from chronic bronchitis for antibiotic therapy alone and antibiotic plus ginseng therapy. It was found that patients receiving antibiotic plus ginseng showed faster bacterial clearance (Francesco Scaglione, Weiser, & Alessandria, 2001). Radiotherapy with ginseng polysaccharide injection improved the immune response and general condition of the nasopharyngeal carcinoma 131 patients used in the study (Xie, Zeng, & Huang, 2001). Single-blind, random-allocation and parallel study in 30 healthy volunteer for 6 weeks by the administration of fermented red ginseng (@ 2 g/day orally) elevated the level of immunoglobulin G and M (Kim et al., 2011). The immune modulatory effect was observed in a clinical study of 96 lung cancer patients who received ginseng polysaccharides plus dentritic cell injections in the thoracic region of the body (Ma, Liu, & Wang, 2014). Ginseng extract was evaluated during chemotherapy in 47 colon cancer patients after surgical treatment. IL-2, IL-8, and IL-10 associated immnunomodulatory effect was observed (Boo, Park, Kim, & Suh, 2007). Standardized ginseng extract (Ginsana G115) showed immune regulatory action in a double-blind sixty healthy adults clinical study (Scaglione et al., 1990).

Chinese formulation named Shenmai containing ginseng was tested in 63 patients who were on chemotherapy for stomach cancer. It was found that the mentioned formulation enhanced the immune function (Lin, Liu, & Wu, 1995). 64 patients randomly selected out of total 131 patients suffering from nasopharyngeal carcinoma and receiving radiotherapy used ginseng polysaccharides and the immune functions were improved (Xie et al., 2001). A proprietary extract based on ginseng (CVT-E002) was found safe, well tolerated and effective in prevention of respiratory syncyntial virus caused influenza followed by respiratory infections in 2 randomized, double-blind, placebo-controlled trials (McElhaney et al., 2004).

A clinical study was conducted in 42 advanced stage 3 gastric cancer, taking ginseng powder during postoperative chemotherapy. The study showed that ginseng taking patients immunity was improved as compared to control group through CD3 and CD4 modulation (Suh et al., 2002). Another study in 39 gastric cancer patients receiving ginseng powder (@ 5400 mg per day) for 2 years after surgery showed immune modulation (Kim, Yoo, Yu, & Yang, 1998). Ginseng was administered in capsule form to 72 patients of GI carcinoma (@ 4500 mg) for 18 months; postoperative immune response was the key outcome of the study (Suh & Jung, 1998). A cohort study of 5 years indicated that frequent intake of fresh ginseng by cancer patients boosts their immunity, (Yun & Choi, 1998). A poly-furanosyl-pyranosylsaccharide enriched extract of ginseng was tested in 323 healthy subjects having history of two times cold in past year. The start of influenza season was chosen the start of the study, after taking the extract for 4 months, it was found that cold occurrence, its severity and duration was significantly reduced. Thus enriched extract of ginseng may be a good prophylactic tool against cold, flu and other respiratory infections (Predy et al., 2005). A study in 18 healthy individuals for 10 days showed that ginseng intake decrease exercise induced muscle damage and inflammation (Jung et al., 2011). Prolonged intake of ginseng increased $CD4^+$ T cell count in HIV patients and decreased/delayed the resistance to antiviral drugs like zidovudine (Cho, Sung, Lee, Joo, & Cho, 2001; Scaglione et al., 1990). Ginseng extract in 60 healthy volunteer for 8 weeks caused modulation of immunity (Scaglione et al., 1990). Treatment of HIV patients with ginseng for 7–15 years showed therapeutic potential through gross deletions in 5′ LTR/gag and nef genes HIV-1while the CD4 T cell counts and CD4/CD8 ratio increased rapidly(Cho, Jung, Sung, Sim, & Kim, 2009). In a recent clinical trial in 80 rheumatoid arthritis patients, it was confirmed that the immune enhancing effect of ginseng has no significant association with worsening adverse events of other drugs. However, this study has limitations like small sample size, 8 weeks study period without wash out period, and the safety of Korean red ginseng cannot be generalized to all rheumatoid arthritis patients because low disease activity patients were only included in the study (Cho et al., 2018). Korean red ginseng tablets 500 mg were given to 41 patients of mild to moderate atopic dermatitis in open non comparative clinical trial for 8 weeks. As dietary supplement, Korean red ginseng improved the conditions of dermatitis (Kim, Park, & Cho, 2018). In a double-blind, randomized, placebo-controlled trial, standardized ginseng extract @ 400 mg in 127 patients of advance cancer for 28 days did not significantly improve cancer related fatigue (Yennurajalingam et al., 2017) however, this study has a major demerit of duration which is short. The cognitive function in increased stress was improved in randomized double blind 6 week trials in 63 individuals. However these clinical trials of ginseng have certain shortcomings that need to be addressed in future studies like the duration of taking ginseng and producing psychological effects should be longer, and maximum number of biological markers should be considered (Baek et al., 2018). A randomized double blind trial was carried out using dry extracts of stem and leaves of ginseng containing 26.66% ginsenosides in 26 irritable bowel syndrome patients for 60 days. Dry extract of ginseng @300 mg showed significant pain management during the disease however the author advised to extend sample size and duration and balance the male/female ratio in future studies (Rocha, Rocha, Nóbrega, Morais, & Diniz, 2018).

14. Ginseng based patents for immunomodulation

The great interest of institutional researchers and pharmaceutical companies is also validated by a surge in number of patents protecting various dosage forms and formulations of ginseng.

Searching the term ginseng in Patent Lens database for patent records showed 67,930 while, 173,237 for Google patent database than searching ginseng and immunity modulators simultaneously in the Patent Lens database 3121 patents 6399 were revealed in the Google patent database (Fig. 6). However, it should be kept in mind that the browsing has drawbacks like inclusion of patents that contains “immune” or “modulator” and the results of term ginseng not necessary to be American or Asian/Chinese as ginseng is used for various plants

species and varieties. But we will describe here patents that are associated with immune modulation.

A patent granted in 2002, is related to pharmaceutical compositions based on ginseng for treating suppressed immune conditions like influenza, cancer and AIDS (Shan, Pang, Huang, & Ling, 2002). Another patent granted by USPTO in 2009 is also based on ginseng for enhancing immune functions (Rangel, 2009b). The process and composition of *Panax ginseng* polysaccharides for potentiating cell mediated immunity has also been patented (Yun, Song, Bae, & Jung, 2003). A multi herb composition contain ginseng was patented with claim to treat HIV infection and related immune disorders with synergistic immune effect and minimum side effects (Rangel, 2009a).

Ginseng based remedy may be used as *in vitro* cells growth stimulator and is a useful agent for cell transplant therapy (Sakata, Taekzono, Yabe, & Matsui, 1994). Polysaccharide obtained from ginseng in beverages enhances the taste of the drink and immunity of the consumer (Zhang, 2009). Ginseng based composition is safe for improving liver functions, preventing liver diseases and can also treat other liver disorders (Jin, Lee, & Lim, 2016). American ginseng based neutraceutical composition is used for activating innate and adaptive immune responses (Adamko, Rosenthal, Shan, Wu, & Sutherland, 2013). A ginseng based composition for immune (innate and acquired) modulation has been developed (Lim, Jin, & Lee, 2010). Another patent is granted for composition and process based on *Panax* genus for immune enhancing potentials, anemia and cancer (Kwak, Shin, Kim, & Park, 2011). Ginsenoside Rb1 as an adjuvant in vaccine has also been registered as patent (Vega, 2005). A patented formulation of ginseng extract, Ginsenoside and its derivatives claimed to treat cytomegalovirus infection however, the mechanism of treatment is not mentioned to be immune based approach (Fu et al., 2018). A patent filed in 2015 and published in 2018 with a claim that Ginsenoside M1 can be used for treating IgA nephropathy (Lee, Lee, Chen, Hua, & Ka, 2018). Another patent published in Dec 2017, a dietary supplement for improving brain health contain ginseng in its composition (Gutierrez & Beer, 2017). In recent years (2017–18) several ginseng as immune modulator are patented e.g. Ginseng is a part of composition registered as patent that is used in apoptosis inducing agent in the treatment of cancer, immune and autoimmune disorders (Tao, Wang, Souers, Catron, & Sullivan, 2017), a composition containing Ginsenoside F1 as an active ingredient to modulate immunity (Kim & Kim, 2017), ginseng is part of the immune modulator capsule (Zhang, 2018), sleep and immune adjusting drink (Shanshan and Yinshi, 2017), red ginseng oral liquid rich in ginsenoside Rg3 (Zhai, Zhang and Ma, 2017), ginsenoside Rb1 in preparation of a drug for treating autoimmune recurrent spontaneous abortion (Liu, 2017) and ginseng floral extract for skin regeneration or wound healing (Kim et al., 2018).

15. Clinical uses

Ginseng is approved by the German Commission E and the World Health Organization for use as an adaptogenic (for stress), anti-fatigue agent, anti-stress agent, and as atonic (Blumenthal, Goldberg, & Brinckmann, 2000). In Germany, ginseng may be labeled as an aid to convalescence and a tonic to treat fatigue, reduced work capacity, and poor concentration (Foster & Tyler, 1999).

16. Dosage

The dosage depends on the ginsenoside content and should start from the lowest possible level. Physicians recommend usage of a standardized product. The typical dosage of the product containing 5 percent ginsenosides is 200 mg taken one to three times daily. For long-term use, the patient should take ginseng in cycles of 15–20 days and then 2 weeks off. Importantly, one study indicated that doses up to 5000 mg were well tolerated in animals. This suggests that ginseng is safe even at very high doses (Lee, Lee, Lee, Kim, & Jeong, 2008). Korean red ginseng in a multicenter, double blind, randomized placebo controlled clinical study in 1000 healthy individual at a dose of 2 g tablet equivalent 3 g of extract per day for 24 weeks were found safe and tolerable (Song et al., 2018).

17. Safety consideration of ginseng and derived products

Few studies have been reported about ginseng toxic effects that is in most cases attributed to the poor quality and greater quantity of ginseng or its products however scientists analyzed the previous studies critically. In fact ginseng or derived products are safe if standardized dosage forms, proper and recommended doses (usually $>$ 0.5–2 g), are taken at proper time and for recommended duration. No carcinogenic and teratogenic effect was reported however the safety studies in pregnancy, lactation and in children are required. Care should be taken or physician should be consulted when diabetics want to use ginseng or its products as they lower blood glucose level slightly (World Health Organization, 1999). Lee and Son reported in 2011 that ginseng has good safety profile in systematic review of clinical trials in 13 databases until March 2009 (Lee & Son, 2011). Another clinical trial for 14 weeks of ginseng polysaccharides proved it safe and effective immune modulator (Cho, Son, & Kim, 2014). Clinical trials about ginseng reported during January 2005 to November 2014 were analyzed for safety consideration and found ginseng safe in limited number of clinical trials with small number of participants, so it is recommended that safety targeted clinical trials should be carried out, with large number of participants with uniform health conditions and for longer duration (Kim, Woo, Han, & Chang, 2015). Toxicological studies demonstrated good safety profile of ginseng (Mancuso & Santangelo, 2017). In response to the need of long term safety analysis study a clinical trial for 24 weeks in 1000 healthy individuals was completed that confirmed the use of in ginseng is safe and tolerable if used in proper doses i.e. 2 g or lower (Song et al., 2018). Adverse events reported from clinical trials are mild, reversible and with no special safety concerns therefore, the benefit/risk balance is considered positive.

18. Drug ginseng interactions

There are three reports of an interaction between ginseng and phenelzine, and other monoamine oxidase inhibitors in which patients experienced psychoactive effects of mania and headache (Charrois, Hrudey, & Vohra, 2006; Jones & Runikis, 1987). The clinical significance of this interaction has not been evaluated. Several case reports and clinical trials in healthy volunteers showed interaction of warfarin and ginseng probably at cytochrome P450 2C9 level that results decrease in area under the curve and maximum concentration level of warfarin (Charrois et al., 2006). One case report shows that ginseng reduced the diuretic effect of furosemide and other loop diuretics but this interaction needs further evaluation (Bressler, 2005; Charrois et al., 2006). Caffeine and ginseng improve cognitive performance so care is needed when used simultaneously (Kennedy, Haskell, Wesnes, & Scholey, 2004). Ginseng interacts with anti-diabetics and insulin via lowering the blood glucose level, as ginseng and is reported to improve insulin sensitivity (Vuksan et al., 2008) so diabetics need more attention while using ginseng. A case was report indicated that ginseng increased lamotrigine plasma concentration producing eosinophilia and systemic symptoms syndrome (Myers, Watson, & Strock, 2015). The reported cases on interactions need to be verified clinically to make the interaction picture clearer. These interactions can be avoided if the patient consults their physician or clinical pharmacist if he/she wants to use ginseng or its products concomitantly with other drugs.

19. Chemistry of ginseng

Numerous compounds like ginsenosides, polysaccharides, peptides, fatty acids and lignans have been reported from ginseng.

Polysaccharides are the most abundant component. Ginsan and other oligosaccharides are the most active saccharides of ginseng. Ginsenosides are the second most abundant component of ginseng that has been isolated; some of their structures are given in Fig. 7. Similarly, alkaloids, glucosides and phenolic acids have also been reported (Ru et al., 2015). Of the various ginsenosides, Rb1, Rg1, Rg3, Re, and Rd are the most frequently studied in immune modulation.

20. Conclusions

In this study, we reviewed the potentials of ginseng to serve as immune-modulators and functional ingredient for the immune system ginseng against various diseases especially via immune modulation. Ginseng or derived products modulate immune functions of cancer patients both at cellular and humoral level. Ginseng has promising role in boosting host immunity actively or passively as vaccine adjuvant against different infections, in autoimmune diseases, osteoporosis and allergies. The immune modulatory role of ginseng can be improved using nano-technological methods. Various patents and clinical trials of ginseng with immune modulatory theme have been registered in patent and clinical trials databases. Ginseng has good safety profile even the untoward effects reported from clinical trials are mild, reversible and with no special safety concerns, therefore, the safety/risk balance has more inclined towards safety.

Ginseng-made biopharmaceuticals against immunity-related disorders have begun to blossom as a field in their own right. This paradigm shift is based on the discovery of extra-ordinary immunity-modulatory potential of ginseng and active role played by its various forms and dosages against immunity-based human diseases. There are several promising avenues that can be explored for development of innovative and low-cost therapeutics targeting remedies from ginseng. Future work will have to focus on the identification of the relevant compounds from ginseng, their preclinical characterization and selection of the candidate bioactives, and the rational design of immunotherapy studies involving objective as well as subjective parameters for measuring clinical efficacy. With the use of defined molecules instead of crude ginseng extract–based mixtures, it will be possible to decipher more precisely the mechanisms underlying immunotherapy and to develop new forms of immunotherapy and perhaps prophylactic immunotherapy strategies. By maintaining some healthy skepticism, we feel that the time is ripe for (re)discovering and exploiting ginseng as an immunity-booster neutraceutical.

Conflicts of interest

The authors declare no conflict of interest.

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