CLINICAL RESEARCH PROGRESS OF GINSENOSIDE RG3 ON ANTI-TUMOR EFFECT

Yang Lan[1], Jenny Chen Jie[2], Jiang Mingqiang[3], Zhang Jiong[4], Brian Sheng-Xian Teo[1,2*]

[1]School of Graduate Studies, Management and Science University, University Drive, Off Persiaran Olahraga, Section 13, 40100 Shah Alam, Selangor Darul Ehsan, Malaysia. yl181890@gmail.com
[2]MSU Centre for Complementary and Alternative Medicine (MyCAM), Management and Science University, University Drive, Off Persiaran Olahraga, Section 13, 40100 Shah Alam, Selangor Darul Ehsan, Malaysia.chen_ji@msu.edu.my
[3]The First Affiliated Hospital of ZhengZhou University, 1 Longhuzhonghuan Road, Jinshui District, 450003 Zhengzhou, Henan, China.jiangmingqiang0418@gmail.com
[4]Henan University of Traditional Chinese Medicine, 1 Renmin Road, Jinshui District, 450000 Zhengzhou, Henan, China.824935622@qq.com
[1,2*]Corresponding author: brian_teo@msu.edu.my

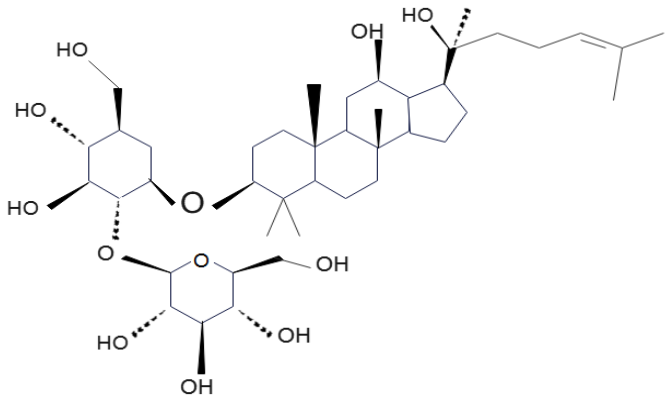
Abstract: Since ancient times in China, ginseng has been a valuable natural Chinese medicinal material. Ginseng has the ability to replenish vitality, stimulate the spleen, increase blood circulation, sooth the nerves and enhance the sleep quality etc. It is well-liked among the wider populace as a health care product, and it operates well as a medicine to treat diseases in sufferers. As the main active substance of ginseng, ginsenoside has the effect of inhibiting tumor cell metastasis, improving immunity and promoting blood circulation. Ginsenoside Rg3 is currently a hot spot in the field of medical research, and a large number of anti-tumor mechanisms have been confirmed. This article summarizes the analysis of the anti-tumor therapeutic effect of ginsenoside Rg3 in the treatment of breast, lung, liver, gastric and colon cancer by reading a large number of papers in recent years. The research on the ginsenoside Rg3 chemical components and its anti-tumor pharmacological properties was reviewed. This paper summarizes the research of ginsenoside Rg3 on the treatment of various tumors, offers the theoretical foundation for further study as well as the basis for the drug's comprehensive development and use which supports the advancement of traditional Chinese medicine.

Keywords: Ginsenoside Rg3; Anti-cancer; Traditional Chinese Medicine; Natural Medicine

Introduction

In modern medicine, cancer occupies a prominent place among the most common diseases. Pain is its most common manifestation, which can seriously threaten and damage the patient's sound body and mind. In actual practice, the two most prevalent types of treatment are surgery and chemotherapy, but the outcomes are generally dismal. The development of new drugs has become an urgent means to improve this situation. Ginseng, as traditional Chinese medicine, improves sleep, immunity, and anti-tumor (Gao & Lv, 2021). Ginsenosides are the main active

compounds in ginseng (Li & Li, 2020). The anti-tumor work of Rg2, Rg3, Rh2, and CK along with other active ingredients is today broader and more in-depth, notably Rg3. Ginsenoside Rg3 is a tetracyclic triterpenoid saponin, it is a trace component in processed products made of fresh ginseng after steaming and drying (Fan, 2018). It has a range of pharmacological actions, including boosting cancer cell apoptosis, lowering chemotherapy toxicity, reversing malignant cells drug resistance, and improving body immunity (Su & Zhang, 2017). The primary focus of this paper's examination of the most recent China and worldwide literature reports are the advancement of research into the pharmacological properties of anti-cancer prescription drugs and the mechanisms of ginsenoside Rg3.



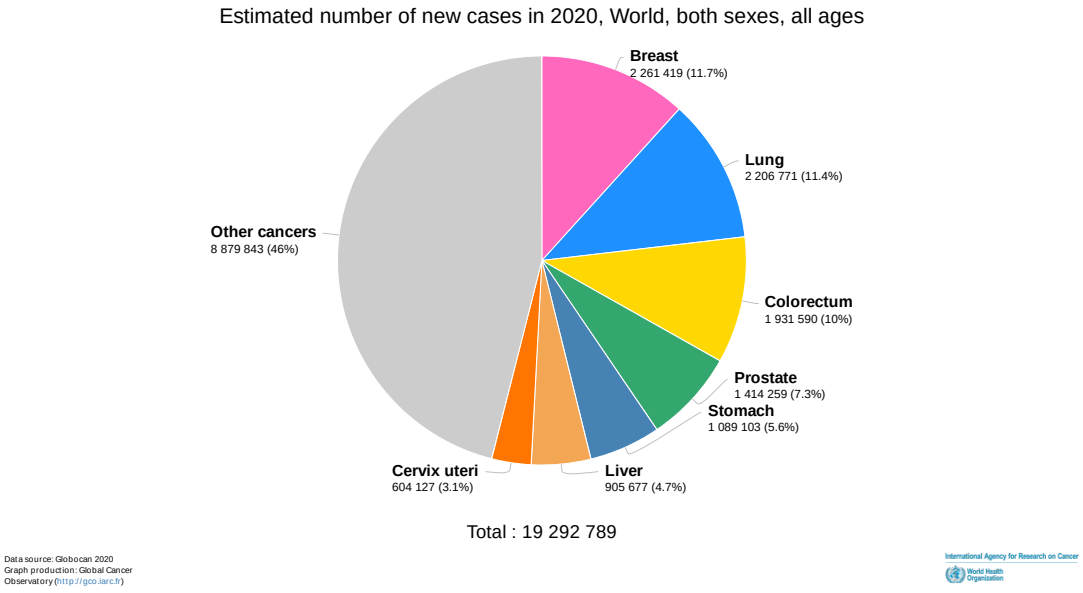
Picture 1 Structure of Ginsenoside Rg3

1. Anti-breast cancer

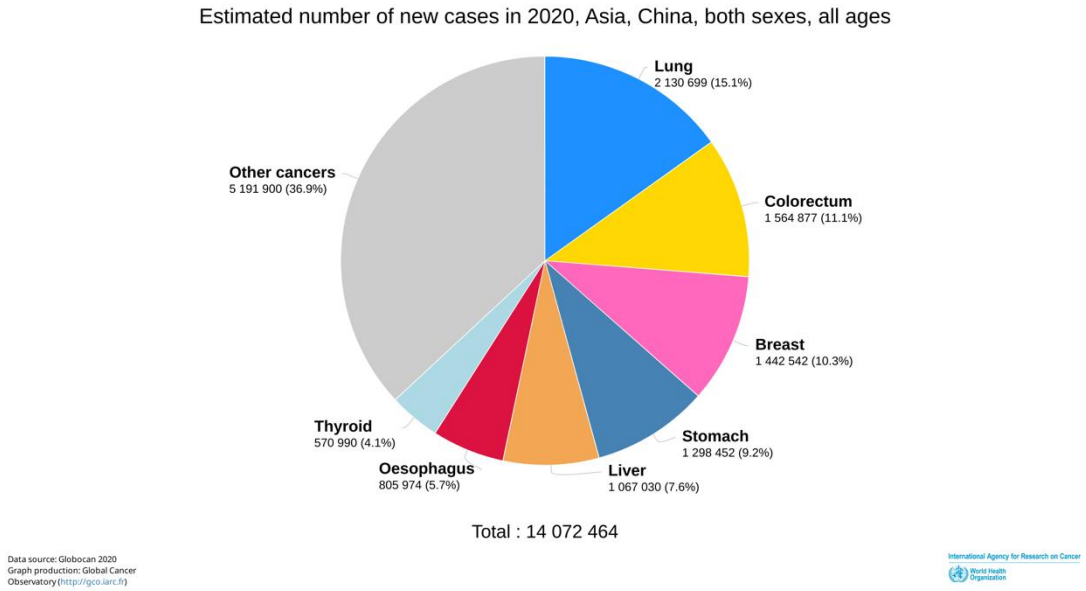
Being the most prevalent pathological cancer in women, breast cancer is expanding yearly, posing the biggest risk in the world, with the greatest mortality rate among female tumors, and having a real young trend (International Agency for Research on Cancer, 2023). Jiao, Meng, Qiao, & Shan observed a comparative test of 96 advanced breast cancer patients split into 2 groups, they discovered that people diagnosed with chemotherapy with ginsenoside Rg3 had greater effectiveness than those treated with chemotherapy alone, in comparison with the control group, its therapeutic remission rate was 43.7% bigger and the rate of adverse events was 20.9% lower; and ginsenoside Rg3 can diminish a patient's serum levels of VEGF (vascular endothelial growth factor) (Jiao, Meng, Qiao, & Shan, 2017). Through a series of tests, Sun, Gu, Li, & Zhang discovered that the addition of the ginsenoside Rg3 can drastically affect MDA-MB-231 breast cancer cells' capacity for expansion and boost their death, with a dose-dependent effect. They hypothesize that its mode of action may involve enhancing the activity of CSE, a crucial enzyme for the synthesis of endogenous H2S in breast cancer cells, by boosting the production of MGBA (mammaglobin-A), played an anti-tumor effect (Sun, Gu, Li, & Zhang, 2017). The same year, the experimental results of Li, Chen, Liang, & Wang cleared that RH-ES combined with ginsenoside Rg3 significantly blocked cells in a period of phase in G_0/and S stations, reduced VEGF mRNA, MMP-2 and MMP-9 proteins express, thereby inhibited the tumor cells proliferate, and its effect was better than using

ginsenoside Rg3 and RH-ES alone (Li, Chen, Liang, & Wang, 2017).

The following year, Guo, Yuan, & Guo examined the anti-tumor effect of ginsenoside Rg3 by using MDA-MB-231 breast cancer cells and discovered that ginsenoside Rg3 displayed an inhibitory effect on tumor cell multiplication in MTT assay and cell scratching assay, and had a dependence on time and dose within a certain range relationship (Guo, Yuan, & Guo, 2018). Dai & Wang initially explored the ways in which ginsenoside Rg3 controls mutation and apoptosis in MDA-MB-453 breast cancer cells. The findings indicates that ginsenoside Rg3 altered MDA-MB-453 cells, and it was discovered that ginsenoside Rg3 could limit tumor cell growth in a concentration-dependent manner, halt tumor cell division in the G_2/M phase, and enhance tumor cell apoptosis ratio; simultaneously, both p-STAT3 and Cylin D1 were decreased in tumor cells, thus conjecturing that ginsenoside Rg3 may reach anti-tumor efficacy by down-regulation of STAT3 signaling pathway (Dai & Wang, 2020). In the meantime, Jiang & Sun adopted different concentrations of ginsenoside Rg3 to handle MCF-7 human breast cancer cells by CCK-8 experimental method, flow cytometry, and other experiments, ginsenoside Rg3 had a considerable effect on MCF-7 human breast cancer cells, where it could dose-concentration-dependently affect tumor cell arrest in the G_2 phase and deter their proliferation (Jiang & Sun, 2020).



Picture 2 Estimated Number of New Cases of cancers in the World in 2020



Picture 3 Estimated Number of New Cases of Lung cancer in China in 2020

2. Anti-lung cancer

Lung cancer is the most prevalent cancer in China, poses a serious threat to human life, and may have the second-highest risk of dying of all malignancies, which ranks first in terms of morbidity rate of malignant tumors (International Agency for Research on Cancer, 2023). Nevertheless, research on lung cancer has not yet clarified its etiological mechanism. The most prevalent type of lung cancer is non-small cell lung cancer (NSCLC). Shi looked at the antitumor feature of ginsenoside Rg3 capsules based on a controlled clinical study of its therapeutic benefits in patients with non-small cell lung cancer, these 62 instances were split into two groups: those who took ginsenoside Rg3 capsules and those who did not. The experiment showed significant effects that the KPS score, CD3+, CD4+, CD4+/CD8+ cell levels in the treatment group were better than that in the chemotherapy group, meanwhile, in treatment group, levels of TGF-β1, VEGF, and CD8+ cells were clearly shorter than chemotherapy group. Ginsenoside Rg3 capsule can impact the level of VEGF and TGF-β1 and the subpopulation of T-lymphocytes during chemotherapy, adjust the immune functionalities of patients, down the ECM and hence restrain the endothelial cell propagation of tumor (Shi, 2018). Jiang et al. then divided 60 cases of generation EGFR-TKI-resistant late-stage non-small cell lung cancer gathered into 2 groups for analysis of the pharmacological clinical outcomes. The studies revealed that patients who received ginsenoside Rg3 together with osimertinib scored much better on the quality-of-life scale than those who received osimertinib alone. Results of the study showed that ginsenoside Rg3 in combination with chemotherapy positively affects patients' quality-of-life (Jiang et al., 2019).

Zhou, Zhou, He, & Xiong looked into the impact of ginsenoside Rg3 on A549 lung cancer cells via the ROS pathway, the study measured significantly elevated ROS levels and tumor cell apoptosis rates in the experimental group with the addition of ginsenoside Rg3 by using experimental methods such as MTT method and flow cytometry. Bcl-2 expression was substantially lower in the treatment group compared

to the control group, while Bax, caspase-3, and caspase-9 mRNA expression levels were all noticeably greater than control group in a concentration-dependent pattern (Zhou, Zhou, He, & Xiong, 2018). Yet, Tao, Wang, Li, & Li discovered that mice using ginsenoside Rg3 had dropped tumor volume, tumor mass, and lymphatic spread in the well-established lung cancer nude mouse model. In the meantime, it was also found to suppress p-ERK/ERK expression and decrease lymphangiogenesis by down-regulating the transactivation level of TGF-β1/ERK signaling pathway, thus restraining the performance of VEGF (Tao, Wang, Li, & Li, 2019). In 2019, Lin, Wang, & Xu observed the response of ginsenoside Rg3 in combination with apatinib on CD8+ T cells and other immune-related factors in Lewis lung cancer mouse model through immunomodulatory pathway. They also found that ginsenoside Rg3 combined with lapatinib was identified to enhance ICOS activation and inhibit tumor outgrowth by boosting the immune defense of lymphocytes (Lin, Wang, & Xu, 2019). Wang et al. assessed the impact of ginsenoside Rg3 on the immune system of Lewis lung cancer model rats, along with the effect of ginsenoside Rg3 on PD-L1 manifestation utilising MTT, flow cytometry, immunofluorescence assay and western blotting. The findings demonstrated that ginsenoside Rg3 could strengthen the killing capacity of T cells and further restrain the proliferation and metastasis of LLC tumor cells by impacting the PI3K/Akt/m TOR pathway, which had a strong link with the expression of PD-L1 (Wang et al., 2019).

3. Anti-liver cancer

Hepatocellular carcinoma is among the world's most endemic and long-plagued clinical practice malignancies. China is a high prevalence region for liver cancer, and its new cases constitute about 45% of the worldwide (China Cancer Center-National Tumor Quality Control Center Liver Cancer Quality Control Expert Committee, 2022). Hepatitis B virus illness and aflatoxin-contaminated food are its key risk factors, and patients are mostly in the intermediate and late-stage at the time of diagnosis, with geographical variations (Guidelines for the screening of liver cancer in Chinese population, 2022). Therefore, the search for appropriate therapies for Chinese liver cancer patients is the present direction to be pursued. Zhang, Zhang, Chen, Wang, & Yu established a nude mouse xenograft model, looked into the effects of paclitaxel and ginsenoside Rg3 on HepG2 hepatoma cells by using MTT and Western Blot. It was shown that the treatment group (paclitaxel + ginsenoside Rg3) could affect the Caspase-3 and Bac-2/Bax values and facilitate hepatocellular carcinoma cell apoptosis, and the anti-tumor cell proliferation effect was clearly better than that in the groups of single ginsenoside Rg3 drug and single paclitaxel drug, and it had time-dependent (Zhang, Zhang, Chen, Wang, & Yu, 2020). Yi et al. added ginsenoside Rg3 and tumorstatin 19 peptides to observe its anti-tumor effect on hepatoma cells HepG2. Using flow cytometry, Western Bolt, CCK-8, Hoechst33342 staining, and other experimental methods, observed the combination group (ginsenoside Rg3+ tumorstatin 19 peptides) had significantly higher tumor cell apoptosis rate, caspase-3, and caspase-9 activity than ginsenoside Rg3 group and tumorstatin 19 peptide group. It also expressed synergistic interactions in the PTEN/P13K/Akt signaling pathway, which had a more pronounced pro-apoptotic effect on hepatocellular carcinoma cells (Yi et al., 2020). The same year, Zhou also observed the effect of 20(R)-ginsenoside Rg3 on liver

and kidney injury in mice models under the P13K/AKT signaling pathway. In the exploration of Western Blot, HE is staining, immunofluorescence staining, and other experimental methods, they found that 20(R)-ginsenoside Rg3 could regulate Bcl-2/Bax express and NF-κB pathway-related proteins, thereby influencing tumor-related cells apoptosis upgrade and liver and kidney tissues have been improved by structural degeneration (Zhou, 2019). A key part in controlling the cell cycle is played by the oncogene p16. Zhan identified that in SMMC-7721 liver cancer cells, factors can be attributed to 20(S) ginsenoside Rg3 decreased the manufacturing of p16. 20(S)-ginsenoside Rg3 group was detected utilizing cell scratch test, PCR method, Western Blot method, etc. when compared to control group. It had clearly effect on hepatoma cell SMMC-7721 proliferation, and it was influenced by time and dose when they fell within a specified range; in SMMC-7721 cells,20(S)-ginsenoside Rg3 can also lessen the methylation level of the p16 promoter and influenced p16INK4a protein express upgrade in SMMC-7721 cells, which had an obvious anti-tumor effect (Zhan, 2019).

4. Anti-gastric cancer

One of the most frequently encountered tumors in China is gastric cancer, largely coupled with food habits and H. pylori infection (Yang et al., 2021). In clinical trials, Sun observed the efficacy of neoadjuvant chemotherapy in two groups of 74 patients with or without ginsenoside Rg3 to understand its immune effect on patients with gastric cancer. The study's outcomes disclosed that the CD3+, CD4+, and CD4+/CD8+ values, alongside the rate of T lymphocyte transformation, and survival rate of the combined treatment group (ginsenoside Rg3+ neoadjuvant chemotherapy) after treatment were clearly higher than that in neoadjuvant chemotherapy group; whereas, the quality of CD8+ cells was vastly shorter than in the neoadjuvant chemotherapy group. Experiments have shown that ginsenoside Rg3 had a significant influence on the patients' immune function during neoadjuvant chemotherapy and it also can enhance their survival rate (Sun et al., 2020). The next year, Zheng, Wang, & Xu selected 104 patients for the treatment to explore the drug efficacy in advanced gastric cancer patients who were treated by XELOX (capecitabine + oxaliplatin) regimen treatment or added ginsenoside Rg3. In the study, the level of CD3+, CD4+, CD4+/CD8+ cell and patients' survival time in the combined treatment group (ginsenoside Rg3+XELOX) had clearly good effects that in the single XELOX group, the CEA and TNF-α levels were where lower in the XELOX group as a whole. The information demonstrated that employing ginsenoside Rg3 in conjunction with XELOX therapy could extend patient survival (Zheng, Wang, & Xu, 2021).

In cellular experiments, Wang, Hun, Wang, & Chen observed the treatment study on gastric cancer SNU-216 cells growth rate in *vitro* by ginsenoside Rg3. In the MTT method, it could be seen that the ginsenoside Rg3 group has a significantly stronger inhibitory effect on gastric cancer cells than the control group, and its effect was concentration-dependent, it can reduce gastric cancer cells' growth rate (Wang, Hun, Wang, & Chen, 2019). However, Lou, Hu, Zhang, & Yuan used some treatment methods, such as Western Blot, MTT, PCR, and CCK-8 to observe the effect of ginsenoside Rg3 on SGC-7901 gastric cancer cells. The research showed that LncRNA

CDKN2B-AS1(Long-stranded non-coding RNA currently being studied more in gastric cancer), VEGF, N-cadherin, Bcl-2 and ERK1/2, p-ERK1/2, MMP-9, and cell proliferation output were slightly lesser in the experimental group compared to the blank control group; Bax and E-cadherin transcription were both elevated, as well as the pace at which cells generate more gradually. Ginsenoside Rg3 was discovered in studies to have an anti-tumor impact by reducing the proliferation of gastric cancer cells (Lou, Hu, Zhang, & Yuan, 2020).

5. Anti-colon cancer

It was detected that ginsenoside Rg3 has a suppressant effect on colon cancer cells by mechanisms such as induction of apoptosis and restraint of cell growth and emigration (Song, Liu, Li, Yang, & Wang, 2015). In the experiment, ginsenoside Rg3 had an effect on colorectal cancer cells apoptosis, Sun et al. observed that ginsenoside Rg3 can reduce Bcl-2 expression and increase the expression of Bax by high-performance liquid chromatography, flow cytometry, PCR, Western Blot, and other experimental methods. It can significantly inhibit colorectal cancer cell proliferation in dependence on time and dose within a certain range and has a good anti-tumor effect (Sun et al., 2021). The other side, Wang & Li observed the effect of ginsenoside Rg3 on human intestinal cancer cells LOVO by using Transwell, CCK-8, and Western Blot. The statistics revealed that in the test group compared to the control group, cancer cell movement and growth were strongly and concentration-dependently decreased; upregulated E-cadherin expression was linked to the protein's anti-tumor properties (Wang & Li, 2018). Tang established the model of nude mouse xenograft in the experiment to explore its inhibition of rectal cancer by ginsenoside Rg3 and adopted the MTT method, cell scratch test, PCR method, flow cytometry, and immunohistochemistry. It was found that ginsenoside Rg3 can be a part of anti-rectal cancer by reducing tumor angiogenesis-related genes express (B7-H1 and B7-H3) improving the drug effects of fluorouracil, oxaliplatin and body's immunity (Tang, 2018). In a clinical observation experiment, Zhu & Gao selected 89 patients with stage III colon cancer as the research objects to observe the effect of ginsenoside Rg3 adjuvant therapy. After a brief course of treatment, it was discovered that the ginsenoside Rg3 adjuvant treatment group had much superior results than the control group (fluorouracil + folinate calcium + oxaliplatin); quality-of-life, IL-2, IFN-γ and TNF-α levels were markedly greater in treatment group compared to control group; while VEGF, p53, IL-4, IL-6, IL-10, and IL-10 levels were substantially lower (Zhu & Gao, 2021).

6. Other cancers

In addition to the above cancer treatment in which ginsenoside Rg3 acted as a noticeable healing power, and in other cancer trials, Huang et al. found in the experiment that ginsenoside Rg3 acts on renal cancer cells, they observed that ginsenoside Rg3 could significantly down-regulate the expression of indoleamine-2,3-dioxygenase in dendritic cells (DC) by flow cytometry, qPCR, ELISA, CCK-8, and other experimental methods. At a particular range, it altered the expression of IL-12 and IFN- levels in mouse bone marrow cells in relation to time and dose, and it

had an influence on killing mouse renal cancer cells (Huang et al., 2021). Yuan used flow cytometry, ELISA method, Western Blot method, Transwell method, and CCK-8 method to observe ginsenoside Rg3 effects on renal tumor cells in RAG mice. These tests revealed that ginsenoside Rg3 can limit the proliferation and metastasis of RAG in mice renal tumor cells and strengthen the cellular immune response driven by DC-activated CTL (cytotoxic T lymphocytes) (Yuan, 2020). Ginsenoside Rg3 could up-regulate Caspase-3 and Caspase-9 protein expression and down-regulate Bcl-2 protein expression, according to studies using CCK-8, flow cytometry, and Western Blot. Ginsenoside Rg3 also had consequences on the emergence and advancement of SKOV-3/DDP cells, and there was a reliance on time and dose within a certain range (Li, 2021). Guo & Lin investigated the effects of subcutaneous transplantation of new blood vessels in pancreatic cancer-stricken naked mice in order to investigate the impact of ginsenoside Rg3 by qRT-PCR, Western Blot, and immunohistochemistry. The experimental results indicated that ginsenoside Rg3 had an influence on the expression of VE-cadherin, EphA2 mRNA, and protein, thereby reduced the formation of new blood vessels in pancreatic cancer subcutaneous transplantation naked mice (Guo & Lin, 2021).

Liu found in his research the molecular mechanism of ginsenoside Rg3 on human osteosarcoma cells. In this study, a series of experimental methods such as MTT assay, flow cytometry, cell scratch assay, Transwell method, Western blot, quantitative PCR, and small interfering RNA showed that ginsenoside Rg3 can affect the P13K/Akt/TOPC1 signaling pathway to enhance cancer cells apoptosis, it can also reduce cancer cells proliferate by activating p53/p21 to control the expression of cyclinD1, CDK-4, and CDK-6 (Liu, 2020). Guo, Guo, Zhang, Liu, & Quan observed the immune effects of ginsenoside Rg3 and PD-1 inhibitors on diffuse large B-cell lymphoma (DLBCL) in *vitro*. The experimental results showed that DLBCL cells can inhibit tumor cell apoptosis and improve the immune T cells proliferation ability under the ginsenoside Rg3 enhancing PD-1 inhibitor effect, improving the immune T cells proliferation ability and corporate these two medicines can enhance the effect of anti-diffuse large B-cell lymphoma (Guo, Guo, Zhang, Liu, & Quan, 2018). Zhao selected 70 patients as the research objects to observe the effect of ginsenoside Rg3 on Th1/Th2 cytokines in nasopharyngeal carcinoma. When comparing the clinical efficacy, Th1/Th2 cytokines, VEGF, and T lymphocyte subsets between the control group (radiotherapy alone) and the experimental group (radiotherapy + *Shenyi* capsule), levels of VEGF, IL-4, IL-6 and IL-10, total effective rate, hazardous and system outputs were identified as being lower in the experimental group than in the control group, whereas IL-2 and IL- levels were elevated in experimental group. Ginsenoside Rg3 improved Th1/Th2 cytokines express in nasopharyngeal carcinoma, inhibited tumor cell angiogenesis, and alleviated the toxic and side effects of radiotherapy (Zhao, 2018).

Conclusion

In this paper, the effect mechanism of ginsenoside Rg3 on MDA-MB-231 breast tumor cells, HepG2 liver tumor cells, SNU-216 gastric tumor cells, and A549 lung tumor cells and other tumors was summarized. From the above, it can be seen that

ginsenoside Rg3, the primary active substance of ginseng, has anti-tumor, immune-boosting properties, reduces the toxic and side effects of chemotherapy, and makes chemotherapy drugs more effective against cancer cells. As a result, it has been established that its key pro mechanism involves boosting, blocking signal pathway transduction, regulating tumor cell proliferation, and suppressing tumor cell angiogenesis. However, the studies in recent years on ginsenoside Rg3 mainly pay close attention to the level of clinical observation and cell experiment, and the research on its targeted therapy and mechanism of action is not enough. We can concentrate on doing in-depth study on its pharmacological anti-tumor activities later on. It is necessary to apply new research methods and technologies to deeply explore new anti-tumor mechanisms and pathways, provide drug principles and ideas for clinical treatments in natural medicines, and solve clinical difficulties.

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