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A Review on the Potential Effective Cytoprotective Role of Ginseng in Rat's Organ

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ABSTRACT

Panax ginseng is among the herbal agents traditionally utilized for thousands of years. It is used commonly as dried roots with possible multifaceted medical characteristics, including anti-inflammatory, anti-neoplastic, tonic, antiviral, antifungal, and antioxidant, besides its potential actions in healing and restoration. Although many studies discussed the action of one of the components of Panax ginseng, several types of this herb include *Panax quinquefolius in America*, *Pan Ginseng* in Korea, and *Panax notoginseng* in China. This study aims to review the articles that focus on the potential roles of ginseng in general, highlighting the effect of *ginseng* on several rats' organs. A brief review of the articles discussed the role of ginseng as an anti-inflammatory, anti-neoplastic, tonic, antiviral, antifungal, and antioxidant agent. Several works concluded the multifaceted actions of ginseng at both clinical and animal levels. The products which are obtained from the natural origins (as ginseng)are gained major concerns as pharmacological agents as they are potentially helpful in treating several disorders by their several cytoprotective roles in oxidative stress, inflammation infection(viral and bacterial), malignancy, diabetes mellitus, problems of sexuality beside the disorders of central nervous and cardiovascular systems as these herbs have little toxicity. There is a need to develop new components of ginseng.

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INTRODUCTION

Historically, *Panax ginseng* is among the herbal agents that traditionally utilized for thousands of years **(Lim *et al*.,2013).** It is used commonly as dried roots **(Issa and El-Sherif, 2017)** with possible multifaceted medical characteristics including anti-inflammatory, anti-neoplastic, tonic, antiviral, antifungal, and antioxidant **(El-Mehi and El-Sherif,2015)** besides its potential actions in healing and restoration **(Lee and Kim,2014).**

This herb has been used, especially in the last 30 years, as products of agriculture, medicines, supplements, and dietary agents **(Yu *et al*., 2017)**. This herb recently has a role in treating stress, hypertension, Alzheimer's disease, Huntington's disease, and Parkinson's disease besides its value in molecular medicine **(Wahid *et al*., 2010, Kim, 2018 and Lee *et al*., 2018).** Ginseng may be included in small amounts of energy drinks or herbal teas or sold as a dietary supplement (Fig. 1).

Its name (Pan ginseng) is the herb that treats all types of diseases in the human body **(Lim *et al*., 2013).** Due to its high value in being the base of many novel drugs, it is called the king of medical plants, especially in Asian countries (Japan, Korea, and China). This is a brief review on the use of ginseng as a cytoprotective agent in general highlighting its effects on several organs in rats.

Fig. 1: A picture of the root of Pan Ginseng (Korean) https://en.wikipedia.org/wiki/Ginseng.

Types

Although many studies discussed the action of one of the components of Pan ginseng, several types of this herb include Panax quinquefolius in America, Pan

ginseng in Korea, and Panax notoginseng in China (**Lim *et al.*,2013; Yu *et al.*,2017**).

Mechanism of action

Although the action of ginseng is from all components of it, ginsenosides(triterpene saponins) are considered as the main active ingredients of ginseng with great concern in reports (**Im *et al.*,2013; Lee *et al.*,2018**). There are two hundred ginsenosides **(Kim, 2018; Kim *et al.*, 2018; Cho *et al.*, 2019)**. They are steroidal substances that have multiple actions as they interfere with the ion channels(membrane-bound), cellular receptors, and membranes to interact with transcription (**Han *et al.*,2018; Mohanan *et al.*,2018).**

Side effects

Many warnings were declared by the United States American Food and drug administration -FDA in 2019, besides those of Federal Trade Commission for the ginseng dietary supplements manufacturers who made untruthful concepts that it has benefits against diseases (**William *et al.*, 2019**).

In general, this herb has a good zone of safety if it is taken in a short period, but it has potential adverse action if it is used for chronic periods including digestive problems insomnia, and headaches (**William, 2018; Cheryl A., 2019; William and marry, 2019).**

Interactions

Low risk of interactions between ginseng and other drugs was found; however, many side effects were reported if it is used with warfarin (**Kim *et al.*, 2015**) phenelzine, with possible interaction with tyrosin kinase inhibitor-imatinib **(Izzo and Ernst, 2001).** In addition, hepatotoxicity was noticed if it is used with lamotrigine **(Bilgi *et al.*, 2010)** with blood pressure fluctuations, anxiety, insomnia, mastalgia, vaginal bleeding, nausea, or diarrhea. Other interactions may be seen with herbal supplements or foods **(Lindsy, 2019).**

Potential roles of ginseng

1. Antioxidant action

Reactive nitrogen species with free radicals are the sources of reactive oxygen species enrolling exogenous as (alcohol, heavy metals, drugs smoking) and endogenous as (endoplasmic reticulum, mitochondria, peroxisomes, and phagocytes) **(Ratan *et al.*, 2021).** Several studies documented the role of free radicals in many diseases, including Diabetes, atherosclerosis, cancer, and degenerative disorders of the eye, with a concern to develop many antioxidants including ginseng**(Lobo *et al.*, 2010).** In fact, reports discussed the role of this herb in ameliorating the antioxidant effect of it as a scavenger of free radicals and increasing the levels of antioxidant enzymes(glutathione peroxidase and superoxide dismutase) and decreasing the level of reactive oxygen species in a clinical study on healthy subjects **(Ratan *et al.*, 2021).** Furthermore, recent work revealed the alleviating role of gensing against malathion hepato-renal injury via its antioxidant action in male rats(**Ghamry *et al.*, 2022)**. Observations of authors indicated that Panax ginseng has nephroprotective effects after exposure to Gentamicin Sulphate in rats due to the scavenging actions of free radicles**(Karadeniz *et al.*,2008).** Recent work by **Sng *et al.* in (2022**) suggested the antioxidant action of ginseng extract and ginsenosides in rats with spinal cord injury which improve their neurological function.

2. Anti-inflammatory action

Commonly, innate and adaptive immune responses are incorporated in inflammation, including pain, fever, oedema, redness, and impaired function **(Yang *et al.*,2015)**. Several works (in vitro, in vivo, and clinical) are concerned with the role of ginseng as an anti-inflammatory herb (**Choi *et al.*, 2018; Lee *et al.*, 2018).** There is a suggestion of involvement of signaling of NF-κB pathway (**Kim,2018; Ratan *et al.*,2021),** while another reported that there is an inhibition of the macrophage-derived cytokines expression and tumor necrosis factor receptor-related NF-kappa-B activator with interferon **(Lee *et al.*, 2012).** Patients who received ginseng postoperatively (after curative surgery) have a more chance of being alive for 5 years than those who did not receive ginseng **(Ahn *et al.*, 2006).**

In recent work, ginsenoside Rb1 and ginseng extract have an attenuating effect on liver injury and fibrosis in rats after exposure to carbon tetrachloride as noticed via the expression of tumor necrotic factor alpha and prostaglandin suggested its anti-inflammatory assignment **(Hou *et al.*, 2014)**. In previous work, there is a modulation of inflammation through receiving Panax ginseng after exposure to thioacetamide liver injury in rats after oophorectomy **(Kim *et al.*, 2013).**

3. Action against microorganisms

Many antimicrobial substances(including herbs) develop as antibiotic resistance increases **(Roca *et al.*, 2015; Ratan *et al.*, 2021).** Extract Korean red ginseng against viral infection (H5N1, H3N2, and H9N2 influenza virus) in the lung by blocking cytokines, increasing the interferon level, and supporting the cell-mediated immunity**(Park *et al.*, 2014).** Clinically, Korean red ginseng had action against HIV type-1 **(Cho *et al.*, 2017)** and recently against Covid 19 (**Lee and Rhee,2021)**.

Many works suggested the role of ginseng against viruses such as hepatitis (A and B) and

enterovirus 71 **(Ratan *et al.*, 2021).** Regarding the action of ginseng against bacteria, this herb has a role in raising the immunity against experimental *E.coli* sepsis via tumor necrosis factor pathway and interferon **(Ahn *et al.*, 2006).** In addition, synergistic action with cefotaxime against *Staphylococcus aureus* (**Ratan *et al.*, 2021).**

4. Action against cardiovascular disease

Universally, death is commonly caused by cardiovascular diseases (enrolling the blood vessels and heart) **(Pagidipati and Gaziano, 2013).** Due to the action of ginseng in the stimulation of the production of nitric oxide, enhancing blood circulation, adjustment of lipid profiles, and inhibiting reactive oxygen production, besides its role in the inhibition of calcium ions Ca^{2+} entry, various works have considered this herb as cardioprotective agent **(Ratan *et al.*, 2021**). In a study by **Kim (2012),** an inhibition of hypertrophy of the heart has reported by ginseng. In addition, Pan ginseng has a role in decreasing blood pressure in rats (**Qin *et al.*, 2008; Moon *et al.*, 2019),** while other works(in vitro and in vivo)suggested an anticoagulant function by suppressing of aggregation of platelet **(Hwang *et al.*,2008**). The in vivo work showed that the extract of Pan notoginseng has a role in the regulation of lipid as cholesterol (total and low-density lipoprotein) and triglyceride -TG) **(Ji and Gong, 2007)**.

5. Action against obesity

There is a need to develop an alternative agent to treat obesity (one of the most fascinating issues in the world) as the drugs that treat this condition have several side effects. Various critical diseases are related to obesity, including cancer, heart diseases, diabetes mellitus, and sleep apnea (**Kopelman, 2000).** Ginseng has been reported to have an Action against obesity via clinical reports with unclear cause. In fact, stimulation of the adenosine monophosphate-activated kinase pathway is suggested on both cell lines and in vivo levels (**Park *et al.*, 2018; Ratan *et al.*, 2021).** A study indicated that administration of ginseng for 2 months leads to a decrease in total cholesterol, low-density lipoprotein, and triacylglycerol level with an increase in high-density lipoprotein **(Kim and Park, 2003).**

6. Action against both categories of Diabetes mellitus

One of the commonest metabolic diseases is Diabetes mellitus which is due to a defect in insulin secretion and/or action. Ginseng (wild type) has been suggested to reduce the fasting blood glucose in mice (**Yun *et al.*,2004**). **Moon *et al.*, 2015** suggested the same action in rats treated with low doses of streptozotocin, while others reported antidiabetic action of ginseng in Alloxane treated rats (**Moon *et al.*, 2015; Gad El-Karim *et al.*, 2017**). In addition, clinical work revealed that Korean red ginseng showed a positive effect in treating Diabetes mellitus(type 2) after three months (**Vuksan *et al.*, 2008**). The ginsenosides (especially its active metabolite) enhance the secretion of insulin by pancreatic islets depending on studies(in -vivo and in -vitro) (**Ratan *et al.*, 2021**).

7. Action against the disorder of the central nervous system

It has been shown that Panax ginseng, especially ginsenosides, may treat anxiety, memory disorders, depressive disorders, and epilepsy (**Choi *et al.*, 2018; Park *et al.*, 2018)**. In cases of depressive disorders, the action may be by upregulating certain receptors5-HT2A by Ginsenoside or increasing the level of noradrenaline in the brain (**Yamada *et al.*, 2011**). Further, several works revealed the effect of ginsenosides in treating Alzheimer's disease(due to accumulation of neurofibrillary tangles and Amyloid plaques) by reducing the amyloid βeta peptide concentration (**Iqbal *et al.*, 2005**). Clinically, ginseng root administration for three months may be helpful in cases of Alzheimer's disease (**Ratan *et al.*, 2021**).

On the other hand, ginsenosides types have been reported to play roles in the treatment of Parkinson's disease (due to cellular death of neurons in the substantia nigra) via its antioxidant and anti-inflammatory actions (**Jenner,2003, Choi *et al.*, 2018**). Ginsenosides have been suggested to protect the neurons against apoptosis from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by diminishing caspase, Bax, and nitric oxide beside the enhancement of Bcl-xl and Bcl-2 levels (**Chen *et al.*, 2002**).

In addition, protection from cerebral ischemia was achieved by ginsenoside Rd (**Liu *et al.*, 2015),** while improvement the memory was performed in mice treated with Ginsenoside (Rg3) (**Liu *et al.*, 2018**). Further**, Zhu *et al.*, (2017)** reported the effect of red ginseng extract after spinal cord injury in rats.

8. Enhancing energy and sexuality

The ability of ginseng to increase sexual activity for both sexes and energy provides it to be a famous agent (**Ratan et al., 2021).** The major source of its activity was saponin **(Smith *et al.*, 1996)** beside ginsenosides (which contain sugar elements such as glucose and arabinose). Ginseng has been used to treat fatigue in rats as an antioxidant agent, down-regulation of free radicles, and increase the activity of mitochondria **(Tan *et al.*, 2018)**. In a recent study **(Lee *et al.*, 2019)**, ginseng was reported to increase the sperm kinematic scores by attenuating action on the expression of several proteins in testes **(Ratan *et al.*, 2021).** At work, there is a marked recovery of the

testicular changes induced by Flutamide by Panax ginseng roots in rats **(Rahim, 2004**).

9. Anticancer activity

The second cause of death (globally) is cancer **(Al Allaf and Al –Ashoo, 2021; Ratan *et al.*, 2021)**. Several side effects due to chemotherapy give the idea to develop complementary treatments for cancer including herbs **(Mostafa *et al.*, 2021)**. Heat's change in ginsenosides' composition (steroids) makes them useful as anticancer agents **(Yu *et al.*, 2018) (Fig. 2).**

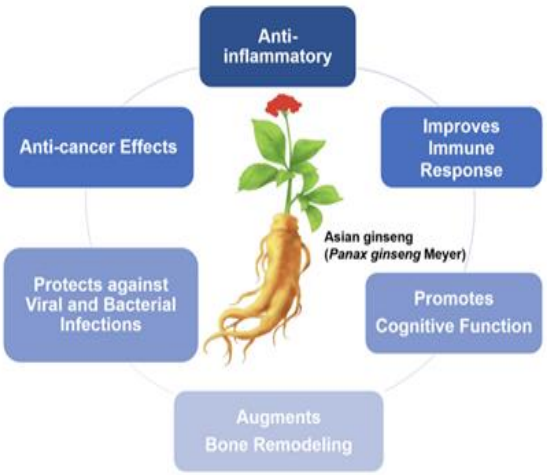

Fig. 2: Multifaceted actions of ginseng (Kim *et al.*, 2022).

Since 1980, there has been inhibition of lung tumors in rodents after exposure to several agents(as Aflatoxin B1, 9,10-dimethyl-l1,2-benzanthracene,and urethane **) (Zidan *et al.*, 2015; Ratan *et al.*, 2021)**. Targeting of growth factors as vascular endothelial one and enzymes as caspases are suggested by ginsenoside Rb1 in cases of lung cancer **(Ahuja *et al.*, 2018)**, while down-regulation of expression of iNOS, COX-2, and NF-κB by ginsenoside Rd in was reported **(Lee *et al.*, 2018; Ratan *et al.*, 2021).**

Inhibitory effects were noticed in skin, prostate, liver, and ovarian cancer **(Baek *et al.*, 2017; Wang *et al.*, 2018**). Recent work revealed ginseng's anti-mitotic action in benign prostatic hyperplasia is better than finasteride besides the anti-fibrotic effects in rats (**Nasr *et al.*, 2021**). Co-administration of chemotherapy with ginseng may improve the organ injury in rats by these anticancer drugs (**Alrashed and El-Kordy, 2019; Raghavendran *et al.*, 2011).**

There was a role of ginseng as a cytoprotective drug in rats' organs after exposure to many toxins such as Aflatoxin B1(**Zidan *et al.*, 2015)**, thioacetamide (**Mostafa *et al.*, 2021),** alcohol (**Liu *et al.*, 2018**), malathion **(Ghamry *et al.*,2018),** and Lambda-cyhalothrin **(Abdul-Hamid *et al.*, 2020)** beside anti-aging activity of this herb **(Kim *et al.*, 2022)**.

CONCLUSION

In conclusion: The products which are obtained from natural origins (such as ginseng)are gained major concerns as pharmacological agents as they are useful potentially to treat several disorders by their several cytoprotective roles in oxidative stress, inflammation infection (viral and bacterial), malignancy, diabetes mellitus, problems of sexuality beside the disorders of central nervous and cardiovascular systems as these herbs have little toxicity. There is a need to develop new components of ginseng. Ginseng will develop a new area for the production of pharmaceuticals. The research on such herbs may be helpful for pharmaceutical industries, healthcare agencies, and governments.

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