ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

Recent Advances in Ginsenoside-mediated Nano Drug Delivery Systems

Xiance Che[1,*], Hao Sun[1]

[1] Cangzhou Aviation Vocational College, Cangzhou 061000, China

[*] Corresponding author

Abstract

Panax ginseng, a widely recognized medicinal plant with significant economic value, has been extensively used in traditional medicine worldwide for millennia. Both in vivo and in vitro studies have demonstrated that ginsenosides exert antitumor, anti-inflammatory, and cardioprotective effects through various mechanisms. However, their clinical applications are limited due to unfavorable physicochemical properties, including low solubility, poor stability, short half-life, and rapid elimination and degradation in vivo. Consequently, ginsenoside-based nano-delivery systems and preparation technologies have attracted significant attention from researchers. This review summarizes recent advances in the study of ginsenoside-related antitumor, anti-inflammatory, and cardioprotective effects, as well as various nano-delivery systems, aiming to provide theoretical guidance for comprehensive research on ginsenosides.

Keywords

Ginsenoside; Anti-tumor; Mechanism of action; Nano-drug delivery system.

1. INTRODUCTION

For over 2000 years, Panax ginseng C.A. Meyer has been revered as a precious traditional medicinal herb, with its medicinal value documented as early as in the "Shen Nong Ben Cao Jing" and it has been acclaimed as the "King of Herbs" since ancient times [1]. Ginsenosides, the primary active components of ginseng, along with polysaccharides, essential oils, proteins, amino acids, organic acids, flavonoids, vitamins, and trace elements, exhibit a wide range of pharmacological effects, including central nervous system stimulation, anti-tumor activity, cardiovascular protection, immune enhancement, anti-aging, lipid-lowering, and anti-fatigue effects (Wang et al., 2024; Ke et al., 2022)[2,3]. However, despite their significant pharmacological effects, the clinical application of ginsenosides is limited by their poor water solubility, short half-life, slow dissolution rate in vitro, slow oral absorption, low plasma concentration, and low bioavailability[4].

Exploring suitable drug delivery systems is a crucial formulation strategy to enhance the medicinal value of ginsenosides. Nanomedicine holds significant potential in improving the efficacy of cancer immunotherapy[5]. Previous studies have reported the development of various drug delivery systems aimed at enhancing the anti-tumor effects of active compounds, such as micelles, liposomes, and nanoparticles[6,7]. These nano drug delivery systems can encapsulate hydrophobic drugs, thereby achieving enhanced therapeutic effects by improving solubility and stability, prolonging circulation time, and altering tissue distribution and pharmacokinetics[8]. Stimuli-responsive nanomedicines can achieve precise and controlled drug release by responding to endogenous changes such as pH, reactive oxygen species, and redox conditions, or external stimuli such as temperature and light, thereby improving the

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

therapeutic efficacy against diseases[9,10]. These stimuli-responsive nanomedicines enable precise spatial and temporal control of drug release. To date, several ginsenoside delivery systems and preparation technologies (e.g., liposomes, micelles, protein nanoparticles, metallic nanoparticles, and inorganic nanoparticles) have been designed to overcome the limitations of ginsenosides by enhancing their solubility, stability, bioavailability, and controlled release, thereby improving their pharmacological effects[11,12].

The development of stimuli-responsive nanomaterials and their design as effective drug carriers is a current research hotspot. This paper highlights the latest advancements in various ginsenoside nano drug delivery systems and their applications in the treatment of cancer, atherosclerosis, and cardiac injury.

2. GINSENOSIDE NANOPARTICLES ANTI-CANCER

2.1. Induced Immunogenic cell death

Immunogenic cell death (ICD) plays a pivotal role in the antitumor process by transforming "cold tumors" into "hot tumors" through the release of damage-associated molecular patterns (DAMPs)[13]. This process ultimately reshapes the immunosuppressive microenvironment and eradicates cancer cells. Certain chemotherapeutic drugs, such as doxorubicin (DOX), oxaliplatin (OXA), cyclophosphamide (CPA), and paclitaxel (PTX), not only induce cancer cell death but also stimulate ICD, triggering specific antitumor immune responses and enhancing the efficacy of chemotherapy[14]. However, DOX exhibits weak immunogenicity in tumor cell elimination, and the DAMPs produced are insufficient to independently initiate a robust antitumor immune response. Recent research has demonstrated that ginsenoside Rg3 can induce ICD in antitumor therapy and enhance the ICD effect of DOX[15]. Chen et al. employed self-assembly techniques to encapsulate ginsenoside Rg3 and DOX into chitosan nanoparticles modified with the cell-penetrating peptide (R6F3), enhancing the ICD effect induced by DOX. When used in combination with PD-L1 inhibitors, this formulation achieved significant antitumor effects in the treatment of triple-negative breast cancer[16]. Studies have shown that G-Rh2 mediates autophagy and endoplasmic reticulum stress via the TFE3/TFEB pathway, accompanied by phosphorylation of eIF2α, and synergizes with methotrexate (MTX) to significantly enhance MTX-induced ICD[17]. Additionally, research indicates that Rh2@HMnO2-AM nanoparticles effectively trigger ICD, activate CD4+/CD8+ T cells in vivo, suppress the generation of FOXP3+ T cells (Tregs) in tumors, and upregulate BAX, BCL-2, and Caspase-3 at the cellular level[18].

Platelet membranes (PM) exhibit significant potential for applications in nano- and micro-scale drug delivery systems due to their excellent biocompatibility, low immunogenicity, and targeting capabilities[19]. Notably, P-selectin on the platelet membrane can effectively recognize and bind to the CD44 receptor on the surface of acute myeloid leukemia (AML) cells, achieving precise targeting of AML cells[20]. In the study, DOX/Rg3 liposomes facilitated by the interaction between P-selectin on the platelet membrane and the CD44 receptor on AML cells not only enhanced drug penetration and retention within the tumor but also increased drug accumulation in AML cells. Furthermore, this drug delivery system (DR@Plip) also upregulated calreticulin (CRT), high mobility group box 1 (HMGB1), and adenosine triphosphate (ATP), inducing ICD and promoting apoptosis in AML cells through the increased production of reactive oxygen species (ROS)[21].

In another study, a polyethylene glycol-modified amphiphilic cyclodextrin nanoparticle (NP) incorporating a folate (FA) targeting moiety was developed to co-encapsulate Rg3 and QTN, effectively generating ROS and enhancing the ICD activity mediated by Rg3. In an in situ colorectal cancer (CRC) mouse model, CD-PEG-FA.Rg3.QTN enhanced the tumor microenvironment by promoting the release of dendritic cells (DCs) and cytokines, increasing the numbers of CD8+ T cells, CD4+ T cells, and activated DCs, while reducing the populations of

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (M2). This led to significant chemimmunotherapeutic effects, highlighting the potential of ICD in cancer therapy as an emerging target for future cancer treatments[22], as shown in Figure 1.

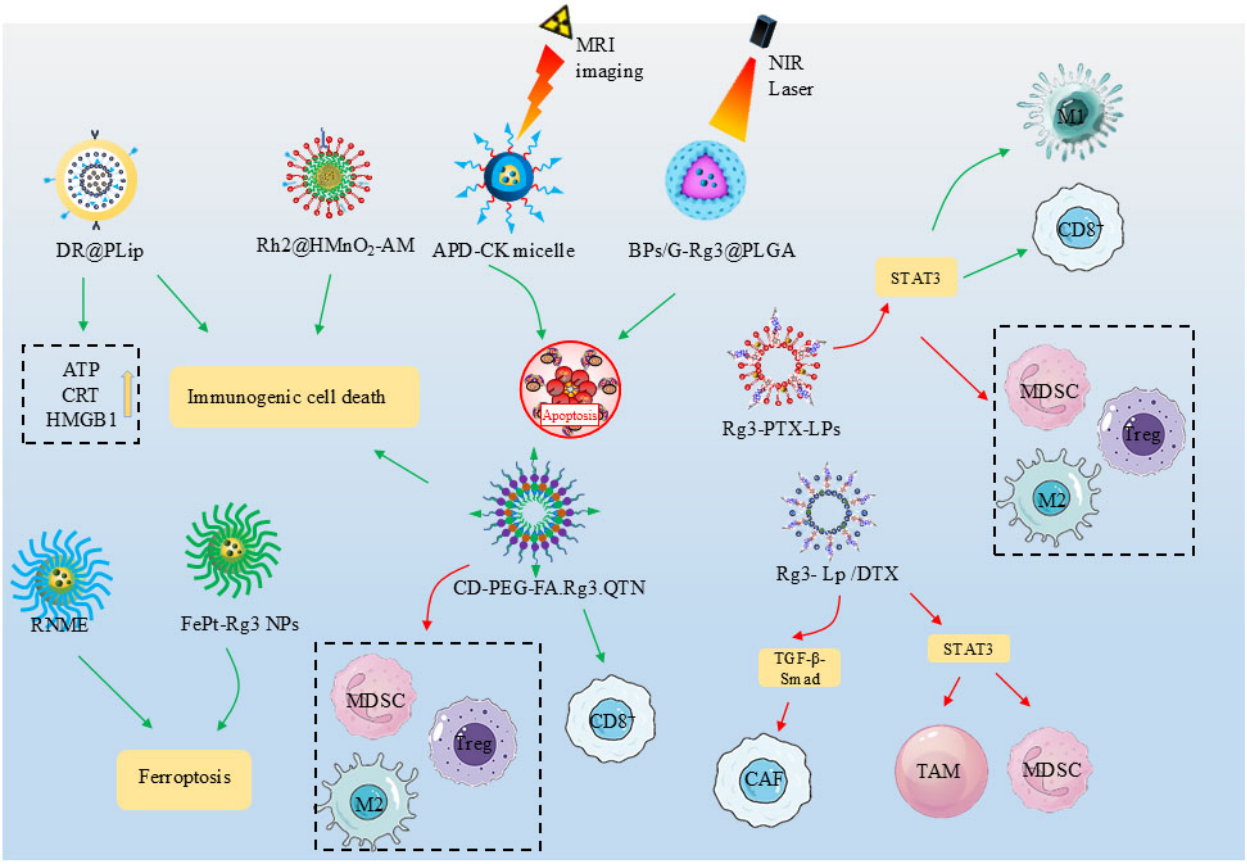

Figure 1. Antitumor mechanisms of ginsenoside nanoparticle delivery systems

2.2. Promote ferroptosis

Chemodynamic therapy (CDT) typically employs Fenton or Fenton-like active metals (such as Co^{2+}、Fe^{2+}、Mo^{5+}、Cr^{6+}、Mn^{2+}、Cu^{+}, etc.) under acidic conditions to convert hydrogen peroxide (H_2O_2) into toxic hydroxyl radicals (•OH)[23].This process effectively depletes glutathione (GSH) and disrupts the redox balance of cancer cells, thereby promoting ferroptosis[24].

Zhao et al. designed FePt-Rg3 nanoparticles (NPs) to address the issue of premature metal ion leakage before reaching the tumor site, ensuring controlled release at the appropriate time and location in vivo. In the presence of H_2O_2, FePt-Rg3 NPs participate in the Fenton reaction, upregulating the expression levels of Bax, cleaved caspase 3/9, ROS, and GSSG, while downregulating Bcl-2, GSH, and GPX4, thereby inducing apoptosis and ferroptosis[25].

The study shows that Zhao et al. developed a novel nanomedicine, RNME, combining secondary ginsenoside Rg3 with $Fe@Fe_3O_4$ nanomaterials, demonstrating dual functionality in tumor therapy. Under neutral conditions, RNME exhibits high reactivity to H_2O_2, generating oxygen, effectively mitigating hypoxia in the tumor microenvironment, and reducing the antioxidant capacity of tumor cells, thereby enhancing oxidative damage. Under acidic conditions, this nanomedicine catalyzes the production of highly toxic ROS from H_2O_2, promoting apoptosis in pancreatic cancer cells. Additionally, the use of RNME in the L3.6pl pancreatic cancer cell line reduces GPX4 and GSH/GSSG levels, inducing oxidative stress and ferroptosis[26].

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

2.3. Regulating tumor microenvironment

The tumor microenvironment (TME) of the brain is emerging as a crucial regulatory factor in the progression of both primary and metastatic brain malignancies. The brain TME is essential for tumor initiation, growth, and metastasis[27]. In experiments, Zhu et al. successfully prepared liposomes co-loaded with ginsenoside Rg3 and paclitaxel (PTX) using the film hydration method. These liposomes demonstrated significant toxicity and targeting ability against C6 mouse glioma cells. Additionally, the Rg3-PTX liposomes enhanced the T-cell immune response by activating the immune microenvironment within the tumor, expanding the CD8+ T cell population, increasing the M1/M2 ratio, and effectively reducing the numbers of regulatory T cells and myeloid-derived suppressor cells, thereby significantly extending the survival time of tumor-bearing mice[28].

A small number of circulating tumor cells (CTCs) can evade immune surveillance, making the removal of CTCs from the bloodstream a critical step in preventing tumor metastasis[29]. Researchers have developed a novel multifunctional liposome (Rg3-Lp/DTX) capable of effectively capturing CTCs. By interacting with the overexpressed glucose transporter 1 (Glut1) on CTCs, Rg3-Lp/DTX exhibits efficient CTC capture capability. Upon reaching the lungs, the Rg3 component can inhibit STAT3 activation, reducing tumor-secreted CCL2 levels. This decreases the accumulation of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) in the metastatic microenvironment, thereby inhibiting distant tumor metastasis[30].

Tumor cells can also promote the formation and infiltration of cancer-associated fibroblasts (CAFs) by secreting transforming growth factor-beta (TGF-β), leading to a stroma-rich and immunosuppressive TME[31]. Xia et al. developed a multifunctional DTX-loaded ginsenoside Rg3 liposome (Rg3-Lp/DTX) for tumor treatment. The study results showed that Rg3-Lp/DTX significantly reduced the viability of 4T1 tumor cells compared to Rg3 alone. The Rg3 component effectively reversed activated CAFs to a quiescent state and weakened the dense stromal barrier by inhibiting tumor cell-secreted TGF-β and modulating the TGF-β/Smad signaling pathway[32].

Reprogramming TAMs to an anti-tumor M1 phenotype is another promising strategy. Zhu et al. prepared ginsenoside liposomes (Rg3-PTX-LPs) using the film hydration method, which exhibited greater toxicity and targeting ability against MCF7/T cancer cells than conventional cholesterol liposomes. Rg3-PTX-LPs induced apoptosis in breast cancer cells and reprogrammed pro-tumor M2 macrophages to anti-tumor M1 macrophages by inhibiting the activation of the IL-6/STAT3/p-STAT3 pathway. They also suppressed MDSCs and reduced tumor-associated fibroblasts (TAFs) and collagen fibers in the tumor microenvironment[33]. Additionally, studies indicated that Rh2 has the potential to convert TAMs from the M2 to M1 phenotype and inhibit lung cancer cell migration, suggesting a therapeutic role for G-Rh2 in lung cancer[34].

2.4. Inducing tumor cell invasion

Metal and metal oxide nanoparticles have garnered significant attention in the field of chemotherapy drug delivery due to their excellent biocompatibility and liver-targeting properties[35]. Studies have shown that a nanodrug developed by combining Fe@Fe_3O_4 nanoparticles with ginsenoside Rg3 (NpRg3) effectively prolonged the survival of mice in a diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) model, inhibiting tumor progression and lung metastasis[36]. Moreover, carrier-free drug delivery systems, through self-assembly or co-assembly of drug molecules, avoid the use of inert carriers, demonstrating excellent antitumor effects and lower systemic toxicity. Zuo et al. developed a carrier-free nanodrug composed of ginsenosides Rg3 and Rb1, which showed significant antitumor and

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

anti-invasive activity in triple-negative breast cancer cells (TNBCs). Additionally, experiments indicated that ginsenoside micelles effectively inhibited lung metastasis of liver cancer by reducing ICAM-1 expression[37]. These advances not only enhance drug delivery efficiency and efficacy but also provide new directions for future cancer treatment strategies.

2.5. Inducing apoptosis of tumor cells

Black phosphorus (BP) has garnered extensive attention due to its excellent drug loading and delivery capabilities, good biocompatibility, and potential in cancer therapy and diagnosis[38]. Xiong et al. designed a multifunctional black phosphorus nanocomposite, BPs/G-Rg3@PLGA, which exhibited strong affinity for both primary and metastatic lung tumors. When combined with near-infrared irradiation, its photothermal effect was significant, effectively inducing tumor apoptosis[39].

Zinc oxide nanoparticles (ZnO NPs) have been extensively studied for cancer treatment due to their specificity, efficiency, low toxicity, and biocompatibility[40]. HA-ZnO nanocomposites prepared by Kim et al. can generate hydroxyl radicals and hydrogen peroxide under light irradiation, leading to cancer cell death, and exhibit significant anticancer effects against A549 lung cancer, HT29 colon cancer, and MCF7 breast cancer cells[41]. On the other hand, Yao et al. developed gold nanoparticles loaded with ginsenoside Rh2, overcoming the low water solubility and poor stability of Rh2, enhancing its anticancer activity and therapeutic efficacy. In A375 human melanoma cells, ginsenoside Rh2 upregulated levels of ROS, caspase-3, -8, and -9, inducing apoptosis[42]. Zhang et al. prepared a biologically stable and targeted nanosystem, APD-CK, loaded with ginsenoside CK. Compared to the free drug, APD-CK micelles demonstrated superior anti-hepatocarcinoma activity and more sustained tumor proliferation inhibition. APD-CK micelles promoted apoptosis in HepG2 cells by upregulating the expression of caspase-3, caspase-9, and PARP proteins[43].

3. CARDIOPROTECTIVE EFFECTS

Oxidative stress is a key pathogenic mechanism in myocardial ischemia-reperfusion injury (MIRI), with the accumulation of ROS leading to various damages. Li et al. designed an ROS-responsive release system by synthesizing PEG-b-PPS nanoparticles loaded with Rg3, achieving ROS-responsive release both in vitro and in vivo. Rg3 targets FoxO3a and regulates its downstream signaling pathways, including Sirt-1, TGF-β/Smad, and NF-κB, effectively inhibiting oxidative stress, inflammation, apoptosis, and fibrosis, providing effective treatment for MIRI [44].

PPARα is a critical transcriptional regulator of fatty acid metabolism, and its downregulation affects the expression of CPT-1, MCAD, and VDAC proteins, leading to an imbalance in fatty acid uptake and oxidation, thereby inducing myocardial fibrosis[45]. Chitosan (CS), with its favorable biological properties and solubility in acidic environments, is a promising drug delivery system[46]. Zhang et al. synthesized CS@TPP nanoparticles containing ginsenoside Rb3 through the ionic gelation method. This system enhanced drug solubility and bioavailability, achieving precise sustained release in a transverse aortic constriction (TAC)-induced chronic heart failure model. NpRb3 may improve fatty acid oxidation and glycolysis by targeting the PPARα signaling pathway, regulating mitochondrial oxidative phosphorylation levels, thus inhibiting myocardial fibrosis[47], as shown in Table 1.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

Table 1. Mechanisms of Cardioprotection, Anti-inflammatory, and Anti-atherosclerotic Effects of Ginsenoside Nanoparticles

Delivery system	Model	Molecular mechanism	Outcomes	Improved properties	References
Rg3~loaded PEG-b-PPS nanoparticles	In vitro: H9C2 cells In vivo: In rat ischemia-reperfusion model	inhibit NF-κB activation, inhibition of TGF-β/Smad signaling,	inhibit oxidative stress, inflammation, and fibrosis	(1) improve the cardiac function and reduced the infarct size. (2) ROS sensitivity	[44]
Dox@Rg1 nanoparticles	In vitro: H9C2 cells In vivo: 4T1 tumor-bearing mice	-	inhibit apoptosis	(1) perfect tumor-targeting ability (2) decrease the cardiotoxicity	[48]
chitosan (CS) @ sodium tripolyphosphate (TPP) nanoparticles conjugation with ginsenoside Rb3 (NpRb3)	In vitro: Cardiac fibroblasts (CFb), cardiomyocytes In vivo: In the chronic heart failure model	-	inhibits cell proliferation	(1) improve the solubility of the drug and the bioavailability of the drug, slow-release properties, prolongs the retention time of the drug in the body and targetability. (2) PH sensitivity	[47]
Man-BSA@ Rb1 NPs	In vitro: Raw264.7 cells In vivo: liver injury model	inhibit NF-κB and MAPK signaling pathways	anti-inflammatory	(1) improve the solubility and increase the cellular uptake (2) improve Rb1 accumulation into the cells through mannose receptor targeted delivery (3) PH sensitivity	[49]

Continue Table 1

Delivery system	Model	Molecular mechanism	Outcomes	Improved properties	References
GNP-CK-CopA3	In vitro: NHDFs, HaCaTs, RAW264.7	inhibit the activation of the NF-κB and MAPK signalling pathways	anti-inflammatory	(1) reducing cytotoxicity of drug (2) inducing more biological activity (3) increasing drug absorption into the target cells	[50]
PM@Se/Rb1 NPs	In vitro: Raw264.7, HUVEC, Matrigel, monocyte U937 In vivo: ApoE-/- mice	-	antioxidant, lipid metabolism and anti-inflammatory effects	(1) increase the biocompatibility and availability of ginsenoside Rb1 (2) improve the ability of nanodrugs to target AS lesions	[51]
Cat/Re@PLGA@UCM	In vitro: U937, HUVEC, RAW264.7 In vivo: ApoE-/-mouse models	-	anti-inflammatory, antioxidant and antiangiogenic activities	(1) target ability and biocompatibility (2) H_2O_2 sensitivity	[52]
The polymer LA-UaGly was then used to encapsulate ginsenoside Rh2 to form Rh2 nanoparticles (Rh2 NPs)	In vitro: L-02 ,RAW264.7 In vivo: DSS-induced mice	-	(1) protect cells from apoptosis (2) regulate the intestinal flora	(1) improve the bioavailability (2) pH/redox dual responsiveness	[53]

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

4. ANTI-INFLAMMATORY

Ginsenoside Rb1 is limited in its anti-inflammatory effects due to non-targeted delivery, low water solubility, and poor bioavailability. Bovine serum albumin (BSA), known for its biodegradability and good biocompatibility, is an ideal carrier for delivering poorly soluble drugs[54]. Fu et al. designed mannose (Man)-modified BSA carriers (Man-BSA) combined with ginsenoside Rb1 to achieve active targeting of pro-inflammatory cells overexpressing mannose receptors[49].

Gold nanoparticles (GNPs) hold potential in diagnostics, therapy, and drug delivery, but toxic reagents limit their biomedical applications[55]. Acetobacter can be used for the non-toxic synthesis of GNPs. Liu et al. developed gold nanoparticles (GNP-CK-CopA3) surface-bound with CopA3 peptide and loaded with ginsenoside compound K. These nanoparticles exhibited significant anti-inflammatory effects by inhibiting the NF-κB and MAPK signaling pathways, reducing levels of ROS, iNOS, COX-2, TNF-α, IL-1β, and IL-6 in LPS-activated RAW264.7 cells[50]. Additionally, experiments showed that using chitosan as a carrier, gold nanoparticles loaded with ginsenoside compound K (CS-CK-AuNPs) were prepared via self-assembly. These nanoparticles reduced NO and inflammatory cytokines (IL-1β, IL-6, TNF-α) production in LPS-stimulated RAW 264.7 cells by inhibiting the NF-κB pathway, becoming new candidates for anti-inflammatory agents[56]. Superparamagnetic iron oxide nanoparticles (SPIONs) loaded with ginsenoside compounds K and Rg3 significantly reduced NO and iNOS production in LPS-induced cells, indicating that SPIONs can serve as effective carriers for ginsenosides in inflammatory diseases[57].

Traditional ulcerative colitis (UC) treatments are limited by poor efficacy and significant side effects[58]. Ginsenosides have shown potential in treating colitis and reducing side effects. Xu et al. synthesized pH and redox-sensitive nanoparticles loaded with ginsenoside Rh2 (LA-UaGly nanoparticles) to achieve rapid release and extended circulation time, increasing drug accumulation at lesion sites, protecting RAW 264.7 cells from apoptosis, and inhibiting inflammatory cytokines[53]. In a monosodium urate (MSU) crystal-induced mouse model, nano-ginsenoside Rb1 (nano-GsRb1) demonstrated anti-inflammatory and anti-gouty arthritis effects by inhibiting IκBα degradation, suppressing the NF-κB signaling pathway, and NLRP3 inflammasome activation, thereby reducing TNF-α, IL-1β, and IL-6 expression[59].

Microneedles (MNs) have gained attention for enhancing permeability and drug delivery efficiency. Formulating Rg3 into liposomes (Rg3-Lipo) improves its solubility and absorption efficiency. Encapsulating Rg3-Lipo in microneedles (Rg3-MNs) is an optimal strategy for psoriasis treatment, capable of inhibiting the pSTAT3 signaling pathway and reducing IL-17, IL-23, and TNF-α levels in an imiquimod (IMQ)-induced psoriasis-like dermatitis mouse model[60].

5. ANTIATHEROSCLEROSIS

Cardiovascular diseases, particularly atherosclerosis (AS), are leading causes of human mortality[61]. Enhancing the targeting ability of nanosystems and developing safe and effective nanotherapies are key challenges in AS treatment. Nanomedicine shows great potential in the diagnosis and treatment of AS. Biomimetic membranes, such as those derived from red blood cells, leukocytes, platelets, and endothelial cells, are used to coat nanoparticles, avoiding macrophage phagocytosis and improving drug utilization[62]. Platelets naturally accumulate at AS plaques, while selenium (Se) and its proteins can inhibit AS progression. Yin et al. developed a biomimetic nanodrug delivery system by loading Rb1 into selenium nanoparticles. Studies indicated that PM@Se/Rb1 NPs effectively treated AS by increasing HDL-c expression and reducing levels of ICAM-1, LDL-c, TG, and TC[51].

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

Shen et al. developed a dual-targeting biomimetic nanosystem (Cat/Re@PLGA@UCM) using porous PLGA nanoparticles modified with U937 cell membranes, loaded with ginsenoside Re and catalase (CAT). This system exhibited excellent antioxidant effects and H_2O_2-responsive drug release capability. It slowed AS progression by reducing levels of ROS, TNF-α, and IL-1β[52]. The formation of cholesterol crystals in AS plaques is associated with acute pathology. AnxV-Rb1-LPs target phosphatidylserine in plaques to clear cholesterol crystals, alleviating inflammation and apoptosis[63].

6. CONCLUSIONS AND FUTURE PERSPECTIVES

Ginseng holds a significant position in traditional Chinese medicine, and its development and utilization have always been of great interest. The active components of ginseng, particularly ginsenosides, play a crucial role in its pharmacological effects. However, their strong hydrophobicity and low oral bioavailability have limited their clinical application. Structural modifications of ginsenosides through methods such as acylation, sulfation, amino acid conjugation, oxidation, and alkylation can effectively enhance their water solubility, stability, and targeting ability, thereby significantly improving their pharmacological activity. In addition to chemical modifications, nano-delivery systems—such as liposomes, nanomicelles, polymer nanoparticles, magnetic nanoparticles, nanospheres, and hybrid nanocomposites—can also effectively overcome the issues of poor solubility, low targeting ability, and low bioavailability of ginsenosides.

Formulating ginsenosides into nanomedicines can improve their bioavailability, and ginsenosides can also serve as carrier materials to enhance the properties of related nanomedicines. When encapsulating other drugs, they can achieve synergistic therapeutic effects, thus holding great development value and application potential. Moreover, stimuli-responsive nanocarriers can precisely trigger drug release remotely and spatiotemporally under external stimuli (such as light, heat, and sound). Therefore, designing novel stimuli-responsive carriers that combine various endogenous and exogenous stimuli-responsive strategies for disease treatment is innovative and challenging. In recent years, with the continuous discovery and development of new technologies and methods in the pharmaceutical field, ginsenoside-based drugs are expected to play a significant role in the treatment of more diseases. Continuing in-depth research on the pharmacological effects of ginsenosides and optimizing their formulation forms are of great significance for their clinical application.

REFERENCES

[1] M. Q. Hou, R. F. Wang, S. J. Zhao, et al. Ginsenosides in Panax genus and their biosynthesis, Acta pharmaceutica Sinica. B, Vol. 11 (2021) No. 7, p.1813-1834.

[2] W. T. Wang, Y. J. Xue, J. K. Zhou, et al. Exploring the antimicrobial activity of rare ginsenosides and the progress of their related pharmacological effects, Phytomedicine, Vol. 133 (2024), p. 155904.

[3] T. Ke, L. Huang, Y. Song, et al. Preparation and pharmacological effects of minor ginsenoside nanoparticles: a review, Frontiers in Pharmacology, Vol.13 (2022), p. 974274.

[4] L. Dai, W. Y. Zhu, C. L. Si, et al. "Nano-Ginseng" for Enhanced Cytotoxicity AGAINST Cancer Cells, International Journal of Molecular Sciences, Vol. 19 (2018) No. 2.

[5] D. H. Fan, Y. K. Cao, M. Q. Cao, et al. Nanomedicine in cancer therapy, Signal Transduction and Targeted Therapy, Vol. 8 (2023) No. 1, p. 293.

[6] G. W. Jin, N. S. Rejinold, and J. H. Choy. Multifunctional Polymeric Micelles for Cancer Therapy, Polymers, Vol. 14 (2022) No. 22.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

[7] M. D'Acunto, P. Cioni, E. Gabellieri, et al. Exploiting gold nanoparticles for diagnosis and cancer treatments, Nanotechnology, Vol. 32 (2021) No. 19, p. 192001.

[8] L. M. Sun, H. M. Liu, Y. Q. Ye, et al. Smart nanoparticles for cancer therapy, Signal Transduction and Targeted Therapy, Vol. 8 (2023) No. 1, p. 418.

[9] D. Doblas, J. Hubertus, T. Kister, et al. A Translucent Nanocomposite with Liquid Inclusions of a Responsive Nanoparticle Dispersion, Advanced materials, Vol. (2018). p. e1803159.

[10] R. S. Kalhapure, J. Renukuntla. Thermo-and pH dual responsive polymeric micelles and nanoparticles, Chemico-Biological Interactions, Vol. 295 (2018), p. 20-37.

[11] L. k. Lu, H. Ao, J. X. Fu, et al. Ginsenoside Rb1 stabilized and paclitaxel/protopanaxadiol co-loaded nanoparticles for synergistic treatment of breast tumor, Biomedicine & pharmacotherapy, Vol. 163 (2023), p. 114870.

[12] Y. Xu, B. W. Zhu, R. Sun. Colon-Targeting Angelica sinensis Polysaccharide Nanoparticles with Dual Responsiveness for Alleviation of Ulcerative Colitis, Acs Applied Materials & Interfaces, Vol. 15 (2023) No. 22, p. 26298-26315.

[13] D. Ding, X. Q. Jiang. Advances in Immunogenic Cell Death for Cancer Immunotherapy, Small Methods, Vol. 7 (2023) No. 5, p. e2300354.

[14] X. P. Duan, C. Chan, W. B. Lin. Nanoparticle-Mediated Immunogenic Cell Death Enables and Potentiates Cancer Immunotherapy, Angewandte Chemie, Vol. 58 (2019) No. 3, p. 670-680.

[15] K. J. Son, K. R. Choi, S. J. Lee, et al. Immunogenic Cell Death Induced by Ginsenoside Rg3: Significance in Dendritic Cell-based Anti-tumor Immunotherapy, Immune Network, Vol. 16 (2016) No. 1, p. 75-84.

[16] H. Wu, G. L. Wei, L. X. Luo, 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, Biomaterials Research, Vol. 26 (2022) No. 1, p. 77.

[17] J. Yang, W. Zhang, L. Jia, et al. A novel autophagy activator ginsenoside Rh2 enhances the efficacy of immunogenic chemotherapy, Vol. 13 (2023), p. e1109.

[18] L.W. Fu, W. Y. Zhang, X. J. Zhou, et al. Tumor cell membrane-camouflaged responsive nanoparticles enable MRI-guided immuno-chemodynamic therapy of orthotopic osteosarcoma, Bioactive Materials, Vol. 17 (2022), p. 221-233.

[19] H. Chen, X. Luo, Q. H. Huang, et al. Platelet membrane fusion liposome loaded with type I AIE photosensitizer to induce chemoresistance cancer pyroptosis and immunogenic cell death for enhancing cancer immunotherapy, Chemical Engineering Journal, Vol. 476 (2023a), p. 146276.

[20] H. J. Wang, D. H. Bremner, K. H. Wu, et al. Platelet membrane biomimetic bufalin-loaded hollow MnO2 nanoparticles for MRI-guided chemo-chemodynamic combined therapy of cancer, Chemical Engineering Journal, Vol. 382 (2020), p. 122848.

[21] M. Chen, Y. Y. Qiao, J. Cao, et al. Biomimetic doxorubicin/ginsenoside co-loading nanosystem for chemoimmunotherapy of acute myeloid leukemia, Journal of Nanobiotechnology, Vol. 20 (2022) No. 1, p. 273.

[22] H. Chen, X. Luo, Q. H. Huang, et al. Platelet membrane fusion liposome loaded with type I AIE photosensitizer to induce chemoresistance cancer pyroptosis and immunogenic cell death for enhancing cancer immunotherapy, Chemical Engineering Journal, Vol. 476 (2023b), p. 146276.

[23] C. Y. Jia, Y. X. Guo, F. G. Wu. Chemodynamic Therapy via Fenton and Fenton-Like Nanomaterials: Strategies and Recent Advances, Small, Vol. 18 (2022) No. 6, p. e2103868.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

[24] M. J. Ko, S. H. Min, H. Hong, et al. Magnetic nanoparticles for ferroptosis cancer therapy with diagnostic imaging, Bioactive Materials, Vol. 32 (2024), p. 66-97.

[25] X. X. Zhao, J. C. Wu, D. J. Guo, et al. Dynamic ginsenoside-sheltered nanocatalysts for safe ferroptosis-apoptosis combined therapy, Acta Biomaterialia, Vol. 151 (2022), p. 549-560.

[26] X. X. Zhao, J. C. Wu, K. X. Zhang, et al. The synthesis of a nanodrug using metal-based nanozymes conjugated with ginsenoside Rg3 for pancreatic cancer therapy, Nanoscale Advances, Vol. 4 (2021) No. 1, p. 190-199.

[27] C. Pasqualini, T. Kozaki, M. Bruschi, et al. Modeling the Interaction between the Microenvironment and Tumor Cells in Brain Tumors, Neuron, Vol. 108 (2020) No. 6, p. 1025-1044.

[28] Y. Zhu, J. M. Liang, C. F. Gao, et al. Multifunctional ginsenoside Rg3-based liposomes for glioma targeting therapy. Journal of controlled release, Vol. 330 (2021), p. 641-657.

[29] X. Y. Kong, R. Cheng, J. Wang, et al. Nanomedicines inhibiting tumor metastasis and recurrence and their clinical applications, Nano Today, Vol. 36 (2021), p. 101004.

[30] J. X. Xia, S. J. Ma, X. Zhu, et al. Versatile ginsenoside Rg3 liposomes inhibit tumor metastasis by capturing circulating tumor cells and destroying metastatic niches, Science Advances, Vol. 8 (2022) No. 6, p. j1262.

[31] I. Kim, S. Choi, S. Yoo, et al. Cancer-Associated Fibroblasts in the Hypoxic Tumor Microenvironment, Cancers, Vol. 14 (2022) No. 14.

[32] J. X. Xia, S. Y. Zhang, R. Zhang, et al. Targeting therapy and tumor microenvironment remodeling of triple-negative breast cancer by ginsenoside Rg3 based liposomes, Journal of Nanobiotechnology, Vol. 20 (2022) No. 1, p. 414.

[33] Y. Zhu, A. N. Wang, S. Y. Zhang, et al. Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells, Journal of Advanced Research, Vol. 49 (2023), p. 159-173.

[34] H. L. Li, N. Huang, W. K. Zhu, et al. Modulation the crosstalk between tumor-associated macrophages and non-small cell lung cancer to inhibit tumor migration and invasion by ginsenoside Rh2, BMC Cancer, Vol. 18 (2018) No. 1, p. 579.

[35] M. S. Dukhinova, A. Y. Prilepskii, A. A. Shtil, et al. Metal Oxide Nanoparticles in Therapeutic Regulation of Macrophage Functions, Nanomaterials, Vol. 9 (2019) No. 11.

[36] Z. G. Ren, X. M. Chen, L. J. Hong, et al. Nanoparticle Conjugation of Ginsenoside Rg3 Inhibits Hepatocellular Carcinoma Development and Metastasis, Small, Vol. 16 (2020) No. 2, p. e1905233.

[37] S. T. Zuo, J. Wang, X. Q. An, et al. Fabrication of Ginsenoside-Based Nanodrugs for Enhanced Antitumor Efficacy on Triple-Negative Breast Cancer, Frontiers in Bioengineering and Biotechnology, Vol. 10 (2022), p. 945472.

[38] Z. J. Li, H. Xu, J. D. Shao, et al. Polydopamine-functionalized black phosphorus quantum dots for cancer theranostics, Applied Materials Today, Vol. 15 (2019), p. 297-304.

[39] J. Xiong, H. M. Yuan, H. G. Wu, et al. Black phosphorus conjugation of chemotherapeutic ginsenoside Rg3: enhancing targeted multimodal nanotheranostics against lung cancer metastasis, Drug Delivery, Vol. 28 (2021) No. 1, p. 1748-1758.

[40] N. Wiesmann, W. Tremel, J. Brieger. Zinc oxide nanoparticles for therapeutic purposes in cancer medicine, Journal of materials chemistry. B, Vol. 8 (2020) No. 23, p. 4973-4989.

[41] Y. J. Kim, H. Perumalsamy, V. Castro-Aceituno, et al. Photoluminescent And Self-Assembled Hyaluronic Acid-Zinc Oxide-Ginsenoside Rh2 Nanoparticles And Their Potential Caspase-9

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

Apoptotic Mechanism Towards Cancer Cell Lines, International Journal of Nanomedicine, Vol. 14 (2019), p. 8195-8208.

[42] H. Yao, X. P. Mu, Z. H. Wei, et al. Facile approach for surfactant-free synthesis of Au@ginsenoside Rh2 nanoparticles and researches on anticancer activity, Cancer Nanotechnology, Vol. 13 (2022), p. 35.

[43] J. M. Zhang, Y. Y. Jiang, Y. P. Li, et al. Micelles modified with a chitosan-derived homing peptide for targeted intracellular delivery of ginsenoside compound K to liver cancer cells, Carbohydrate Polymers, Vol. 230 (2020), p. 115576.

[44] L. Li, Y. L. Wang, R. Guo, et al. Ginsenoside Rg3-loaded, reactive oxygen species-responsive polymeric nanoparticles for alleviating myocardial ischemia-reperfusion injury, Journal of controlled release, Vol. 317 (2020a), p. 259-272.

[45] Z. R. Qiu, Y. W. Zhao, T. Tao, et al. Activation of PPARα Ameliorates Cardiac Fibrosis in Dsg2-Deficient Arrhythmogenic Cardiomyopathy, Cells, Vol. 11 (2022) No. 20.

[46] L. Mu, R. N. Dong, C. Y. Li, et al. ROS responsive conductive microspheres loaded with salvianolic acid B as adipose derived stem cell carriers for acute myocardial infarction treatment, Biomaterials, Vol. 314 (2024), p. 122849.

[47] Y. Zhang, H. X. Ji, O. Qiao, et al. Nanoparticle conjugation of ginsenoside Rb3 inhibits myocardial fibrosis by regulating PPARα pathway, Biomedicine & pharmacotherapy, Vol. 139 (2021a), p. 111630.

[48] C. Q. Li, X. B. Gou, H. Gao. Doxorubicin nanomedicine based on ginsenoside Rg1 with alleviated cardiotoxicity and enhanced antitumor activity, Nanomedicine, Vol. 16 (2021) No. 29, p. 2587-2604.

[49] Z. H. Fu, X. H. Wang, X. Lu, et al. Mannose-decorated ginsenoside Rb1 albumin nanoparticles for targeted anti-inflammatory therapy, Frontiers in Bioengineering and Biotechnology, Vol. 10 (2022a), p. 962380.

[50] Y. Liu, H. Perumalsamy, C. H. Kang, et al. Intracellular synthesis of gold nanoparticles by Gluconacetobacter liquefaciens for delivery of peptide CopA3 and ginsenoside and anti-inflammatory effect on lipopolysaccharide-activated macrophages, Artif Cells Nanomed Biotechnol, Vol. 48 (2020a) No. 1, p.777-788.

[51] M. D. Yin, J. F. Lin, M. Y. Yang, et al. Platelet membrane-cloaked selenium/ginsenoside Rb1 nanosystem as biomimetic reactor for atherosclerosis therapy. Colloids Surf B Biointerfaces, Vol. 214 (2022a), p. 112464.

[52] J. W. Shen, C. Li, M. Y. Yang, et al. Biomimetic nanoparticles: U937 cell membranes based core-shell nanosystems for targeted atherosclerosis therapy, International Journal of Pharmaceutics, Vol. 611 (2022a), p. 121297.

[53] Y. Xu, B. W. Zhu, X. Li, et al. Glycogen-based pH and redox sensitive nanoparticles with ginsenoside Rh (2) for effective treatment of ulcerative colitis. Biomaterials, Vol. 280 (2022a), p. 121077.

[54] N. I. O. da Silva, E. A. Salvador, I. Rodrigues Franco, et al. Bovine serum albumin nanoparticles induce histopathological changes and inflammatory cell recruitment in the skin of treated mice, Biomedicine & pharmacotherapy, Vol. 107 (2018), p. 1311-1317.

[55] H. Zhao, H. Zhao, Y. Tang, et al. Skin-permeable gold nanoparticles with modifications azelamide monoethanolamine ameliorate inflammatory skin diseases, Biomarker Research, Vol. 12 (2024) No.1, p. 118.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202412_10(12).0009

[56] X. J. Mi, H. S. Choi, H. R. Park, et al. Structural characterization and anti-inflammatory properties of green synthesized chitosan/compound K-gold nanoparticles, International Journal of Biological Macromolecules, Vol. 213 (2022), p. 247-258.

[57] H. Singh, J. Du, P. Singh, et al. Development of superparamagnetic iron oxide nanoparticles via direct conjugation with ginsenosides and its in-vitro study. J Photochem Photobiol B, Vol. 185 (2018), p. 100-110.

[58] J. Ohn, M. Y. Jang, B. M. Kang, et al. Dissolving Candlelit Microneedle for Chronic Inflammatory Skin Diseases, Advanced science, Vol. 8 (2021) No. 14, p. 2004873.

[59] Y. Liu, H. Y. Zhu, W. Zhou, et al. Anti-inflammatory and anti-gouty-arthritic effect of free Ginsenoside Rb1 and nano Ginsenoside Rb1 against MSU induced gouty arthritis in experimental animals, Chemico-Biological Interactions, Vol. 332 (2020), p. 109285.

[60] C. Huang, K. J. Gou, X. Yue, et al. A novel hyaluronic acid-based dissolving microneedle patch loaded with ginsenoside Rg3 liposome for effectively alleviate psoriasis, Materials & Design, Vol. 224 (2022), p. 111363.

[61] P. Libby. The changing landscape of atherosclerosis, Nature, Vol. 592 (2021) No. 7855, p. 524-533.

[62] S. M. Moghimi, A. C. Hunter, J. C. Murray. Nanomedicine: current status and future prospects, FASEB journal, Vol. 19 (2005) No. 3, p. 311-330.

[63] F. L. Gong, Z. B. Wang, R. Mo, et al. Nano-sponge-like liposomes remove cholesterol crystals for antiatherosclerosis, Journal of controlled release, Vol. 349 (2022), p. 940-953.