

Research Progress of Ginsenosides in Anti-tumor Field

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Abstract: The high incidence of malignant tumors and the limitations of existing therapies have driven the development of efficient, low-toxicity antitumor drugs. Ginsenosides, as the core components of medicinal plants, have attracted significant attention due to their multi-target antitumor effects and the innovative application of nano-delivery systems. This article reviews the structural classification, antitumor mechanisms, and research progress of delivery systems such as liposomes, polymeric micelles, and nanoparticles for ginsenosides. Furthermore, the article suggests that future efforts should focus on optimizing delivery technologies and exploring synergistic strategies across multiple mechanisms to facilitate the clinical translation of ginsenosides and their related nano-drugs

Keywords: Ginsenosides, Structure and Classification, Anti-tumor, Drug Delivery Systems

1. Introduction

In recent years, the incidence and mortality rates of malignant tumors have been on a continuous rise. Traditional treatment methods such as chemotherapy and radiotherapy[1], due to their severe side effects and poor selectivity, struggle to meet clinical demands. Against this backdrop, the search for new anti-tumor drugs that are highly effective and low-toxicity has become a crucial direction in current drug research.

Ginsenosides (GS) represent the primary bioactive constituents derived from botanical sources such as ginseng and Sanqi, exhibiting a wide range of pharmacological effects, including potent anti-tumor, anti-inflammatory, anti-fatigue, and antioxidant properties[2]. Their complex composition and structure have limited their application to some extent. By formulating them into nano-formulations through pharmaceutical science[3], the water solubility and targeting of ginsenosides can be effectively improved, thereby enhancing bioavailability and significantly increasing the drug activity of ginsenosides while reducing side effects. This article aims to review the research progress of ginsenosides in the field of anti-tumor, providing references for the dosage form design and clinical application of ginsenosides by summarizing the latest research progress in the structural classification, anti-tumor mechanisms, nano-delivery systems, and clinical applications of ginsenosides.

2. The organization and categorization of ginsenosides

Ginsenosides represent a category of triterpene glycosides with significant medicinal value, whose unique structure is formed by the connection of aglycone and sugar moieties through glycosidic bonds. The chemical structure of ginsenosides is complex and diverse. Based on the differences in aglycone structures, they are mainly divided into dammarane-type and oleanane-type two major categories.

Among them, dammarane-type saponins, due to their extensive biological activities such as anti-tumor, anti-fatigue, and immune modulation, have become a research hotspot in recent years.

The basic structure of dammarane-type saponins consists of 30 carbon atoms forming a steroid nucleus with four rings, which endows them with rich biological activities. According to the different positions of substituents on the aglycone, dammarane-type saponins can be further divided into PPD and protopanaxatriol PPT two major series. Compounds in the PPD and PPT series each have their unique biological activities. For example, compounds such as Rb1, Rb2, Rc, and Rd in the PPD series have significant neuroprotective and immune-modulating effects[4]; while compounds such as Rg3 and Rh2 in the PPT series perform well in anti-tumor and cardiovascular protection[5]. The structural and activity differences of these compounds provide rich material for in-depth study of their pharmacological mechanisms.

Oleanane-type (C-type) saponins have oleanolic acid as their aglycone, with ginsenoside Rh1 being a typical representative. Although oleanane-type saponins are not as widely biologically active as dammarane-type saponins, they also have unique effects in certain specific physiological functions, such as showing potential in anti-inflammatory and antioxidant aspects. In addition, the presence of oleanane-type saponins also enriches the chemical diversity of ginsenosides.

Ocotillol-type saponins have an aglycone with an ocotillol skeleton of tetracyclic triterpenes, mainly differing from dammarane-type in the configuration at the 20th and 24th carbon atoms. Due to their special chemical structure, ocotillol-type saponins play a role under certain specific pathological factors, such as the representative compound ginsenoside F11, which significantly improves cognitive impairment and white matter injury by enhancing autophagy and reducing lysosomal defects in oligodendrocytes[6].

This classification system of ginsenosides not only helps us better understand their structural characteristics but also provides an important basis for the study of the structure and function of ginsenosides. By in-depth study of the relationship between the structure and activity of different types of saponins, theoretical support can be provided for the development of new drugs and health products, further tapping into the great value of ginseng, a traditional Chinese medicinal material. The structural classification of ginsenosides is shown in Table 1:

Table 1: Structural categorization of ginsenosides

Classification name	parent nucleus	Structural differences	Representative compound
Original panaxadiol type PPD	Damane type tetracyclic triterpenes	C-20 position is hydroxyl (original panaxadiol) The sugar group is usually connected to the hydroxyl groups at positions C-3 and C-20	Ginsenoside Rb ₁ , Rd, Rg ₃ , CK, Rh ₂
Original ginseng triol type PPT	Damane type tetracyclic triterpenes	The C-6 and C-20 positions are hydroxyl groups (original panaxatriol) The sugar group is usually connected to the hydroxyl groups at positions C-6 and C-20	Ginsenoside Rg ₁ , Re, Rh ₁ , Rf
Quercetin type	Pentacyclic triterpenoids (oleanolic acid skeleton)	Five ring skeleton (A/B/C/D/E rings) The sugar group is usually connected to the hydroxyl groups at positions C-3 and C-28	Ginsenoside Ro

Table 1: (continued).

Oketilon type	Tetracyclic triterpenoids (Octylone skeleton)	C-20 and C-24 have special configurations (such as 20S, 24R) Glycosyl linkage at positions C-20 and C-24	Ginsenoside F11, RT5, RT2
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3. Anti-tumor Mechanisms of Ginsenosides

3.1. Inhibition of Cell Proliferation

Ginsenosides can inhibit tumor cell proliferation through various pathways. For example, ginsenoside Rh2 can target microRNA (miRNA) and cell signaling pathways to inhibit tumor cell proliferation. Specifically, Rh2 promotes the expression of miR-150-3p, blocking the Wnt/ β -catenin signaling pathway, thereby inhibiting the proliferation of colon cancer cells[7]. Additionally, ginsenoside Rg1 can inhibit the phosphorylation of histone H3 and the aggregation of the centromere complex, disrupting the integrity of cell mitosis and subsequently inhibiting tumor cell proliferation[8].

3.2. Induction of Apoptosis

Ginsenosides function as signaling molecules capable of activating diverse cellular signaling pathways, thereby inducing apoptosis and facilitating autophagy, which contribute to their anti-tumor effects. For example, ginsenoside Rh2 has been demonstrated to inhibit the proliferation of breast cancer cells via the ER β -TNF α signaling pathway. As a constituent of the PPD-type ginsenosides, Rh2 exhibits potential as an estrogen receptor ligand with moderate estrogenic activity. Research indicates that ginsenoside Rh2 can induce apoptosis in MCF-7 cells and induce cell cycle arrest at the G1/S phase[9]. A separate investigation revealed that Rg5 diminishes the phosphorylation of phosphoinositide 3-kinase (PI3K), as well as the activation of Akt and mTORC1, thereby initiating the autophagy process facilitated by microtubule-associated protein light chain 3 (LC3). This process notably enhances the activity of caspase-3, ultimately leading to apoptosis in human osteosarcoma cells[10]. Furthermore, CK facilitates apoptosis and autophagy in non-small cell lung cancer cells through the activation of the AMPK/mTOR and JNK signaling pathways[11].

3.3. Inhibition of Tumor Angiogenesis

Angiogenesis plays a crucial role in tumor growth and metastasis, and anti-angiogenesis therapy has become a core research focus in clinical oncology treatment. Ginsenoside Rg3 has demonstrated the capacity to impede the proliferation and viability of endothelial cells, in addition to suppressing the expression of several factors associated with angiogenesis. Specifically, ginsenoside Rg3, as a drug or prodrug, enters the body and interacts with VEGF and VEGFR2, maintaining low expression levels of these molecules. Furthermore, Rg3 reduces the activation of multiple signaling pathways, including VEGF-induced Akt/eNOS, ER/PI3K/eNOS, or AMPK/eNOS, as well as the PI3K/Akt/mTOR pathway, STAT3, ERK1/2, and JNK, thereby weakening the activation effect of eNOS[12]. Zhao Y et al.'s research further confirmed that the combination of ginsenoside Rg3 and 5-fluorouracil (5-FU) can significantly inhibit tumor angiogenesis and tumor growth in mice[13].

3.4. Regulation of Immune Response

Numerous studies have shown that ginsenosides directly induce apoptosis and inhibit the growth of cancer cells in tumor cells and enhance anti-tumor immunity by activating cytotoxic T lymphocytes and natural killer cells[14]. The experimental findings presented by Chunmei Yang and colleagues

indicate that ginsenoside Rh2 markedly inhibits the proliferation and metastasis of breast cancer by augmenting the cytotoxic activity of natural killer (NK) cells. In particular, Rh2 diminishes the expression of ERp5, a protein that directly interacts with protein disulfide isomerase family member 6 (ERp5), as well as the levels of Rh2 in human breast cancer cells and recombinant proteins. Furthermore, Rh2 obstructs the production of soluble MICA (sMICA) and enhances the expression levels of MICA both in vivo and in vitro.[15]. Furthermore, ginsenoside Rg3 has been demonstrated to enhance the functionality of CD8⁺ T cells through the modulation of the circFOXP1-miR-4477a-PD-L1 signaling pathway in vivo. More specifically, Rg3 disrupts the circFOXP1-miR-4477a-PD-L1 signaling axis, thereby promoting the immune activity of CD8⁺ T cells, which ultimately leads to the induction of ferroptosis and apoptosis in gallbladder cancer (GBC) cells.[16].

3.5. Influence on Tumor Cell Invasion and Metastasis

The invasion and metastasis of tumor cells in the human body involve various complex mechanisms. Epithelial-mesenchymal transition (EMT) represents a critical mechanism that facilitates the metastasis of cancer cells. Prostaglandin E2 (PGE2), as a factor that enhances cell proliferation, is closely related to the cyclooxygenase (COX) family, especially COX2, which is the main enzyme for PGE2 production. Numerous studies have shown that Rh2 can effectively impede tumor invasion and metastasis through the suppression of matrix metalloproteinases (MMPs) expression and the modulation of epithelial-mesenchymal transition (EMT) biomarkers. [17]. Qi-Rui Hu et al.'s experimental results demonstrated that ginsenoside Rh2 and Rh2-O can inhibit the invasion and metastasis of hepatocellular carcinoma by inhibiting EMT mediated by the c-Jun/COX2/PGE2 pathway[18].

4. Ginsenoside Drug Delivery Systems

4.1. Liposomes

Liposomes are vesicular structures composed of biologically degradable and biocompatible lipid bilayers, commonly used as intelligent delivery systems for both hydrophobic and hydrophilic bioactive substances. The physical structure and chemical properties of liposomes, such as the charge interactions between lipids and DNA, ester bond composition, size, and ligand binding characteristics, are crucial for their efficacy as carriers for drugs and genes [19]. Currently, they are widely applied to enhance the therapeutic effects of active ingredients and achieve controlled drug release, which helps to prolong the biological half-life of active ingredients or reduce their toxicity [20].

With the advancement of modern technology and processes, ginsenoside-based liposomes (LP) have become a powerful tool in the treatment of various tumors. For instance, Rg3-PTX-LPs have been demonstrated to be a multifunctional potential drug for the treatment of gliomas. In comparison to cholesterol liposomes (C-LPs), Rg3-LPs demonstrate a substantial enhancement in cellular uptake and penetration of glioma spheroids in vitro, while also significantly improve active targeting of glioma and facilitate intra-tumoral diffusion in vivo. Research results by Ying Zhu et al. suggest that ginsenoside Rg3 serves as a viable substitute for cholesterol in drug delivery liposomes and exhibits a synergistic effect when combined with the incorporated anticancer agents[21]. Furthermore, experimental results by Chao Hong et al. show that using ginsenoside Rh2 instead of cholesterol and PEG, and preparing Rh2-lipo with an ethanol-water system, can enhance the uptake of tumor growth factors (TAF) and tumor cells, improve targeting and penetration capabilities, enhance cellular toxicity to TAF, improve normalization of the vascular network, and deplete stromal collagen [22].

4.2. Polymeric Micelles

Polymeric micelles are nanostructures formed by the simple self-assembly of amphiphilic polymers. By exploring combinations of polymer blocks with varying degrees of hydrophobicity and a certain level of hydrophilicity, it is possible to achieve optimal drug loading, stability, systemic circulation, and targeted delivery to cancerous tissues. Hydrophobic polymers include poly(lactic acid) (PLA), poly(caprolactone) (PCL), poly(lactic-co-glycolic acid) (PLGA), polyesters, poly(amino acids), and lipids. Hydrophilic polymers used to encapsulate the hydrophobic core include poly(ethylene glycol) (PEG), poly(oxazoline), chitosan, dextran, and hyaluronic acid. The conjugation of drugs with polymers results in the preparation of pharmacologically active polymer systems. These systems not only improve the solubility and stabilization of the conjugates but also facilitate the potential for combined administration. Their nanoscale dimensions enable them to accumulate within TME via the growth permeability and retention (EPR) influence. [23]. These nanocarriers exhibit multiple advantages in vitro and in vivo and offer higher stability and solubility for hydrophobic drugs.

A substantial number of experimental studies have shown that ginsenoside-based polymeric micelle drug delivery possesses various advantages. For example, experimental research results by Yan Zhao et al. indicate that polymeric micelles prepared with curcumin and ginsenoside Rg3 can be used to treat triple-negative breast cancer (TNBC). Specifically, by bonding Cur with N-O amphiphilic polymers via vinyl ether bonds and encapsulating ginsenoside Rg3, the hyperbranched amphiphilic drug-loaded micelles OPDEA-PGED-5HA@Cur@Rg3 (PPH@CR) can induce immunogenic cell death (ICD) in tumor cells, facilitate the maturation of dendritic cells (DCs), and the proliferation of CD4⁺ T cells and CD8⁺ T cells, thereby transforming the relatively "cold" TNBC TME into an "hot" TME with immune cell infiltration[24]. Additionally, polymeric micelles based on ginsenoside Rg5 can be used for targeted therapy of paclitaxel (PTX)-resistant tumors[25]. Specifically, ginsenoside Rg5, with its hydrophilic structure and neuroprotective and anti-inflammatory pharmacological effects, significantly strengthen the water-solubility and initiative targeting of PTX in the prepared paclitaxel-ginsenoside polymeric micelles (RPM), inhibiting chemoresistance in cancer cells.

4.3. Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLN) is a type of nanocarrier composed of a solid lipid core that maintains solid at both ambient and physiological temperatures, and is encapsulated by surfactants or emulsifiers. These surfactants stabilize the SLN by reducing the interfacial tension between the lipid core and the aqueous medium. In some formulations, co-surfactants are also added to further reduce interfacial tension and enhance the stability of the SLN. The unique composition and physicochemical characteristics of SLNs make them adaptable to various routes of administration and applications. Currently, SLNs are widely used in the development of various drug formulations to deliver different therapeutic payloads, including chemotherapeutic agents and genetic materials, for the treatment of a variety of cancers. Moreover, surface modification of SLNs can effectively achieve targeting of specific cells or tissues, enhancing the precision of treatment while reducing unnecessary side effects [26].

Numerous studies have shown that ginsenosides exhibit great potential in the adjuvant treatment of cancer. For example, in the treatment of cancer, the efficacy of immune checkpoint blockade therapy is low due to the immunosuppressive characteristics of the tumor microenvironment (TME). Both in vitro and in vivo experiments have confirmed that ginsenoside Rg3 exhibits great potential as an immunogenic cell death (ICD) inducer against colorectal cancer (CRC) cells. The research results of Dandan Sun et al. showed that the nanodrug (CD-PEG-FA.Rg3.QTN) encapsulating Rg3 and quercetin (QTN) through folic acid (FA) targeting polyethylene glycol (PEG) modified

amphiphilic cyclodextrin nanoparticles (NP) significantly prolonged the blood circulation time and enhanced the tumor targeting effect in CRC mouse models, leading to the transformation of immunosuppressive TME [27]. In addition, compared with the single drug of adriamycin (DOX), the nanoparticles loaded with ginsenoside Rg3 enhanced the DOX-induced immunogenic cell death (ICD) effect. Hao Wu et al. prepared nanoparticles (PNP) modified with chitosan and cell-penetrating peptide (R6F3) loaded with ginsenoside Rg3 (Rg3) using self-assembly technology, and then co-encapsulated with DOX in a thermosensitive hydrogel. The results of the study confirmed that the hydrogel containing DOX and highly permeable Rg3-PNPs provides an effective therapeutic approach for reconfiguring the immunosuppressive TME and transforming immune "cold" tumors into "hot" tumors [28].

5. Summary and outlook

Ginsenosides, as the main bioactive components of ginseng, have been widely demonstrated to possess anti-inflammatory, anti-fatigue, and antioxidant pharmacological effects, and have shown significant anti-tumor activity and control capabilities in the occurrence and development of various cancers [29]. Through literature review, it has been concluded that ginsenosides have multi-pathway, multi-target intervention effects on various tumor cells, including inhibiting cancer cell proliferation, inducing apoptosis, inhibiting tumor angiogenesis, regulating immunity, and inhibiting the invasion and metastasis of tumor cells, thereby contributing to the prevention and treatment of cancer.

Research has demonstrated that ginsenosides exhibit a significant inhibitory effect on tumor progression. However, since their low water-solubility and bioavailability, there are still limitations to using ginsenosides alone as a first-line anti-tumor drug[30]. At present, researchers have developed various collaborative drug delivery vehicles, such as ginsenoside-based liposomes and nanoparticles, to construct new drug delivery systems to enhance tumor targeting and increase tumor inhibition rates. Therefore, improving the targeted delivery of ginsenosides is key to using ginsenosides for anti-tumor treatment and is also an important research direction for improving the therapeutic effects of ginsenosides in the field of anti-tumor treatment in the future. In summary, ginsenosides have significant clinical application value and are worth further in-depth and systematic research.

References

- [1] Wang S, Long S, Deng Z, Wu W. Positive role of chinese herbal medicine in cancer immune regulation. *Am J Chin Med* 2020;48:1577–92. <https://doi.org/10.1142/S0192415X20500780>.
- [2] Zhou G, Wang C-Z, Mohammadi S, Sawadogo WR, Ma Q, Yuan C-S. Pharmacological effects of ginseng: multiple constituents and multiple actions on humans. *Am J Chin Med* 2023. <https://doi.org/10.1142/S0192415X23500507>.
- [3] Du L, Lu H, Xiao Y, Guo Z, Li Y. Preparation, characterization and in vivo pharmacokinetic study of ginsenoside Rb1-PLGA nanoparticles. *Sci Rep* 2023;13:18472. <https://doi.org/10.1038/s41598-023-45858-x>.
- [4] Zhao Q, Yan W, Han X, Xu Y, Xing Y. [alpha(25-35) and ginsenoside Rb1 influence on the expression of GSK-3beta, CDK-5 and PP2A in differentiated neural stem cells of rats]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi = Zhongguo Yingyong Shenglixue Zazhi = Chin J Appl Physiol* 2010;26:187–90.
- [5] Nakhjavani M, Smith E, Townsend AR, Price TJ, Hardingham JE. Anti-angiogenic properties of ginsenoside Rg3. *Mol (Basel Switz)* 2020;25:4905. <https://doi.org/10.3390/molecules25214905>.
- [6] Wang H, Liu Y, Cui M, Guo Z, Zhao Y, Yang J, et al. Pseudoginsenoside-F11 reduces cognitive impairment and white matter injury in vascular dementia by alleviating autophagy-lysosomal pathway deficiency. *Phytomed: Int J Phytother Phytopharm* 2024;133:155883. <https://doi.org/10.1016/j.phymed.2024.155883>.
- [7] Li S, Han W, He Q, Wang Y, Jin G, Zhang Y. Ginsenoside Rh2 suppresses colon cancer growth by targeting the miR-150-3p/SRCIN1/wnt axis. *Acta Biochim Biophys Sin* 2023;55:633–48. <https://doi.org/10.3724/abbs.2023032>.
- [8] Hong J, Gwon D, Jang C-Y. Ginsenoside Rg1 suppresses cancer cell proliferation through perturbing mitotic progression. *J Ginseng Res* 2022;46:481–8. <https://doi.org/10.1016/j.jgr.2021.11.004>.
- [9] Peng K, Luo T, Li J, Huang J, Dong Z, Liu J, et al. Ginsenoside Rh2 inhibits breast cancer cell growth via ERβ-TNFα pathway. *Acta Biochim Biophys Sin* 2022;54:647–56. <https://doi.org/10.3724/abbs.2022039>.

- [10] Liu M-Y, Liu F, Li Y-J, Yin J-N, Gao Y-L, Wang X-Y, et al. Ginsenoside Rg5 inhibits human osteosarcoma cell proliferation and induces cell apoptosis through PI3K/akt/mTORC1-related LC3 autophagy pathway. *Oxid Med Cell Longevity* 2021;2021:5040326. <https://doi.org/10.1155/2021/5040326>.
- [11] Liu J, Wang Y, Yu Z, Lv G, Huang X, Lin H, et al. Functional mechanism of ginsenoside compound K on tumor growth and metastasis. *Integr Cancer Ther* 2022;21:15347354221101203. <https://doi.org/10.1177/15347354221101203>.
- [12] Nakhjavani M, Smith E, Townsend AR, Price TJ, Hardingham JE. Anti-angiogenic properties of ginsenoside Rg3. *Mol (Basel Switz)* 2020;25:4905. <https://doi.org/10.3390/molecules25214905>.
- [13] Zhao Y, Deng L, Cao Y, Ma B, Li Y, Xu J, et al. [inhibitory effect of ginsenoside Rg3 combined with 5-fluorouracil on tumor angiogenesis and tumor growth of colon cancer in mice: an experimental study]. *Sichuan Xue Xue Bao, Yi Xue Ban = J Sichuan Univ, Med Sci Ed* 2024;55:111–7. <https://doi.org/10.12182/20240160506>.
- [14] Zhang Y, Qiu Z, Qiu Y, Su T, Qu P, Jia A. Functional regulation of ginsenosides on myeloid immunosuppressive cells in the tumor microenvironment. *Integr Cancer Ther* 2019;18:1534735419886655. <https://doi.org/10.1177/1534735419886655>.
- [15] Yang C, Qian C, Zheng W, Dong G, Zhang S, Wang F, et al. Ginsenoside Rh2 enhances immune surveillance of natural killer (NK) cells via inhibition of ERp5 in breast cancer. *Phytomed: Int J Phytother Phytopharm* 2024;123:155180. <https://doi.org/10.1016/j.phymed.2023.155180>.
- [16] Ye Z, Ding J, Huang J, Hu Z, Jin F, Wu K. Ginsenoside Rg3 activates the immune function of CD8+ T cells via circFOXP1-miR-4477a-PD-L1 axis to induce ferroptosis in gallbladder cancer. *Arch Pharmacol Res* 2024;47:793–811. <https://doi.org/10.1007/s12272-024-01516-y>.
- [17] Hu Q, Pan Y, Wu H, Dai Z, Huang Q, Luo T, et al. The ways for ginsenoside Rh2 to fight against cancer: the molecular evidences in vitro and in vivo. *J Ginseng Res* 2023;47:173–82. <https://doi.org/10.1016/j.jgr.2022.09.011>.
- [18] Hu Q-R, Huang Q-X, Hong H, Pan Y, Luo T, Li J, et al. Ginsenoside Rh2 and its octyl ester derivative inhibited invasion and metastasis of hepatocellular carcinoma via the c-jun/COX2/PGE2 pathway. *Phytomed: Int J Phytother Phytopharm* 2023;121:155131. <https://doi.org/10.1016/j.phymed.2023.155131>.
- [19] Akkewar A, Mahajan N, Kharwade R, Gangane P. Liposomes in the targeted gene therapy of cancer: a critical review. *Curr Drug Deliv n.d.*;20:350–70. <https://doi.org/10.2174/1567201819666220421113127>.
- [20] Dymek M, Sikora E. Liposomes as biocompatible and smart delivery systems - the current state. *Adv Colloid Interface Sci* 2022;309:102757. <https://doi.org/10.1016/j.cis.2022.102757>.
- [21] Zhu Y, Liang J, Gao C, Wang A, Xia J, Hong C, et al. Multifunctional ginsenoside Rg3-based liposomes for glioma targeting therapy. *J Control Release: Off J Control Release Soc* 2021;330:641–57. <https://doi.org/10.1016/j.jconrel.2020.12.036>.
- [22] Hong C, Wang A, Xia J, Liang J, Zhu Y, Wang D, et al. Ginsenoside Rh2-based multifunctional liposomes for advanced breast cancer therapy. *Int J Nanomed* 2024;19:2879–88. <https://doi.org/10.2147/IJN.S437733>.
- [23] Ghosh B, Biswas S. Polymeric micelles in cancer therapy: state of the art. *J Control Release: Off J Control Release Soc* 2021;332:127–47. <https://doi.org/10.1016/j.jconrel.2021.02.016>.
- [24] Zhao Y, Bai Y, Li M, Nie X, Meng H, Shosei S, et al. A pH-triggered N-oxide polyzwitterionic nano-drug loaded system for the anti-tumor immunity activation research. *J Nanobiotechnol* 2024;22:420. <https://doi.org/10.1186/s12951-024-02677-0>.
- [25] Gao F, Ma Z, Luo X, Wang Y, Liu X, Tang M, et al. Self-assembled micelles based on ginsenoside Rg5 for the targeted treatment of PTX-resistant tumors. *Mol Pharmaceutics* 2024;21:3502–12. <https://doi.org/10.1021/acs.molpharmaceut.4c00204>.
- [26] German-Cortés J, Vilar-Hernández M, Rafael D, Abasolo I, Andrade F. Solid lipid nanoparticles: multitasking nano-carriers for cancer treatment. *Pharmaceutics* 2023;15:831. <https://doi.org/10.3390/pharmaceutics15030831>.
- [27] Sun D, Zou Y, Song L, Han S, Yang H, Chu D, et al. A cyclodextrin-based nanoformulation achieves co-delivery of ginsenoside Rg3 and quercetin for chemo-immunotherapy in colorectal cancer. *Acta Pharm Sin, B* 2022;12:378–93. <https://doi.org/10.1016/j.apsb.2021.06.005>.
- [28] Wu H, Wei G, Luo L, Li L, Gao Y, Tan X, et al. Ginsenoside Rg3 nanoparticles with permeation enhancing based chitosan derivatives were encapsulated with doxorubicin by thermosensitive hydrogel and anti-cancer evaluation of peritumoral hydrogel injection combined with PD-L1 antibody. *Biomater Res* 2022;26:77. <https://doi.org/10.1186/s40824-022-00329-8>.
- [29] Yang Y, Nan Y, Du Y, Liu W, Ning N, Chen G, et al. Ginsenosides in cancer: proliferation, metastasis, and drug resistance. *Biomed Pharmacother* 2024;177:117049. <https://doi.org/10.1016/j.biopha.2024.117049>.
- [30] Valdés-González JA, Sánchez M, Moratilla-Rivera I, Iglesias I, Gómez-Serranillos MP. Immunomodulatory, anti-inflammatory, and anti-cancer properties of ginseng: a pharmacological update. *Molecules* 2023;28:3863. <https://doi.org/10.3390/molecules28093863>.