



International Journal of Pharmacology

ISSN 1811-7775



Review Article

Herbal Traditional Medicines Ginseng (*Panax quinquennium* L.) Effects on Anti-nose Cancer and Anti-toxin in Systematic Pharmacology Treatment Mechanism for Nose Cancer: A Review

^{1,2}Akhtar Hussain Shar, ^{1,2,3}Mohamed Shahren, ⁴Liujingjing, ⁴Shenfengxia and ^{1,2}Yonghua Wang

¹College of Life Science, Northwest A&F University, Yangling, 712100 Shaanxi, China

²Center of Bioinformatics, Northwest A and F University, Yangling, 712100 Shaanxi, China

³Department of Zoology, Faculty of Science, Tanta University, Tanta 31527, Egypt

⁴College of Life Science, Northwest University, Xi'an, 710069 Shaanxi, China

First and second author contributed equally to this work.

Abstract

Cancer is an alarming condition whose occurrence has increased dramatically in the last few decades. This, in turn, has increased the medicinal cost and health care burdens of society. Unfortunately, a lack of effective and safe pharmacological therapy and strategies has been found to overcome this issue. Now-a-days nose cancer is an alarming health disorder that requires scientific attention to find an effective and safe pharmacological approach to overcome this serious issue. Currently, various treatments are used for this life threatening disease. Chinese traditional medicine like ginseng is one of the choices used as an effective and safe therapeutic tool for the treatment of cancer. Some previously published studies proved that ginseng not only kills the cancer cells but also inhibits the further multiplication of cancer cells with minimum side effects compared to the rest of treatment therapies. However, the exact mechanism of action behind ginseng's ability to kill cancer cells has not been completely explored, there are still many research areas waiting to be studied, such as molecular pathways involved in the ginseng-derived flavonoids that attack cancer cells. The target of this review is to highlight the importance of the medicinal effects of ginseng and their flavonoids used in cancer therapy. Another objective of this paper is to attract the attention of the scientific community, to find out the mechanism of action behind ginseng herbal medicine in order to develop safe and non-toxic drugs for the cure of nose cancer.

Key words: Ginseng, nose cancer, herbal medicines, therapeutic anticancer, anti-toxic effects

Received: July 04, 2017

Accepted: September 05, 2017

Published: December 15, 2018

Citation: Akhtar Hussain Shar, Mohamed Shahren, Liujingjing, Shenfengxia and Yonghua Wang, 2019. Herbal traditional medicines ginseng (*Panax quinquennium* L.) effects on anti-nose cancer and anti-toxin in systematic pharmacology treatment mechanism for nose cancer. Int. J. Pharmacol., 15: 10-18.

Corresponding Author: Yonghua Wang, Center of Bioinformatics, Northwest A&F University, Yangling, 712100 Shaanxi, People's Republic of China
Tel: +86-15102959781

Copyright: © 2019 Akhtar Hussain Shar *et al.* This is an open access article distributed under the terms of the creative commons attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cancer is the worldwide fatal health problem. In recent decades, cancer has become a new field of pharmacology and clinical research. According to the type of the organ affected by cancer, there are several kinds of cancer diseases such as skin cancer, lung cancer, nasal cancer, colon cancer, breast cancer, etc. The usual kinds of cancer treatments include surgery, radiation and chemotherapy^{1,2}. According to the American Cancer Society, seven types of cancer diseases can affect the paranasal sinuses or the nasal cavity, although squamous cell carcinoma is the most common type. The other examples are Mucoepidermoid carcinoma, Adenocarcinoma and Adenomyosis. Each rhino cancer has some unique symptoms, however, these following symptoms are common in all the types: Headaches, nasal congestion, odor drops, frequent nasal bleeding, abnormal flu, weight loss and fatigue^{3,4}. Different tests are used for the diagnosis of cancer including a physical examination, biopsies, nanoscopy and an X-ray examination. The specific cause of certain nasal cancers suggests that some factors make a person a higher risk of developing nasal cancer⁵. These risk factors include persistent exposure to dust pollution, wood dust and cigarette smoke⁶. Traditional Chinese medicine (TCM), an important branch of natural medicine, can play an important role in clinical treatment⁷. Although, traditional Chinese medicine has accumulated a clinical experience framework and given a large number of successful applications, it has not been widely accepted in modern Chinese medicine.

Ginseng is a small genus of the family *Araliaceae*. In this century, all kinds of *Panax* have been modulated, such as *Panax ginseng*, American ginseng, Asian ginseng and *Panax Notoginseng* which are all important herbs used for different medical conditions. Five thousand years ago, China's Manchu ginseng was identified as a highly valued medicinal plant⁸. It was used to treat serious heart problems and to overcome weaknesses. Prehistoric literature shows that ginseng was often considered a high-profile transaction of gold value. The scientific method of chemical characterization of ginseng begins with a mixture of saponins when Garrigues is isolated and named for quinone 1854. Ancient Chinese people used it for a variety of health benefits, from fatigue to severe heart problems. "Shen Nong Encyclopedia of Beijing" written about 100 years ago, noted that ginseng inspires ideas and increases wisdom⁹. Ginseng contains more than 30 kinds of ginsenosides, with a variety of physiological and biochemical effects^{10,11}. Polyacetylene is shown to exhibit anti-tumor activity in various cancers¹² and phenolic compounds feature antioxidant activities¹³. The protein was used as radiation

protection with the victims of the atomic bomb attack¹⁴. Acidic polysaccharides with immunosuppressive activity are shown in mouse model experiments¹⁵.

The chemical structure of ginsenoside is the main pharmacologically active compound in ginseng, which is recognized by the Tea Group of the University of Tokyo¹⁶. Wild ginseng is naturally grown and harvested anywhere. In recent years, the product demand has led to wild plant discovery and harvesting rather than reliance on domestic plants which take years to reach maturity. Wild ginseng can be either Asian or American and can be processed to be red ginseng. This article will discuss the use of ginseng in the treatment of nasal cancer through the traditional Chinese medicine system pharmacology.

Traditional Chinese medicines (TCM) as an alternative therapy:

Traditional Chinese medicine has been described as a natural herbal product for the treatment of different diseases. More and more researchers have found that these drugs are being used for short and long-term diseases¹⁷. These drugs are thought to have a wide range of benefits but less than other treatment options. In the western world, traditional Chinese medicine (TCM) is used as effective remedies for different health problems. For example, traditional Chinese medicine (TCM) has been used for the treatment of cancer^{18,19}. Nasal cancer is a unique form of cancer. One of the most commonly used drugs for the treatment of nasal cancer is ginseng, a slowly growing perennial plant²⁰. The use of traditional drugs for the treatment of nasal cancer has some important challenges. On the other hand, the effects of ginseng herbs are systemic, complex or unexplained, which has hindered its acceptance as modern Chinese medicine²¹. Therefore, the model based on pharmacological actions of these drugs is based on the theoretical framework of systems pharmacology and describes ADME/T evaluation. The model combines knowledge about drug uptake, distribution, metabolism, excretion and toxicity and describes the appropriate goals that can provide target predictions. In addition, these compounds are based on the anticancer activity of 492 different cancer cell lines^{7,18}. Users can search for information in the nasal cancer search box by herbal name, chemical name, target name, CAS number and bioactivity. In addition, other forms provided by the operator can be found easily through the method of internal access links such as herbs and target information. Articles about the data collected on related topics have been published in various famous journals²². The choice of research is based on exclusion and inclusion criteria. The selected research criteria describes the types of research used for the critical literature review.

Treatment methods for nasal cancer: After the diagnosis of nasal cancer, the cancer team will have to develop a method for cancer treatment after evaluating cancer's concerts and grouping them. The decision for the patient is based on a treatment plan that takes into account all options available for the treatment of nasal cancer^{23,24}. In developing a treatment plan, this stage of cancer and the age of the patient are taken into account^{25,26}. A critical review of the literature provides information on the different methods used to treat nasal cancer by means of chemotherapeutic agents, radiotherapy, surgery, palliative care and targeted therapy²⁷. Evidence-based studies have also shown that goals, benefits and side effects are associated with different types of cancer so that treatment decisions can be made by considering all the best fitting methods.

It is very difficult to assess the best method for a way to treat nasal cancer because it is a rare form of cancer. Some studies have explained the benefits and risks associated with the use of different therapies and highlighted the need for alternative therapies for nasal cancer²⁸. Chemotherapy is the most important approach used for the treatment of cancer disease in the world, however, there are several side effects which are associated with the use of chemotherapeutic agents. These are a loss of appetite, mouth sores, hair loss, nausea, vomiting, low blood count, a negative impact on bone marrow's capability to form red blood cells, decreased immunity and increased exposure to different types of infections. Once the treatment is stopped, these negative effects are decreased²⁹. That is why some studies have highlighted the importance of using alternative therapies to treat cancer, the use of Chinese medicine is an effective choice.

Ginseng for prevention and treatment of nose cancer: For the last few decades, the most common methods used for the treatment of nose cancer were included early detection, surgical treatment and gene therapy. However, one strategy that has been gaining extensive importance in the recent years is the use of ginseng or *Panax ginseng* for the treatment of nose cancer. In the study of cancer treatment, the effectiveness of the treatment is directly related to the ability to target cells and the ability to attack cancer cells, as well as to minimize damage to the number of healthy cells³⁰⁻³³. Ginseng is not only associated with the treatment of nose cancer but also prevents the progression of most kinds of cancer according to several studies conducted on the treatment of cancer as discussed above. Although, the role of ginseng has not been assigned to any organ, current

studies have been done to evaluate the drug mechanism, as well as to target the pharmacological treatment of the rhino carcinoma system³⁴.

Clinical trials of using this drug to treat different types of cancer are still under investigation. Chinese ginseng has been used alone or in combination with other drugs for the treatment of different sources and types of cancer³³⁻³⁵. With the raising of awareness and data related to the use of this alternative approach to cancer treatment, the use of ginseng with the evaluation mechanism of clinical trials, the role of the drug has been developed. However, the pharmacokinetics (distribution, absorption, excretion and metabolism, (ADME) properties of a drug) and the goal of these products have not been adequately assessed. As the time passes, the costs of traditional methods, have become one of the major complications for the development of anticancer drugs and their function. The several natural products and their bioactivity potentially afford an extraordinary resource for new drug discovery and have been employed in cancer treatment. The pharmacology system's targets for multi-scale analysis of rhino carcinoma (Fig. 1) show the human pathophysiology (yellow arrow) design of the human body in different scales and the method system of Pharmacology. Furthermore, holistic estimation was achieved for each compound. At the molecular level, the target's protein of the ingredients is obtained through computational estimates and literature. At the cellular level, anticancer activities of these compounds based on cancer cell lines were obtained from the literature. After all recording cell lines to a primary organ or tissue locations, the therapeutic effects of each compound were emergent at the organ or tissue level. Nose cancer consists of six major parts of data: (1) Targets with action mode for ingredients, (2) Anti-cancer ingredients for each herb, (3) Anti-cancer herbs, (4) anticancer activities for ingredients based on cancer cell lines, (5) primary sites (organ or tissue) of cell lines and (6) pharmacokinetic properties (ADME) of ingredients (Fig. 1).

Bioactive compounds of ginseng used for the treatment of nose cancer: The various bioactive compounds of ginseng that can be used for the treatment of cancer include ginsenosides from ginseng compounds (Fig. 2). There are nearly 150 kinds of ginseng saponins, which are separated from the flower head, flowers, roots, fruits and leaves³⁶. Several research studies are now targeting ginsenosides because these are considered as the active part that is associated with the efficacy of ginseng. Ginsenoside, which has therapeutic activity, can be used for the

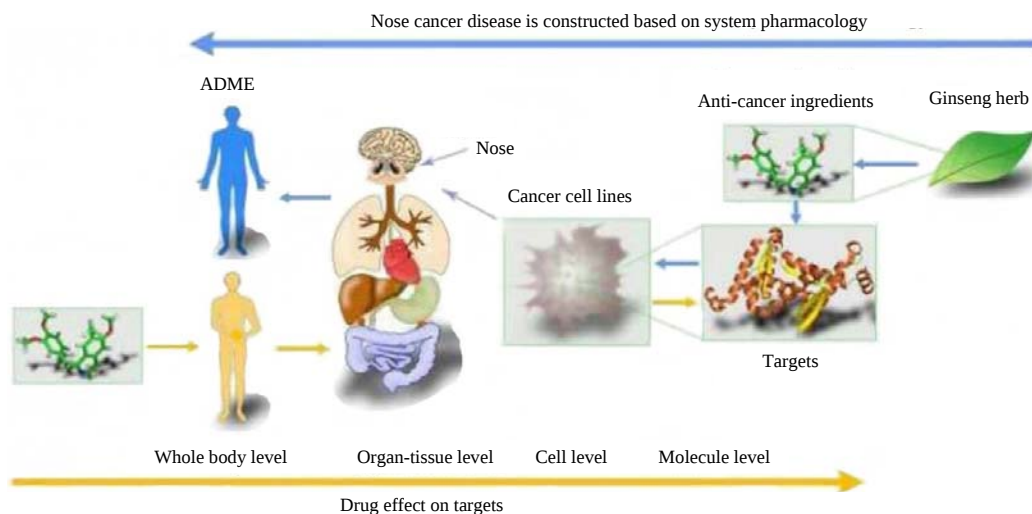


Fig. 1: Multi-scale analyses in nose cancer with a schematic illustration of different scales of organization involved in human pathophysiology

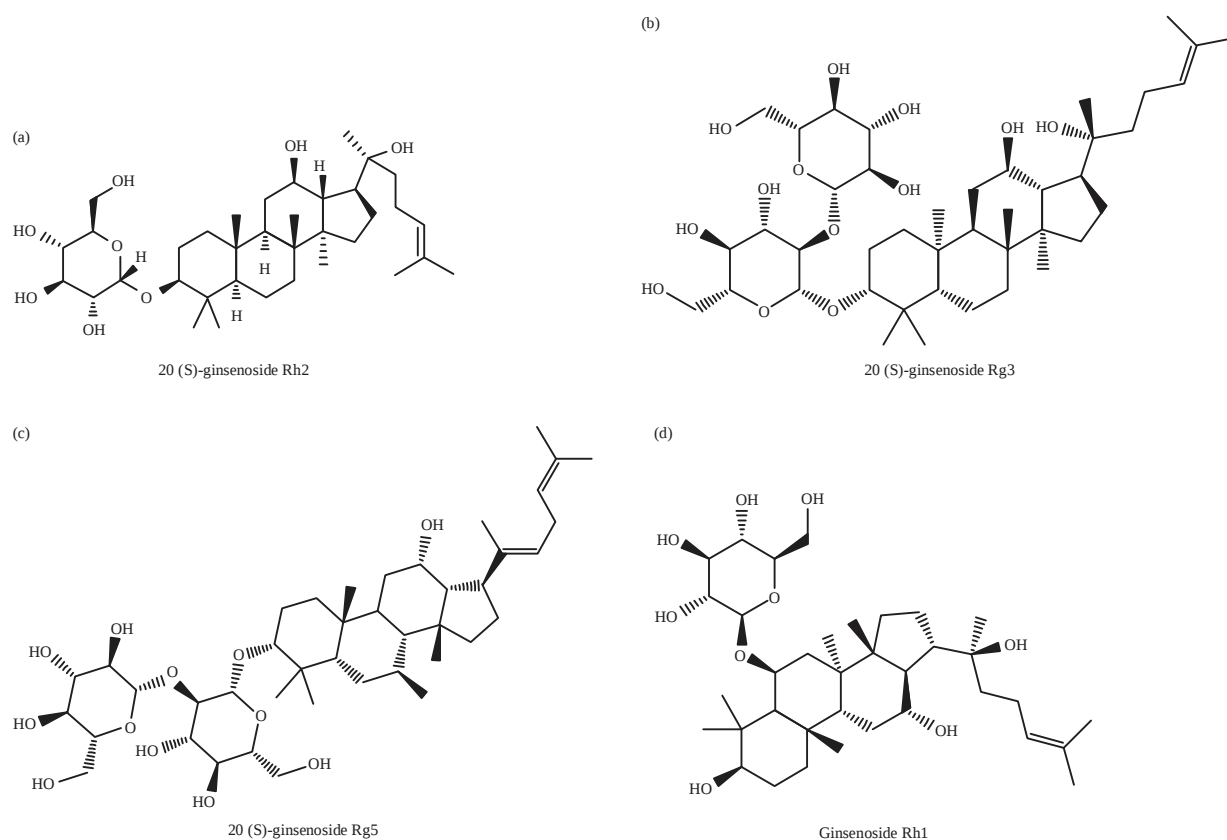


Fig. 2: Different forms of therapeutically active ginsenosides

treatment of various cancers, including rhino carcinoma. Ginsenosides are absorbed and metabolized by acid hydrolysis and the gastrointestinal tract under bacterial hydrolysis³⁷. After the metabolism, these are converted into the other forms of ginsenosides that are more

bioactive and bioavailable. The drying and steaming are also used to convert less active ginsenosides into more active forms. These ginsenosides play a key role in targeting cancer cells in the nasal cavity and kill the abnormal growth of cells^{38,39}.

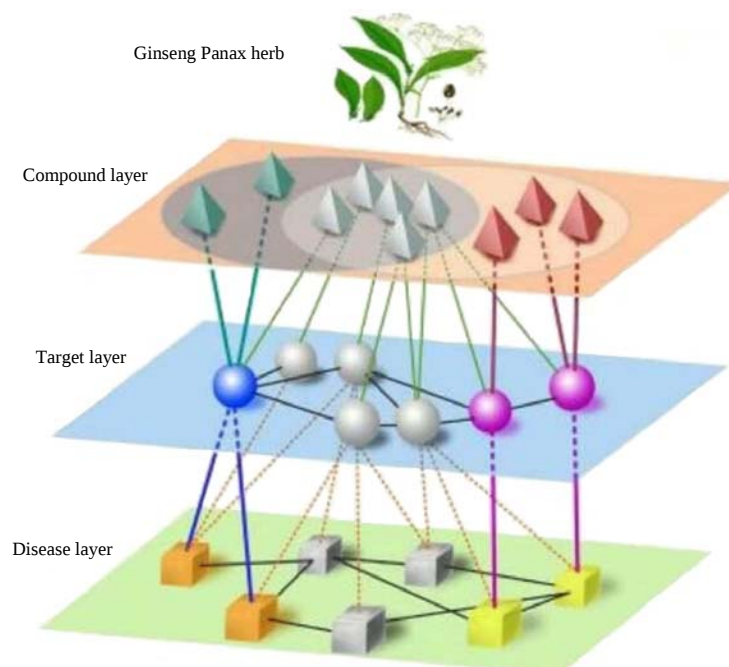


Fig. 3: A model of the mechanism of action of ginseng for addition and subtraction theory of TCM

Targets of ginseng: In the case of chronic inflammation, the expression of tumor genes is controlled by cytokines that affect the type of reactive oxygen species, causing DNA damage, disruption of DNA damage pathways, the proliferation of DNA, apoptosis and angiogenesis⁴⁰. Moreover, the chronic inflammation is also associated with the suppression of the immune system thus increasing the risks of causing cancer. Therefore, the current strategies with ginseng have been applied to target the chronic inflammation. This is the major reason for the composition of ginseng and its treatment of nasal cancer as it can induce the prevention and treatment with a long-term effect^{41,42}. However, the evaluation of the molecular pathways and related cancer and the application of these therapeutic agents in the treatment of cancer still needs investigation. To sum up, the therapeutic changes in nasopharyngeal cancer appear to be mainly due to the specific stabilizer drug application with different pharmacological effects.

The above results provide a new understanding of the efficacy of traditional Chinese medicine treatment. The dosing of herbal medicine may be by two methods: (1) The initial formula takes charge of the basic therapeutic effects through intensively targeting the dysfunction of the complete body and (2) Compounds in stabilizer herbs support or assist roles to the initial formula shown in Fig. 3.

System pharmacology of ginsenoside and ginseng: The therapeutic benefits of ginseng have been extensively studied, ginsenosides which are an active component of ginseng, are involved in the regulation of various physiological functions⁴³. The actions of many organisms make ginsenosides imperative for the development of a new source system. However, the low bioavailability of ginsenoside is one of the greatest challenges that need to be overcome in order to improve its use in medical facilities. Ginseng is usually the three terpene saponin, mostly composed of the most ginseng sugar fragments in the four-ring structure of 17 carbon atoms (such as sugar, glucose, rhamnose and xylose) and the attachment positions of these sugars are C-3 and C-20^{44,45}. The term "g" for ginsenosides is "Rx". In this term, "R" is used to represent the roots and "x" is used to represent the alphabetical order of the polarity of the chromatogram, for example, Ra is considered to be the minimum polarity and Rb has a polarity that is greater than Ra⁴⁶. The identification of the 30 ginsenosides is still carried out and these are divided into two groups, (S)-protopanaxadiol (PPD) groups and the components of this group are (Rb1, Rb2, Rb3, Rc, Rd3, Rh2, Rs1, Re, Rf, Rg1, Rg2, Rh). The point of the difference between PPT and PPV is the position of the carboxyl group⁴⁷. The identified rare components include pentacyclic Olean saponins ginsenoside and saponins ocotillos F11 (24-R-dummy ginsenoside)³⁹.

The quality and composition of ginsenosides are affected by several factors, such as species, age and plant parts, crop production methods, harvest season and conservation methods. For example, ginseng ginsenoside Rf and the unique beauty of American ginseng (F11) is the exclusive composition of American ginseng^{48,49}. The total content of saponins and the therapeutic effect of ginseng on cancer depends on the age of ginseng- 6 years old. Red ginseng is considered to be a more effective drug for cancer treatment. It is made from dried or steamed ginseng^{40,43,50}. For example, ginseng root air drying is an effective way to form red ginseng by steam, thus improving the therapeutic effect. The increase in the medicinal value of ginseng is the cause of these ginsenosides for the treatment of tumors and nasal cancer or other areas⁵¹. The butanol resolvable fraction of ginseng is achieved by the formulation of KG-135 and the prime antitumor ginsenosides.

Bioavailability of ginsenosides: In the human body, research on how the absorption and transport of ginsenosides occur is still elusive. In this method, the energy and sodium-dependent transport of ginsenoside is considered to be complex and the actual mechanism is still unknown^{44,52,53}. An important area of discussion is the effect of ginsenosides on bioavailability and uptake. The bioavailability of ginseng is low and some experiments are under way to assess the bioavailability of ginsenosides⁵⁴. Experimental studies have confirmed that the combination of epinephrine and ginsenosides is an effective method for improving bioavailability and therapeutic benefits, with the use of ginseng for the treatment of nose and other cancers.

Multidrug resistance studies have been described as major barriers associated with the treatment of different types of cancer⁵²⁻⁵⁵. This glycoprotein reduces the efficacy of different therapies because it is resistant to the therapeutic effect of the drug. This method is used for cancer chemotherapy because ginsenoside Rg3 effectively blocks drug efflux and action and the associated mechanism is the activity of P-glycoprotein, resulting in a decrease in cell membrane mobility and inhibition of activity⁵⁶. Those mechanism and benefits are associated with this approach, cancer chemotherapy is used to provide effective support in the treatment⁵⁷. In addition to the known mechanism of ginseng treatment of cancer, some of the ingredients in red ginseng such as Rg3, Rg5 and Rh2 are thought to be effective in inhibiting cancer and can produce synergistic effects for the treatment of nasal cancer⁵⁸. Thus, it is believed that the heat treated red is more effective than normal ginseng and is therefore effective for the prevention and treatment of different types of cancer, including nasal cancer⁵⁹. Another

focus of this study is that ginsenoside is a non-organ-specific cancer clinical trial and therefore needs to describe the efficacy of this drug in the treatment of nasal cancer^{60,61}. There is also a need for clinical trials to determine the pharmacological mechanisms involved in the role of these drugs in the prevention of cancer.

Other active components

Panaxatriol: These are steroids compound that is found in ginseng and are similar to the anabolic steroids present in the human body. This is a safe alternative to being used by athletes instead of using synthetic steroids.

Germanium: This is another active compound that is used for strong hydrogenating impact on different body organs and especially on the liver. The smell of ginseng and the presence of sufficient TCM to determine the quality and effectiveness of the constituents.

Polyacetylene: This is a non-steroid compound that boosts the immune system, is used for preventing thrombosis and inhibiting lipid peroxidation.

Phenolic compounds: Different phenolic compounds are considered as active compounds that are anti-aging and antioxidant.

Acidic polysaccharide: These are well-known because of anti-aging effects and beneficial for reducing the side effects of certain anticancer drugs, immune system and preventing hyperlipidemia.

Insulin analogue: This compound is active and lowers the blood-sugar level. As a result, ginseng plants are being studied to develop antidiabetic drugs.

Ginseng is a novel herbal medicine for treatment of cancer:

As an incomplete antagonistic of different steroid receptors, ginsenoside is a vital public asset that has been made into a new model that may replace the steroid in this procedure to reduce adverse reactions⁶². The bioavailability of ginsenosides and their metabolites may be low and most of these mixtures cannot reach the organic backbone⁶³. In addition, this review highlighted the key role of how ginsenoside changes its application in the mammalian skeleton for the most significant impact, in this way speeding up the treatment. This process will contribute to the expansion of ginsenoside⁵⁴ and will continue to promote ginseng to improve the possibility of clinical application of ginseng⁴³. It is generally believed that

the useful merit of ginseng is ginsenoside, the dynamic parts of ginseng have a great contribution to the adjustment of different physiological ability. Many life forms of activity make ginsenosides the basis for improving another source framework^{64,65}. The low bioavailability of ginsenosides is one of the worst difficulties to overcome, keeping in mind the ultimate goal of increasing its medicinal use.

A review of the different studies associated with the use of ginseng in the treatment of nasal cancer suggests that this traditional Chinese medicine is not only effective in the treatment of nasal cancer but also has an important therapeutic effect on the treatment of cancer in general⁶¹⁻⁶⁶. However, pharmacological systems, methods and mechanisms require further investigation. Red ginseng is thought to be more effective than other forms of treatment, so clinical trials should also compare these two types of benefits⁴⁴ to solve the problems which are associated with the systemic pharmacological and mechanical effects of ginseng and its active ingredients and to open a new treatment door for the treatment of nasal cancer.

CONCLUSION

The oncologist and clinical researchers have suggested the use of a multi-targeted therapy in which the chemotherapeutic agent, as well as traditional Chinese medicine such as ginseng, is used for the treatment of nose cancer disease. Even though there are many pharmacological, therapeutic and safety advantages with both of the two therapies, Chinese traditional medicine is not considered a mainstream drug for the treatment of cancer. Ginseng is an effective traditional medicine that consists of several active ingredients that can cure nose cancer. Despite the many benefits associated with the use of ginseng in the treatment of nasal cancer, the systemic pharmacological effects and targets of the drug remain unclear. In the future, the pharmacology of the system is likely to assess the overall mechanism of the use of these drugs with the help of pharmacological and pharmacokinetic tools. Further studies on the pharmacological system associated with the use of ginseng in the treatment of cancer require further clinical trials.

SIGNIFICANCE STATEMENTS

This study suggested the ginseng herb compound 'ginsenoside' used for Nose cancer disease. Nowadays the nose cancer is an alarming health complaint and that requires scientific attention to find out the effectiveness either need a safe pharmacological approach to overcome this issue.

ACKNOWLEDGMENTS

All the authors of the manuscript are immensely grateful to their respective universities and institutes for their technical assistance and valuable support in the completion of this research project. This study was supported by Grants from Northwest A & F University, National Natural Science Foundation of China (31170796 and 81373892, respectively). It was also supported in part by Grants from National Natural Science Foundation of China (31540008).

REFERENCES

1. Edwards, B.K., A.M. Noone, A.B. Mariotto, E.P. Simard and F.P. Boscoe *et al*, 2014. Annual report to the nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*, 120: 1290-1314.
2. Haldorsen, T., J.I. Martinsen, K. Kjaerheim and T.K. Grimsrud, 2017. Adjustment for tobacco smoking and alcohol consumption by simultaneous analysis of several types of cancer. *Cancer Causes Control*, 28: 155-165.
3. Rosen, L.S., M.S. Gordon, F. Robert and D.E. Matei, 2014. Endoglin for targeted cancer treatment. *Curr. Oncol. Rep.*, Vol. 16. 10.1007/s11912-013-0365-x.
4. Hoppe, B.S., L.D. Stegman, M.J. Zelefsky, K.E. Rosenzweig and S.L. Wolden *et al*, 2007. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting: The MSKCC experience. *Int. J. Radiat. Oncol. Biol. Phys.*, 67: 691-702.
5. Alexis, F., J.W. Rhee, J.P. Richie, A.F. Radovic-Moreno, R. Langer and O.C. Farokhzad, 2008. New frontiers in nanotechnology for cancer treatment. *Urol. Oncol.*, 26: 74-85.
6. Widakowich, C., G. de Castro, Jr., E. de Azambuja, P. Dinh and A. Awada, 2007. Review: Side effects of approved molecular targeted therapies in solid cancers. *Oncologist*, 12: 1443-1455.
7. Tao, L., F. Zhu, C. Qin, C. Zhang and F. Xu *et al*, 2014. Nature's contribution to today's pharmacopeia. *Nature Biotechnol.*, 32: 979-980.
8. Hemmerly, T.E., 1977. A ginseng farm in Lawrence county, Tennessee. *Econ. Bot.*, 31: 160-162.
9. Dharmananda, S., 2002. The nature of ginseng: From traditional use to modern research. *J. Am. Bot. Council*, 54: 341-354.
10. Park, J.D., 1996. Recent studies on the chemical constituents of Korean ginseng (*Panax ginseng* C.A. Meyer). *Korean J. Ginseng Sci.*, 20: 389-415.
11. Yokozawa, T., T. Kobayashi, H. Oura and Y. Kawashima, 1985. Studies on the mechanism of the hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats. *Chem. Pharm. Bull.*, 33: 869-872.

12. Matsunaga, H., M. Katano, H. Yamamoto, M. Mori and K. Takata, 1989. Studies on the panaxytriol of *Panax ginseng* C.A. Meyer: Isolation, determination and antitumor activity. Chem. Pharm. Bull., 37: 1279-1281.
13. Suh, D.Y., Y.N. Han and B.H. Han, 1996. Maltol, an antioxidant component of Korean red ginseng, shows little prooxidant activity. Arch. Pharm. Res., 19: 112-115.
14. Kim, C.M. and G.S. Han, 1985. Radioprotective effects of ginseng proteins. Yakhak Hoeji, 29: 246-252.
15. Jie, Y.H., S. Cammisuli and M. Baggiolini, 1984. Immunomodulatory effects of *Panax Ginseng* C.A. Meyer in the mouse. Agents Actions, 15: 386-391.
16. Shibata, S., O. Tanaka, T. Ando, M. Sado, S. Tsushima and T. Ohsawa, 1966. Chemical studies on oriental plant drugs. XIV. Protopanaxadiol, a genuine sapogenin of ginseng saponins. Chem. Pharm. Bull., 14: 595-600.
17. Amato, P., S. Christophe and P.L. Mellon, 2002. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause, 9: 145-150.
18. Ru, J., P. Li, J. Wang, W. Zhou and B. Li *et al.*, 2014. TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. J. Cheminform., Vol. 13. 10.1186/1758-2946-6-13.
19. Yun, T.K., 2001. *Panax ginseng*: A non-organ-specific cancer preventive? Lancet Oncol., 2: 49-55.
20. Christensen, L.P., 2008. Ginsenosides: Chemistry, biosynthesis, analysis and potential health effects. Adv. Food Nutr. Res., 55: 1-99.
21. Yun, T.K., Y.S. Lee, Y.H. Lee, S.I. Kim and H.Y. Yun, 2001. Anticarcinogenic effect of *Panax ginseng* C.A. Meyer and identification of active compounds. J. Korean Med. Sci., 16: S6-S18.
22. Lee, Y., Y. Jin, W. Lim, S. Ji, S. Choi, S. Jang and S. Lee, 2003. A ginsenoside-Rh1, a component of ginseng saponin, activates estrogen receptor in human breast carcinoma MCF-7 cells. J. Steroid Biochem. Mol. Biol., 84: 463-468.
23. Kim, Y.J., H.C. Kwon, H. Ko, J.H. Park, H.Y. Kim, J.H. Yoo and H.O. Yang, 2008. Anti-tumor activity of the ginsenoside Rk1 in human hepatocellular carcinoma cells through inhibition of telomerase activity and induction of apoptosis. Biol. Pharm. Bull., 31: 826-830.
24. Binazzi, A., P. Ferrante and A. Marinaccio, 2015. Occupational exposure and sinonasal cancer: A systematic review and meta-analysis. BMC Cancer, Vol. 15. 10.1186/s12885-015-1042-2.
25. PDQATE Board, 2015. Paranasal sinus and nasal cavity cancer treatment (PDQ®). National Cancer Institute, USA.
26. Eskander, A., M. Merdad, J.C. Irish, S.F. Hall and P.A. Groome *et al.*, 2014. Volume-outcome associations in head and neck cancer treatment: A systematic review and meta analysis. Head Neck, 36: 1820-1834.
27. Leung, K.W., F.P. Leung, N.K. Mak, J. Tombran Tink, Y. Huang and R.N. Wong, 2009. Protopanaxadiol and protopanaxatriol bind to glucocorticoid and oestrogen receptors in endothelial cells. Br. J. Pharmacol., 156: 626-637.
28. Furukawa, T., C.X. Bai, A. Kaihara, E. Ozaki and T. Kawano *et al.*, 2006. Ginsenoside Re, a main phytosterol of *Panax ginseng*, activates cardiac potassium channels via a nongenomic pathway of sex hormones. Mol. Pharmacol., 70: 1916-1924.
29. Gao, Q.G., W.F. Chen, J.X. Xie and M.S. Wong, 2009. Ginsenoside Rg1 protects against 6 OHDA induced neurotoxicity in neuroblastoma SK N SH cells via IGF I receptor and estrogen receptor pathways. J. Neurochem., 109: 1338-1347.
30. Leung, K.W., F.P. Leung, Y. Huang, N.K. Mak and R.N. Wong, 2007. Non genomic effects of ginsenoside Re in endothelial cells via glucocorticoid receptor. FEBS Lett., 581: 2423-2428.
31. Brannon-Peppas, L. and J.O. Blanchette, 2004. Nanoparticle and targeted systems for cancer therapy. Adv. Drug Deliv. Rev., 56: 1649-1659.
32. Leung, K.W., Y.K. Cheng, N.K. Mak, K.K. Chan, T.P. Fan and R.N. Wong, 2006. Signaling pathway of ginsenoside-Rg1 leading to nitric oxide production in endothelial cells. FEBS Lett., 580: 3211-3216.
33. Qi, L.W., C.Z. Wang and C.S. Yuan, 2011. Isolation and analysis of ginseng: Advances and challenges. Natural Prod. Rep., 28: 467-495.
34. Hofseth, L.J. and M.J. Wargovich, 2007. Inflammation, cancer and targets of ginseng. J. Nutr., 137: 1835-1855.
35. Yun, T.K., S.Y. Choi and H.Y. Yun, 2001. Epidemiological study on cancer prevention by ginseng: Are all kinds of cancers preventable by ginseng. J. Korean Med. Sci., 16: S19-S27.
36. Choi, S., S.Y. Jung, J.H. Lee, F. Sala and M. Criado *et al.*, 2002. Effects of ginsenosides, active components of ginseng, on nicotinic acetylcholine receptors expressed in *Xenopus oocytes*. Eur. J. Pharmacol., 442: 37-45.
37. Kwon, H.Y., E.H. Kim, S.W. Kim, S.N. Kim, J.D. Park and D.K. Rhee, 2008. Selective toxicity of ginsenoside Rg3 on multidrug resistant cells by membrane fluidity modulation. Arch. Pharm. Res., 31: 171-177.
38. Leung, K.W. and A.S.T. Wong, 2010. Pharmacology of ginsenosides: A literature review. Chin. Med., Vol. 5. 10.1186/1749-8546-5-20.
39. Spelman, K., J. Burns, D. Nichols, N. Winters, S. Ottersberg and M. Tenborg, 2006. Modulation of cytokine expression by traditional medicines: A review of herbal immunomodulators. Altern. Med. Rev., 11: 128-150.
40. Kim, S.W., H.Y. Kwon, D.W. Chi, J.H. Shim and J.D. Park *et al.*, 2003. Reversal of P-glycoprotein-mediated multidrug resistance by ginsenoside Rg3. Biochem. Pharmacol., 65: 75-82.

41. Chang, T.K., J. Chen and S.A. Benetton, 2002. *In vitro* effect of standardized ginseng extracts and individual ginsenosides on the catalytic activity of human CYP1A1, CYP1A2 and CYP1B1. *Drug Metab. Dispos.*, 30: 378-384.
42. Schlag, E.M. and M.S. McIntosh, 2006. Ginsenoside content and variation among and within American ginseng (*Panax quinquefolius* L.) populations. *Phytochemistry*, 67: 1510-1519.
43. Fu, Y., Y. Wang and B. Zhang, 2014. Systems pharmacology for traditional Chinese medicine with application to cardio-cerebrovascular diseases. *J. Trad. Chinese Med. Sci.*, 1: 84-91.
44. Chen, X.W., K.B. Sneed, S.Y. Pan, C. Cao, J.R. Kanwar, H. Chew and S.F. Zhou, 2012. Herb-drug interactions and mechanistic and clinical considerations. *Curr. Drug Metab.*, 13: 640-651.
45. Harnack, L.J., S.A. Rydell and J. Stang, 2001. Prevalence of use of herbal products by adults in the Minneapolis/St Paul, Minn, metropolitan area. *Mayo Clin. Proc.*, 76: 688-694.
46. Li, P., Y. Fu and Y. Wang, 2015. Network based approach to drug discovery: A mini review. *Mini Rev. Med. Chem.*, 15: 687-695.
47. Zhang, W., Y. Bai, Y. Wang and W. Xiao, 2016. Polypharmacology in drug discovery: A review from systems pharmacology perspective. *Curr. Pharm. Design*, 22: 3171-3181.
48. Xiang, Y.Z., H.C. Shang, X.M. Gao and B.L. Zhang, 2008. A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials. *Phytother. Res.*, 22: 851-858.
49. Lim, W., K.W. Mudge and F. Vermeylen, 2005. Effects of population, age and cultivation methods on ginsenoside content of wild American ginseng (*Panax quinquefolium*). *J. Agric. Food Chem.*, 53: 84898-8505.
50. Zheng, C., T. Pei, C. Huang, X. Chen and Y. Bai *et al.*, 2016. A novel systems pharmacology platform to dissect action mechanisms of traditional Chinese medicines for bovine viral diarrhea disease. *Eur. J. Pharm. Sci.*, 94: 33-45.
51. Li, W., C. Gu, H. Zhang, D.V. Awang, J.F. Fitzloff, H.H. Fong and R.B. van Breemen, 2000. Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish *Panax ginseng* C.A. Meyer (Asian Ginseng) and *Panax quinquefolius* L. (North American ginseng). *Anal. Chem.*, 72: 5417-5422.
52. Assinewe, V.A., B.R. Baum, D. Gagnon and J.T. Arnason, 2003. Phytochemistry of wild populations of *Panax quinquefolius* L. (North American ginseng). *J. Agric. Food Chem.*, 51: 4549-4553.
53. Liu, J., J. Mu, C. Zheng, X. Chen and Z. Guo *et al.*, 2016. Systems-pharmacology dissection of traditional chinese medicine compound saffron formula reveals multi-scale treatment strategy for cardiovascular diseases. *Scient. Rep.*, Vol. 6. 10.1038/srep19809.
54. Xiong, J., M. Sun, J. Guo, L. Huang, S. Wang, B. Meng and Q. Ping, 2009. Enhancement by adrenaline of ginsenoside Rg1 transport in Caco 2 cells and oral absorption in rats. *J. Pharm. Pharmacol.*, 61: 347-352.
55. Han, M., X. Sha, Y. Wu and X. Fang, 2006. Oral absorption of ginsenoside Rb1 using *in vitro* and *in vivo* models. *Planta Med.*, 72: 398-404.
56. Chi, H. and G.E. Ji, 2005. Transformation of ginsenosides Rb1 and Re from *Panax ginseng* by food microorganisms. *Biotechnol. Lett.*, 27: 765-771.
57. Kaneko, H. and K. Nakanishi, 2004. Proof of the mysterious efficacy of ginseng: Basic and clinical trials. Clinical effects of medical ginseng, Korean red ginseng. Specifically, its anti-stress action for prevention of disease. *J. Pharmacol. Sci.*, 95: 158-162.
58. Xiong, J., J. Guo, L. Huang, B. Meng and Q. Ping, 2008. The use of lipid-based formulations to increase the oral bioavailability of *Panax notoginseng* saponins following a single oral gavage to rats. *Drug Dev. Ind. Pharm.*, 34: 65-72.
59. Kwon, S.W., S.B. Han, I.H. Park, J.M. Kim, M.K. Park and J.H. Park, 2001. Liquid chromatographic determination of less polar ginsenosides in processed ginseng. *J. Chromatogr. A*, 921: 335-339.
60. Liu, W.K., S.X. Xu and C.T. Che, 2000. Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. *Life Sci.*, 67: 1297-1306.
61. Xu, T.M., Y. Xin, M.H. Cui, X. Jiang and L.P. Gu, 2007. Inhibitory effect of ginsenoside Rg3 combined with cyclophosphamide on growth and angiogenesis of ovarian cancer. *Chin. Med. J.*, 120: 584-588.
62. Yoo, J.H., H.C. Kwon, Y.J. Kim, J.H. Park and H.O. Yang, 2010. KG-135, enriched with selected ginsenosides, inhibits the proliferation of human prostate cancer cells in culture and inhibits xenograft growth in athymic mice. *Cancer Lett.*, 289: 99-110.
63. Park, S. A., E.H. Kim, H.K. Na and Y.J. Surh, 2007. KG 135 inhibits COX 2 expression by blocking the activation of JNK and AP 1 in phorbol ester-stimulated human breast epithelial cells. *Ann. NY Acad. Sci.*, 1095: 545-553.
64. Hall, T., Z.Z. Lu, P.N. Yat, J.F. Fitzloff and J.T. Arnason *et al.*, 2001. Evaluation of consistency of standardized Asian ginseng products in the ginseng evaluation program. *Herbal Gram*, 52: 31-45.
65. Cui, W., L. Cheng, C. Hu, H. Li, Y. Zhang and J. Chang, 2013. Electrospun poly (L-lactide) fiber with ginsenoside Rg3 for inhibiting scar hyperplasia of skin. *PloS One*, Vol. 8. 10.1371/journal.pone.0068771.
66. Tanaka, H., N. Fukuda and Y. Shoyama, 1999. Formation of monoclonal antibody against a major ginseng component, ginsenoside Rb1 and its characterization. *Cytotechnology*, 29: 115-120.