Review

Nano Biomed Eng

Nanoparticle-based Traditional Chinese Medicine for Immunotherapy in Gastrointestinal Tumors

Linjia Peng[1,2], Yanfeng Liang[1,2], Qiuli Zhang[1,2], Xiaonan Guo[1,2], Zixuan Gao[1,2], Daxiang Cui[1,2,3]

[1] The First Afffliated Hospital of Henan University, Kaifeng 475004, China
[2] Medical and Engineering Cross Research Institute, Henan University School of Medicine, Kaifeng 475004, China
[3] Institute of Nano Biomedicine and Engineering, School of Sensing Science and Engineering, School of Electronic Information and Electrical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China

Corresponding author. E-mail: dxcui@sjtu.edu.cn

Received: Dec. 28, 2024; **Revised:** Dec. 30, 2024; **Accepted:** Jan. 8, 2025

Citation: L.J. Peng, Y.F. Liang, Q.L. Zhang, et al. Nanoparticle-based traditional chinese medicine for immunotherapy in gastrointestinal tumors. *Nano Biomedicine and Engineering*, 2025, 17(2): 161−178.

http://doi.org/10.26599/NBE.2025.9290115

Abstract

The combination of traditional Chinese medicine (TCM) nanoparticles with modern immunotherapy presents a promising approach to enhancing the treatment of gastrointestinal tumors. TCM nanoparticles can significantly augment the efficacy of conventional immunotherapies by enhancing immune cell activation, modulating the tumor microenvironment, and overcoming immune evasion mechanisms. This review explores the integration of TCM nanoparticles with existing immunotherapy strategies such as immune checkpoint inhibitors, cancer vaccines, and cytokine therapies. It also summarizes the progress in preclinical studies and clinical trials, analyzing their efficacy and safety profiles. Current research indicates that this combinatory approach has shown substantial improvements in anti-tumor immune responses in animal models, with promising early-stage clinical trial results demonstrating favorable safety and potential therapeutic effects. However, further large-scale clinical trials are necessary to confirm its clinical efficacy and safety. Future studies should focus on optimizing treatment regimens and identifying suitable patient populations to advance the clinical application of TCM nanoparticle-based immunotherapy in gastrointestinal cancers.

Keywords: traditional Chinese medicine (TCM) nanoparticles; immunotherapy; gastrointestinal tumors; tumor microenvironment

Introduction

Gastrointestinal (GI) tumors, encompassing a range of malignancies such as colorectal, gastric, and esophageal cancers, pose significant epidemiological and clinical challenges worldwide [1]. These cancers are among the leading causes of cancer-related morbidity and mortality, often diagnosed at advanced stages due to asymptomatic progression in early stages [2]. Traditional therapeutic approaches, including surgery, chemotherapy, and radiation, have limitations in terms of efficacy and associated toxicity [3–5].

In recent years, the integration of traditional Chinese medicine (TCM) into cancer treatment has garnered increasing attention, particularly due to its potential to enhance therapeutic outcomes and reduce side effects [6–8]. TCM, widely used in traditional practices, offer a rich source of bioactive compounds that can exert various pharmacological effects [9, 10].

However, their clinical efficacy is often hindered by poor bioavailability and targeted delivery challenges [11]. This has led to a growing interest in the nanonization of TCM, a process that enhances the solubility and bioavailability of these compounds, thereby facilitating their use in modern therapeutic regimens [12].

The rapid advancement of immunotherapy represents a paradigm shift in the treatment of GI tumors, aiming to harness the body's immune system to recognize and eliminate cancer cells [4, 13]. Despite promising outcomes, many patients exhibit limited responses to current immunotherapeutic strategies, including immune checkpoint inhibitors and chimeric antigen receptor T (CAR-T) cell therapies [14, 15]. This underscores the need for innovative approaches to augment the effectiveness of these treatments.

This review aims to explore how the nanonization of TCM can enhance the efficacy of immunotherapy in treating gastrointestinal tumors. By focusing on the mechanisms through which TCM nanoparticles can improve immune responses and modulate the tumor microenvironment, this work highlights the innovative potential of combining TCM with cutting-edge nanotechnology in the quest for more effective cancer therapies.

Nanoparticle Formulation of TCM

The development of nanoparticle formulations for TCM has opened new avenues for enhancing the therapeutic potential of TCM. Nanonization, or the process of reducing TCM compounds to nanoscale dimensions, significantly improves their solubility, bioavailability, and targeted delivery, overcoming some of the limitations associated with TCM [16–18]. This section explores the various methods of nanonization, along with the design principles of nanocarriers that ensure effective delivery and therapeutic outcomes.

Nanonization methods

The nanonization of TCM compounds involves transforming TCM extracts into nanoparticles, thereby enhancing their absorption and efficacy. Different methods can be employed, each with distinct advantages and limitations. The various nanonization methods for TCM compounds, along with their advantages and representative examples, are summarized in Table 1.

Physical methods

Physical nanonization techniques rely on mechanical forces to break down TCM particles into nanoscale dimensions without altering their chemical properties.

High-energy ball milling

This technique uses mechanical grinding to reduce the size of TCM particles [19]. The process involves placing the material in a chamber with balls, which rotate at high speeds, causing the particles to collide and fragment. It is effective for producing uniform nanoparticles but may require prolonged milling times.

Table 1 Methods of nanonization for TCM compounds.

Method	Sub-type	Application in Immunotherapy	Advantages	Examples
Physical methods	High-energy ball milling	Used for formulating nanoparticles that deliver TCM compounds for enhancing immune cell activation	Produces uniform nanoparticles	TCM particles ground to nanoscale
	Jet milling	Maintains the stability of sensitive immunomodulatory compounds in nanoparticle form	Maintains stability of sensitive compounds	TCM powders processed via jet milling
	Ultrasonication	Enhances dispersion of immunostimulatory compounds, improving their distribution and efficacy	Enhances dispersion	Epimedium polysaccharide nanoparticles
Chemical methods	Solvent evaporation	Used to formulate nanoparticles that encapsulate immune modulators, enhancing the immune response	Consistent size and shape	Curcumin nanoparticles
	Co-precipitation	Used for encapsulating anti-cancer agents that enhance antigen presentation and immune cell infiltration	Narrow size distribution	Steroid nanoparticles from cane toad poison
	Emulsion techniques	Applied in the preparation of hydrophobic immune adjuvants that increase antigen presentation and immune responses	Effective for hydrophobic compounds	Ginkgolides nanoparticles
Biological methods	Green synthesis using plant extracts	Plant-based nanoparticles can enhance immune response by activating immune cells like T cells and NK cells	Eco-friendly, biocompatible	Neem silver nanoparticles
	Enzymatic synthesis	Enzyme-catalyzed synthesis of nanoparticles for delivering TCM compounds that activate immune responses	High specificity, mild conditions	β-Cyclodextrin nanoparticles
	Microbial synthesis	Microbial synthesis can produce nanoparticles that modulate immune responses, enhancing immune cell infiltration	Scalable, cost-effective	Selenium nanoparticles by Fusarium oxysporum

Jet milling

Jet milling utilizes high-velocity air or steam to grind particles into nanoparticles [20]. It is a dry process that can be applied to temperature-sensitive TCM components without affecting their stability. This method is advantageous for maintaining the integrity of TCM compounds.

Ultrasonication

Ultrasonication involves the use of ultrasonic waves to induce cavitation in a liquid medium, breaking down larger particles into smaller ones [21]. It is particularly useful for dispersing nanoparticles in solution and can be used in combination with other methods for improved results. Ultrasonication has been employed in the preparation of water-soluble Epimedium polysaccharides nanoparticles [22]. By combining ultrasonication with other methods, researchers achieved a more homogenous dispersion of nanoparticles, enhancing their therapeutic effects in preclinical studies [23].

Chemical methods

Chemical approaches to nanonization involve the use of solvents, surfactants, or other reagents to create nanoparticles. These methods allow for precise control over particle size and morphology, but require careful consideration of solvent toxicity and removal.

Solvent evaporation

TCM compounds are dissolved in a solvent, which is then evaporated, leaving behind nanoparticles [24]. The technique is effective for forming nanoparticles with consistent size and shape, but the choice of solvent is critical to ensure biocompatibility [25]. For example, the use of solvent evaporation has been reported for preparing nanoparticles from *Curcuma longa* (turmeric). Curcumin, the active ingredient, was dissolved in ethanol, and upon evaporation, nanoparticles with enhanced solubility and stability were formed. These nanoparticles demonstrated improved anticancer activity in vitro compared to free curcumin [26].

Co-precipitation

This technique involves dissolving TCM components in a solvent, followed by the addition of a non-solvent to induce precipitation. The nanoparticles form as the solute precipitates out of the solution [27]. Co-precipitation is useful for creating nanoparticles with a narrow size distribution. Co-precipitation has been effectively utilized to produce nanoparticles from various TCM compounds [28]. For instance, researchers have successfully created nanoparticles from cane toad poison-derived steroids by dissolving the active ingredients in a suitable organic solvent and then adding water as a non-solvent to induce precipitation. This process resulted in the formation of nanoparticles with uniform size and morphology. The resulting nanoparticles demonstrated enhanced bioavailability and bioactivity compared to their bulk counterparts, highlighting the potential of co-precipitation for improving the therapeutic properties of TCM [29].

Emulsion techniques

Emulsion-based methods, such as oil-in-water or water-in-oil emulsions, are used to encapsulate TCM components in nanoparticles [30]. Once the emulsion is formed, the solvent is removed, leaving behind stable nanoparticles. These techniques are advantageous for encapsulating hydrophobic compounds [31]. For example, emulsion techniques have been utilized to encapsulate the bioactive components of Ginkgo biloba. By using an oil-in-water emulsion method, researchers encapsulated ginkgolides in nanoparticles, which demonstrated enhanced stability and bioavailability, providing a more effective delivery system for the therapeutic compounds found in Ginkgo biloba [32].

Biological synthesis

Biological methods for nanonization are gaining traction due to their eco-friendly and biocompatible nature. These methods utilize natural agents, such as plant extracts, enzymes, or microorganisms, to produce nanoparticles for clinical use.

Green synthesis using plant extracts

Plant extracts containing bioactive compounds can act as reducing and capping agents, facilitating the formation of nanoparticles [33]. This method is environmentally sustainable and results in nanoparticles that are generally more biocompatible, enhancing their safety for clinical use [34]. For instance, researchers have demonstrated the synthesis of silver nanoparticles using extracts from *Azadirachta indica* (neem) [35]. The phytochemicals in the neem extract effectively reduced silver ions to form nanoparticles, which exhibited potent

antibacterial activity against various pathogens. These neem-synthesized nanoparticles not only showed improved antimicrobial properties but also displayed low cytotoxicity, underscoring their potential for clinical applications [36].

Enzymatic synthesis

Enzymes can catalyze the formation of nanoparticles by reducing metal ions or modifying TCM molecules [37]. This approach is highly specific, allowing for controlled synthesis under mild conditions, which preserves the integrity of sensitive TCM components. A notable example involves the use of enzymatic and ultrasound-assisted extraction of β-cyclodextrin to isolate active ingredients from Forsythia suspensa. This method not only enhances the extraction efficiency of the active compounds but also retains their antioxidant and anti-inflammatory activities [38].

Microbial Synthesis

Microorganisms, such as bacteria or fungi, can be used to synthesize nanoparticles through their metabolic processes [39]. This method is not only cost-effective but also scalable for mass production. The nanoparticles produced often exhibit unique properties that enhance their therapeutic potential [37]. For example, Fusarium oxysporum, a fungal species, has been successfully utilized to produce selenium nanoparticles. The fungal extract facilitated the reduction of selenite ions to form nanoparticles, which exhibited notable anticancer activity against breast cancer cell lines. The unique properties of these selenium nanoparticles, such as their size and shape, contributed to their enhanced therapeutic effects [40, 41].

Design of nanocarriers

The design of nanocarriers is critical to enhancing the delivery and efficacy of TCM medicine components for cancer therapy. By engineering these nanocarriers to be multifunctional, they can achieve specific targeting, controlled release, and improved therapeutic outcomes while minimizing adverse effects. Tailoring nanocarrier structures and properties allows for precise delivery of TCM compounds within the tumor microenvironment, optimizing treatment impact and ensuring safety.

Targeting mechanisms

Nanocarriers can be customized with targeting ligands like antibodies, peptides, or aptamers, enabling them to selectively bind to receptors on cancer cells and improve the specificity of treatment [42, 43]. Active targeting is achieved through these ligand attachments, which allow nanocarriers to home in on overexpressed receptors specific to tumor cells [44]. This targeted approach not only maximizes drug accumulation at the tumor site but also reduces off-target effects, thus enhancing treatment efficacy [45]. Additionally, passive targeting leverages the Enhanced Permeability and Retention (EPR) effect [46], a unique feature of tumor environments characterized by leaky vasculature and limited lymphatic drainage [47]. By designing nanocarriers that utilize the EPR effect, drug molecules can accumulate more effectively in tumor tissues, even without active ligands, ensuring selective drug distribution in cancerous sites [48].

Controlled release

Controlled release mechanisms are crucial for maintaining optimal therapeutic concentrations at the target site over prolonged periods, which improves efficacy while reducing systemic toxicity. Stimuli-responsive nanoparticles allow for precise control over drug release, responding to specific internal triggers such as pH changes or enzyme levels in the tumor microenvironment, or external stimuli like temperature or magnetic fields [49]. For example, pH-sensitive nanoparticles release their contents specifically within the acidic environment of a tumor, ensuring localized drug delivery with minimal impact on healthy tissue [50]. Additionally, by utilizing biodegradable polymers in the nanocarriers, it is possible to design systems that gradually degrade and release therapeutic compounds in a sustained manner, reducing the need for frequent dosing and minimizing systemic exposure, thus providing continuous treatment coverage and reducing potential side effects [51, 52].

Multifunctionality

Incorporating multifunctionality into nanocarriers enhances the overall treatment potential by allowing for simultaneous therapeutic, diagnostic, and synergistic capabilities. Theranostic nanoparticles, for example, integrate both therapeutic and diagnostic functions, allowing real-time monitoring of treatment progress alongside the drug delivery [53]. These nanoparticles can be loaded with TCM compounds for therapy as well as imaging agents to track drug

distribution and therapeutic effectiveness directly within the tumor [54]. Co-delivery systems represent another powerful approach, as they allow for the transportation of multiple drugs or TCM compounds within a single nanocarrier [55]. By delivering a combination of therapeutic agents that target various aspects of disease progression, these systems enhance the overall treatment effect and provide a comprehensive, multi-targeted therapeutic approach, which is especially valuable in tackling the complexity of tumor growth and resistance.

Immunotherapy for Gastrointestinal Tumors

Immunotherapy offers significant advantages over traditional cancer treatments by modulating the immune system to recognize and eliminate cancer cells, potentially providing long-lasting therapeutic effects. Key immunotherapy strategies for GI cancers include immune checkpoint inhibitors, CAR-T cell therapy, and therapeutic vaccines, all of which aim to enhance the body's immune response to combat cancer.

Current immunotherapy strategies

Immunotherapy offers significant advantages over traditional cancer treatments by targeting cancer cells with precision, potentially leading to long-lasting therapeutic effects. Key immunotherapy strategies for GI cancers include immune checkpoint inhibitors, CAR-T cell therapy, and therapeutic vaccines, all of which aim to modulate the immune response to fight cancer. Figure 1 illustrates the current immunotherapy approaches for gastrointestinal tumors.

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by targeting specific proteins such as PD-1, PD-L1, and CTLA-4, which act as brakes on the immune system [56, 57]. By blocking these inhibitory signals, ICIs enable T cells to remain active and attack cancer cells. Drugs like pembrolizumab and nivolumab, which target PD-1/PD-L1, have shown promising results, particularly in advanced colorectal cancer (CRC) with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors [58, 59]. These inhibitors enhance T cell activation and proliferation, improving the immune system's ability to target cancer cells. Additionally, anti-CTLA-4 therapies like ipilimumab, often combined with PD-1 inhibitors, can further boost immune responses by blocking T cell inhibition through multiple pathways [60, 61].

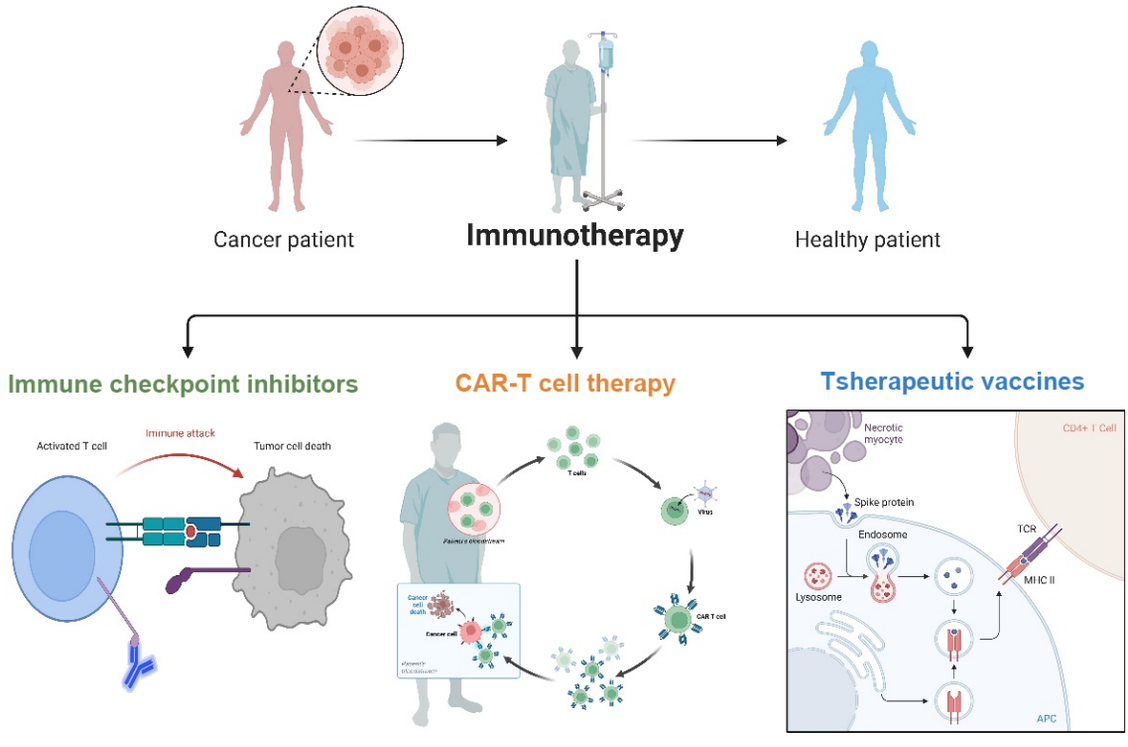

Fig. 1 Current immunotherapy for gastrointestinal tumors. (Figure created with BioRender.com)

However, the efficacy of ICIs is limited in patients without specific biomarkers, and resistance to these therapies remains a significant challenge. For example, in advanced colorectal cancer (CRC), patients with microsatellite stable (MSS) tumors or those without dMMR typically show poor responses to PD-1/PD-L1 inhibitors, as they lack the genetic instability that makes them susceptible to ICI therapy. Similarly, in gastric cancer, where PD-L1 expression is often heterogeneous, patients who do not exhibit high PD-L1 expression may not benefit from nivolumab or pembrolizumab [62]. An example of resistance is seen in hepatocellular carcinoma (HCC), where upregulation of alternative immune checkpoints like TIM-3 and LAG-3 in the tumor microenvironment can impair the effectiveness of PD-1 inhibitors, leading to resistance [63]. This underscores the need for biomarkers to predict the response to immunotherapy. As a result, combination therapies, such as pairing ICIs with targeted therapies or tumor microenvironment-modulating agents, are being explored to enhance treatment efficacy and overcome resistance mechanisms in GI cancers [64, 65].

CAR-T cell therapy

CAR-T cell therapy has demonstrated considerable success in hematological cancers and is now being investigated for use in solid tumors, including GI cancers [66]. In GI cancers, CAR-T cells are designed to target antigens, which are overexpressed in some tumor types [67]. While preclinical and early clinical trials have shown promising results, the solid tumor microenvironment presents significant barriers to the success of CAR-T therapy, including immune suppression, insufficient T cell infiltration, and antigen heterogeneity [68]. Overcoming these challenges is critical to improving the efficacy and therapeutic potential of CAR-T cell therapy for GI cancers.

Therapeutic vaccines

Therapeutic cancer vaccines aim to elicit a targeted immune response by introducing tumor-associated antigens to stimulate the immune system to recognize and destroy cancer cells. Various types of vaccines, including peptide-based and DNA-based vaccines targeting specific tumor antigens (such as CEA and MUC1) [69, 70], have been developed to enhance T cell responses against GI tumors. These vaccines function by priming the immune system to recognize tumor cells as foreign and mount a cytotoxic response. However, their success is highly dependent on the immunogenicity of the target antigens, as well as overcoming immune tolerance mechanisms within the tumor microenvironment. Another promising approach involves dendritic cell (DC) vaccines, which aim to directly activate T cells by presenting tumor antigens to the immune system, promoting a more specific and robust anti-tumor response [71, 72]. Despite progress, significant challenges, such as tumor heterogeneity and immune escape mechanisms, continue to hinder the widespread effectiveness of these immunotherapies.

Potential of TCM in immunotherapy

TCM provides a complementary approach to modern immunotherapy by offering TCM compounds that can modulate the immune system and improve the tumor microenvironment. The integration of TCM with current immunotherapeutic strategies has the potential to enhance the efficacy of treatment and overcome the limitations of existing therapies. Figure 2 illustrates the potential mechanisms of action of TCM in GI cancer immunotherapy.

Enhancement of immune responses

Several TCM compounds have been identified for their ability to stimulate immune responses, making them potential candidates for enhancing the effects of immunotherapy. Polysaccharides derived from herbs like *Ganoderma lucidum* (Reishi mushroom) and *Astragalus membranaceus* (Astragalus) have demonstrated immunostimulatory properties by promoting the activation and proliferation of immune cells such as T cells, dendritic cells, and natural killer (NK) cells [73, 74]. By enhancing the body's natural immune defenses, these TCM components may synergistically improve the therapeutic outcomes of immunotherapies like checkpoint inhibitors [75].

Improvement of tumor microenvironment

The tumor microenvironment (TME) is often immunosuppressive features that allow cancer cells to evade immune surveillance and proliferate unchecked. Certain TCM herbs have shown potential in modulating the TME to create a more favorable environment for immune activity. For example, extracts from Scutellaria baicalensis (Baikal skullcap) and Panax ginseng have been found to inhibit the production of immunosuppressive cytokines like IL-

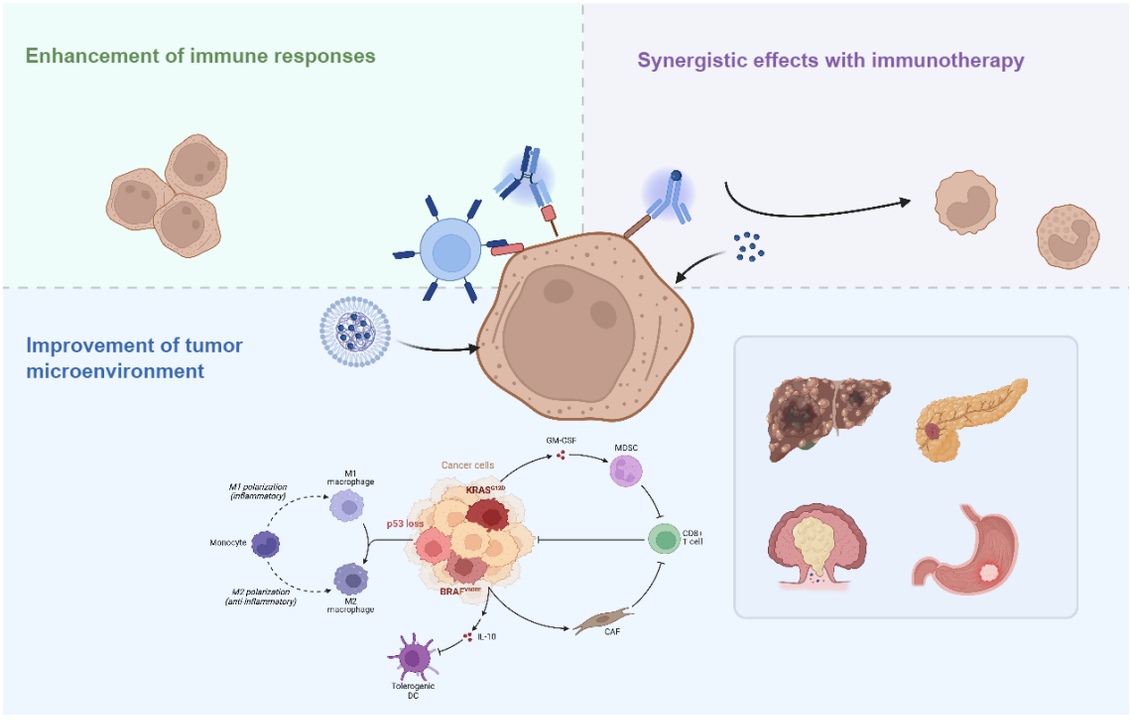

Fig. 2 The potential mechanism of traditional chinese medicine in GI cancer immunotherapy. (Figure created with BioRender.com)

10 and TGF-β [76–78]. This modulation can alleviate immune suppression, facilitating a more favorable environment for immune cell infiltration and enhancing the effectiveness of immunotherapies. Additionally, TCM compounds have been shown to promote the recruitment of effector immune cells such as T cells and NK cells to tumor sites, which is crucial for therapies relying on immune-mediated tumor cell killing [79–81]. For example, Astragalus polysaccharides significantly increased the activation and proliferation of CD8+ T cells within the tumor microenvironment, leading to enhanced tumor cell killing and improved survival rates in animal models [82]. Similarly, Ginsenoside Rg1, derived from Panax ginseng, has been shown to promote the recruitment of T cells to tumor sites, boosting the innate immune response [83].

These findings provide strong evidence that TCM compounds not only enhance the overall immune response but also specifically increase the recruitment and activity of effector immune cells like T cells and NK cells in the tumor microenvironment, thereby improving the effectiveness of immune-based cancer therapies.

Synergistic effects with immunotherapy

The combination of TCM with conventional immunotherapy holds significant promise for inducing synergistic effects that can improve overall treatment outcomes. For instance, TCM compounds with immune-modulatory properties can be used in conjunction with immune checkpoint inhibitors to enhance therapeutic responses. Furthermore, TCM can play a role in mitigating the side effects of immunotherapy [84]. TCM compounds with anti-inflammatory and antioxidant properties can help reduce the adverse effects of conventional treatments, improving patient tolerance and quality of life during therapy [85]. By integrating TCM with current immunotherapeutic strategies, there is potential to improve patient outcomes in GI cancers, particularly by enhancing immune activation, modulating the TME, and providing a synergistic boost to existing treatments.

Mechanisms of Traditional Chinese Medicine Nanoparticles in Enhancing Immunotherapy

Immune system activation

TCM nanoparticles enhance the immune response to tumors through multiple, interconnected mechanisms, offering a comprehensive approach to tumor immunotherapy. The activation of both innate and adaptive immune responses is central to their action,

stimulating a variety of immune cells, including T cells, natural killer (NK) cells, and macrophages [86–88]. These immune cells are key to detecting, targeting, and eliminating tumor cells [89–91]. A significant feature of TCM nanoparticles is their ability to enhance the activation and cytotoxicity of CD4+ helper T cells and CD8+ cytotoxic T cells. These cells are crucial for immune responses and directly targeting tumor cells. By promoting CD4+ T cell proliferation and activation, TCM nanoparticles also facilitate the activation of CD8+ T cells, which are crucial for killing tumor cells. A key factor in this process is the increased production of cytokines, especially interleukin-2 (IL-2) and interferon-gamma (IFN-γ). IL-2 supports T cell expansion and survival, while IFN-γ enhances the cytotoxic activity of T cells and NK cells. A novel nanoplatform, (As+Ce6)@MSNs-PEG, was developed, consisting of astragaloside III (As), an innate immune activator, and Ce6, a photosensitizer for photodynamic therapy (PDT). This nanoplatform effectively activates NK cells and suppresses tumor cell proliferation. It also boosts NK cell and CD8+ T cell cytotoxicity and stimulates IFN-γ secretion, further enhancing anti-tumor immune responses [92] (Fig. 3). Furthermore, IFN-γ activates various immune cells, including macrophages and dendritic cells, improving their ability to attack cancer cells. This boost in cytokine production is not just a byproduct of the nanoparticles but a critical element of their ability to enhance immune responses. The effect of TCM nanoparticles on NK cells further exemplifies their capacity to modulate immune activity. By increasing the expression of activation receptors, such as NKG2D and NKp30, TCM nanoparticles enhance NK cell recognition of tumor cells. These receptors are crucial in the detection of "stressed" or malignant cells that would otherwise evade immune surveillance. Once activated, NK cells release cytotoxic molecules, including perforin and granzymes, which lead to the direct destruction of tumor cells.

In addition to their effects on T cells and NK cells, TCM nanoparticles influence macrophage function, particularly through polarization. Macrophages can adopt different phenotypic states, with the M1 phenotype being pro-inflammatory and supportive of anti-tumor immunity, while the M2 phenotype is associated with immune suppression and tumor progression. A study developed a novel nanoparticle-based vaccine capable of promoting dendritic cell maturation, inhibiting VEGF signaling, and reducing M2 macrophage differentiation, thereby enhancing CD8+ T cell activation to achieve antitumor effects [93]. TCM nanoparticles promote the polarization of macrophages toward the M1 phenotype, which enhances their role in driving immune activation. M1 macrophages produce a range of cytokines that activate other immune cells, facilitate antigen presentation, and stimulate the immune response. At the same time, these nanoparticles suppress the M2 phenotype, reducing the immunosuppressive signals that tumors rely on to evade immune detection. By shifting the balance in favor of M1 macrophages, TCM nanoparticles not only bolster the immune response but also prevent the tumor from co-opting macrophages to create an immune-suppressive environment. Furthermore, TCM nanoparticles can activate dendritic cells to enhance the effects of immunotherapy. LNT-UA is a self-assembled traditional Chinese medicine nanoparticle formulation, where UA (ursolic acid) induces immunogenic cell death (ICD) in tumor cells. LNT (lipid nanoparticles) can promote dendritic cell maturation and shift tumor-associated macrophages from the pro-tumor M2 phenotype to the anti-tumor M1 phenotype. When combined with anti-CD47 antibodies, LNT-UA further enhances anti-tumor immunity by promoting the phagocytosis of dying tumor cells and tumor-associated antigens, effectively inhibiting the growth of both primary and metastatic tumors [94] (Fig. 4).

Through these actions-activating T cells and NK cells, boosting cytokine production, and modulating macrophage polarization-TCM nanoparticles strengthen the immune system's ability to fight cancer. This multi-targeted approach provides a powerful tool to improve the body's natural defenses against tumors. By targeting multiple components of the immune system simultaneously, TCM nanoparticles could significantly enhance immunotherapy effectiveness, leading to improved patient outcomes.

TEM remodeling

Nanoparticles have emerged as powerful tools for remodeling the TME, a critical factor in cancer progression and immune suppression. Among these, TCM-derived nanoparticles provide a unique, multifunctional approach to targeting various immunosuppressive components of the TME,

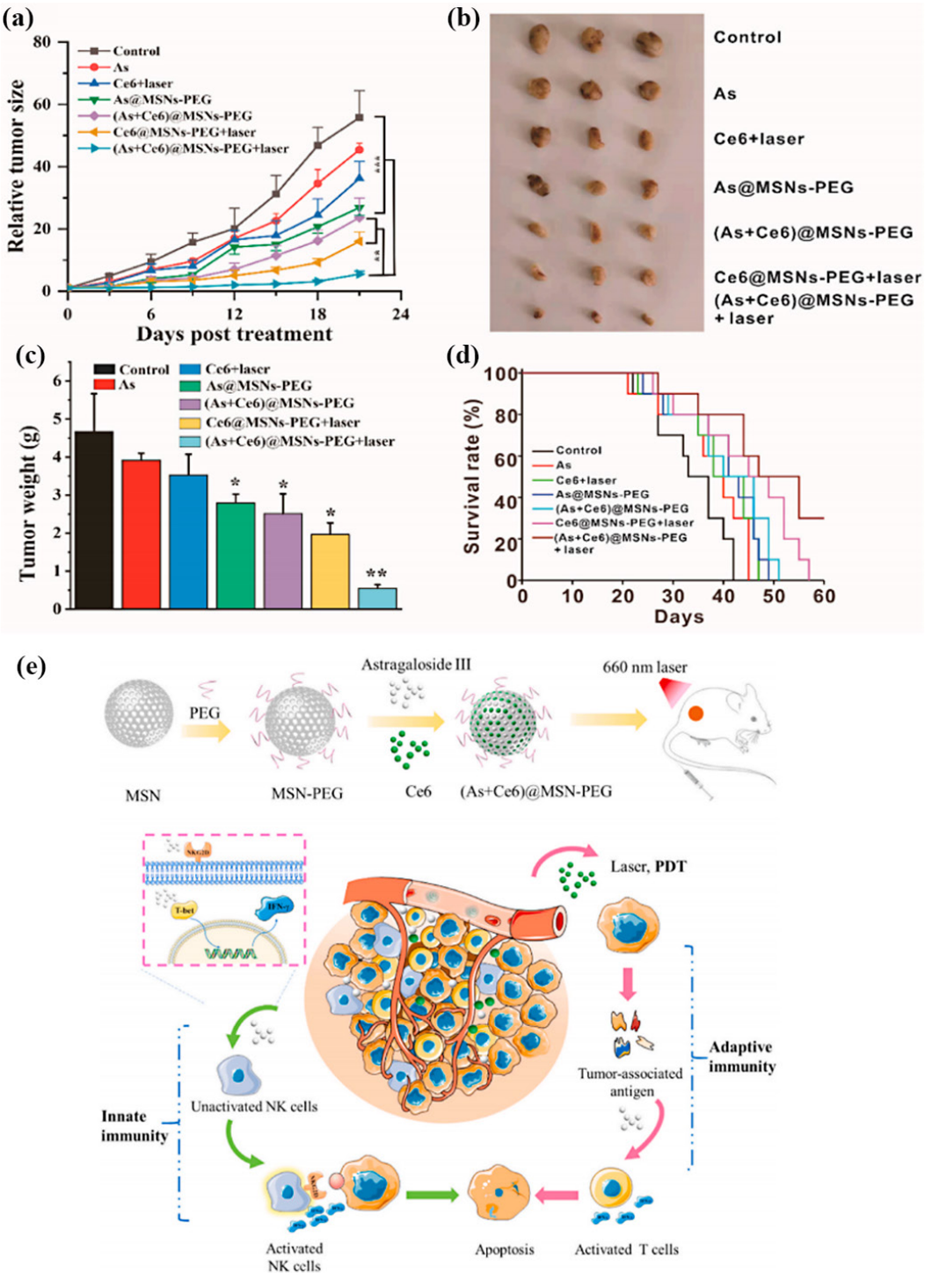

Fig. 3 *In vivo* imaging and synergistic antitumor immunotherapy mechanism of (As+Ce6)@MSNs-PEG nanoparticles. (a) Fluorescence imaging of CT26 tumor-bearing mice at pre-injection and 2, 6, 12, and 24 h post-injection of control, Ce6, and (As + Ce6)@MSNs-PEG groups. (b) *Ex vivo* fluorescence imaging of major organs and tumor in the (As + Ce6)@MSNs-PEG group 24 h post-injection. (c–d) *Ex vivo* images and statistical fluorescence intensity of tumors in control, Ce6, and (As + Ce6)@MSNs-PEG groups 24 h after injection. *$p < 0.05$. (e) Schematic synthesis and synergistic antitumor immunotherapy mechanism of (As+Ce6)@MSNs-PEG nanoparticles. Reproduced with the permission from Ref. [92]. ©2021 Elsevier Ltd.

enhancing anti-tumor immune responses, and improving therapeutic efficacy.

A major advantage of TCM nanoparticles is their ability to enhance immune cell infiltration into tumor tissues. GDNPs reprogram tumor-associated macrophages (TAMs) to downregulate the expression of ARG1, which enhances T cell activity. Specifically, GDNPs polarize M2 macrophages to M1

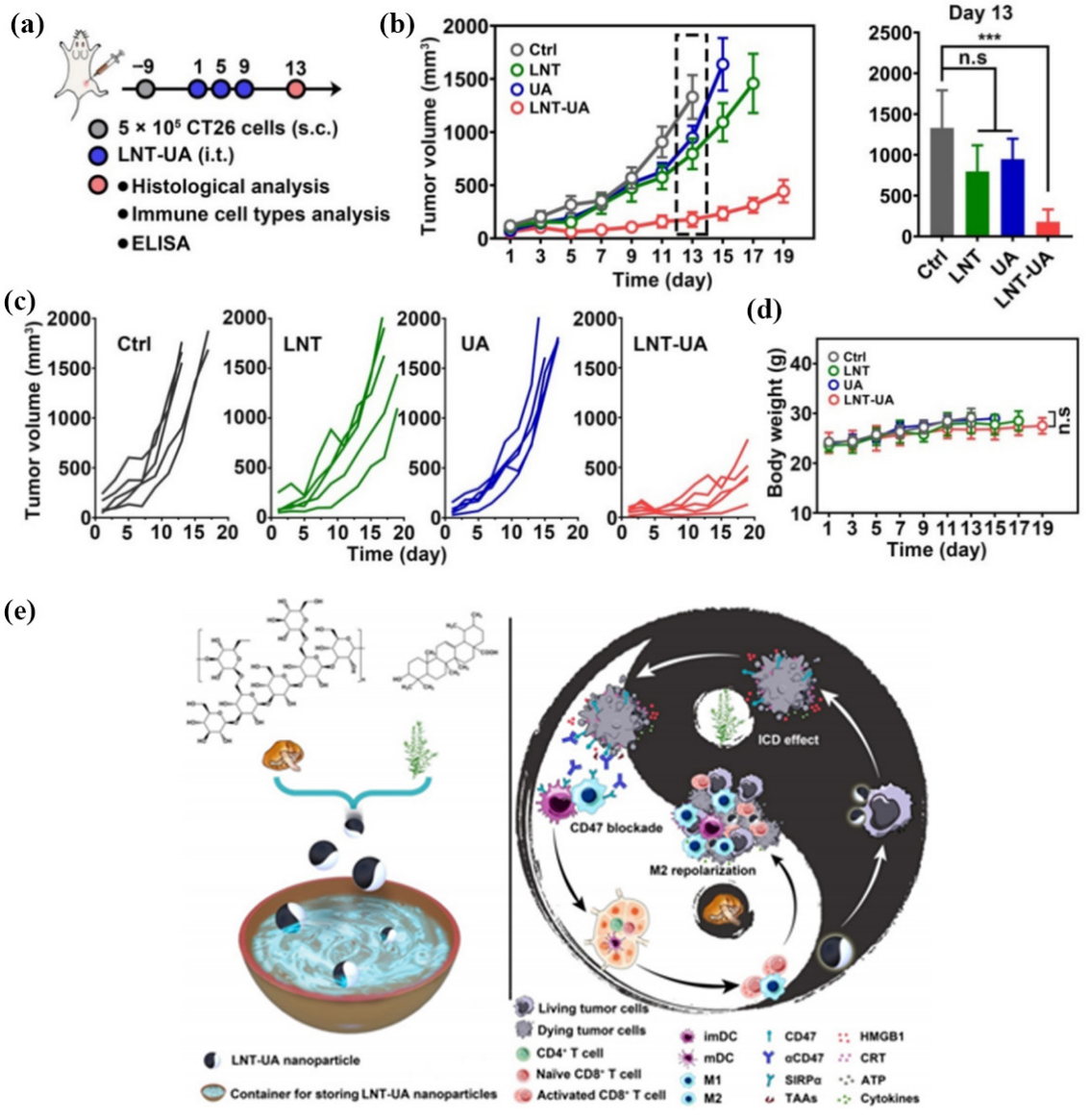

Fig. 4 TCM nanoparticles activate dendritic cells to enhance the effects of immunotherapy. (a) Experimental plan schematic. (b–c) Tumor growth curves for saline, LNT, UA, and LNT-UA treatments. Data presented as mean ± SEM (n = 5). ***p < 0.001. (d) Body weight changes of mice during the experiment. Data presented as mean ± SD (n = 5). (e) Schematic of LNT-UA preparation and its combination with αCD47 for CRC immunotherapy. LNT-UA nanoparticles co-deliver UA (inducing immunogenic cancer cell death) and LNT (promoting dendritic cell maturation and repolarizing TAMs from M2 to M1 phenotype). Reproduced from Ref. [94] ©2022 The Authors.

macrophages, reducing ARG1 release, which promotes T cell proliferation and activation, particularly the cytotoxic function of CD8+ effector T cells (CD8Teff). GDNPs also reduce the expression of immune checkpoint molecules (such as ICOS, PD-1, and TIGIT), alleviating T cell exhaustion and enhancing anti-tumor immune responses. Furthermore, GDNPs activate the mTOR-T-bet signaling pathway, further improving T cell function and boosting the effectiveness of immunotherapy [95] (Fig. 5).

In addition to enhancing immune infiltration, traditional Chinese medicine (TCM) nanoparticles play a key role in overcoming tumor cell immune evasion mechanisms. One key mechanism is the overexpression of immune checkpoint molecules like PD-L1. TCM nanoparticles can downregulate PD-L1 expression, restore immune surveillance, and enhance the efficacy of checkpoint inhibitors, such as anti-PD-1/PD-L1 therapy. For example, Ab@Rg1/Att-ZIF, a nanoparticle designed to deliver ginsenoside Rg1 and atractyloside-I (Att), targets MSS-CRC tumors. It releases Rg1, which promotes tumor antigen processing in dendritic cells, aiding their maturation. Meanwhile, Att enhances the activity of the 26S

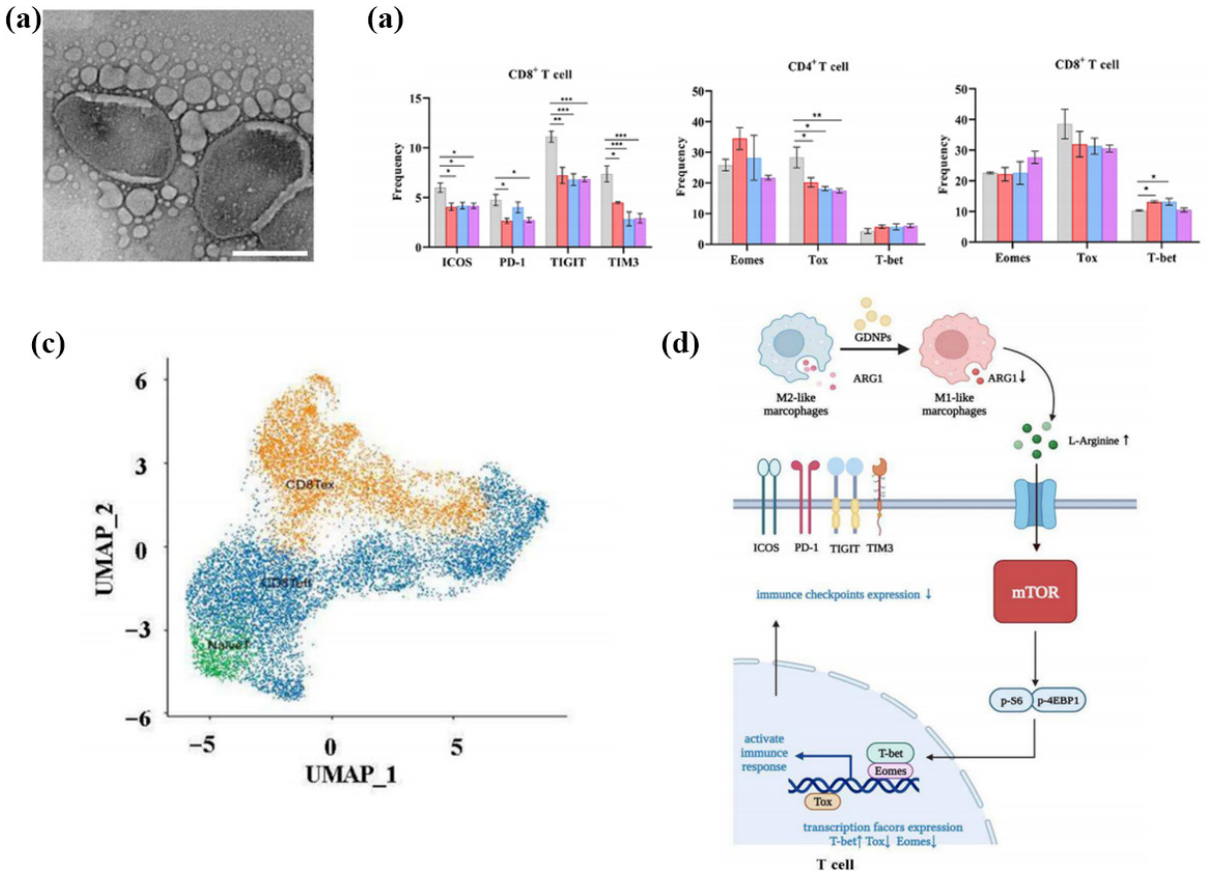

Fig. 5 Characterization and mechanism of GDNPs in modulating T cell exhaustion and macrophage reprogramming. (a) TEM image of GDNPs purified using differential ultracentrifugation. (b) Representative quantification of immune checkpoints (ICOS, PD-1, TIGIT, and TIM3) on CD8+ T cells. The expression levels of transcription factors Eomes, Tox, and T-bet in both CD4+ and CD8+ T cells were analyzed. Data represent the mean ± SEM from three independent experiments. Statistical analysis was performed using one-way ANOVA. (c) UMAP analysis depicting the T cell composition, colored by cluster. (d) Schematic illustrating the mechanism by which GDNPs alleviate T cell exhaustion through macrophage reprogramming. Reproduced from Ref. [95] ©2021 The Authors.

proteasome complex in tumor cells, leading to increased expression of major histocompatibility complex class I (MHC-I). These coordinated effects enhance CTL infiltration and recognition in MSS-CRC, significantly improving the tumor suppression efficacy of PD-1 therapy [96] (Fig. 6).

Metabolic reprogramming of the TME represents another promising avenue for TCM nanoparticles. Tumor cells often create an acidic, immunosuppressive environment by producing lactic acid due to the Warburg effect [97, 98]. TCM nanoparticles can mitigate these effects by shifting tumor metabolism from glycolysis to oxidative phosphorylation, thereby reducing lactate production and normalizing pH levels. Additionally, these nanoparticles enhance mitochondrial function in immune cells, improving their energy metabolism and allowing them to sustain effective anti-tumor activities. For instance, ginseng-derived nanoparticles have demonstrated the potential to restore metabolic balance in preclinical models, significantly boosting the anti-tumor immune response [95].

Another critical target of TCM nanoparticles is the cancer-associated fibroblasts (CAFs) within the TME. CAFs contribute to tumor progression, immune evasion, and metastasis by producing extracellular matrix components, cytokines, and growth factors such as TGF-β and VEGF [99, 100]. TCM nanoparticles disrupt these processes by modulating CAF activity. For example, nanoparticles loaded with α-mangostin and triptolide inhibit CAF activation and reduce extracellular matrix production, promoting tumor blood vessel normalization and improving blood perfusion in tumor areas [101].

TCM nanoparticles represent a promising frontier in cancer therapy, offering a multi-targeted strategy to transform the immunosuppressive TME and amplify the efficacy of existing treatments. Future research

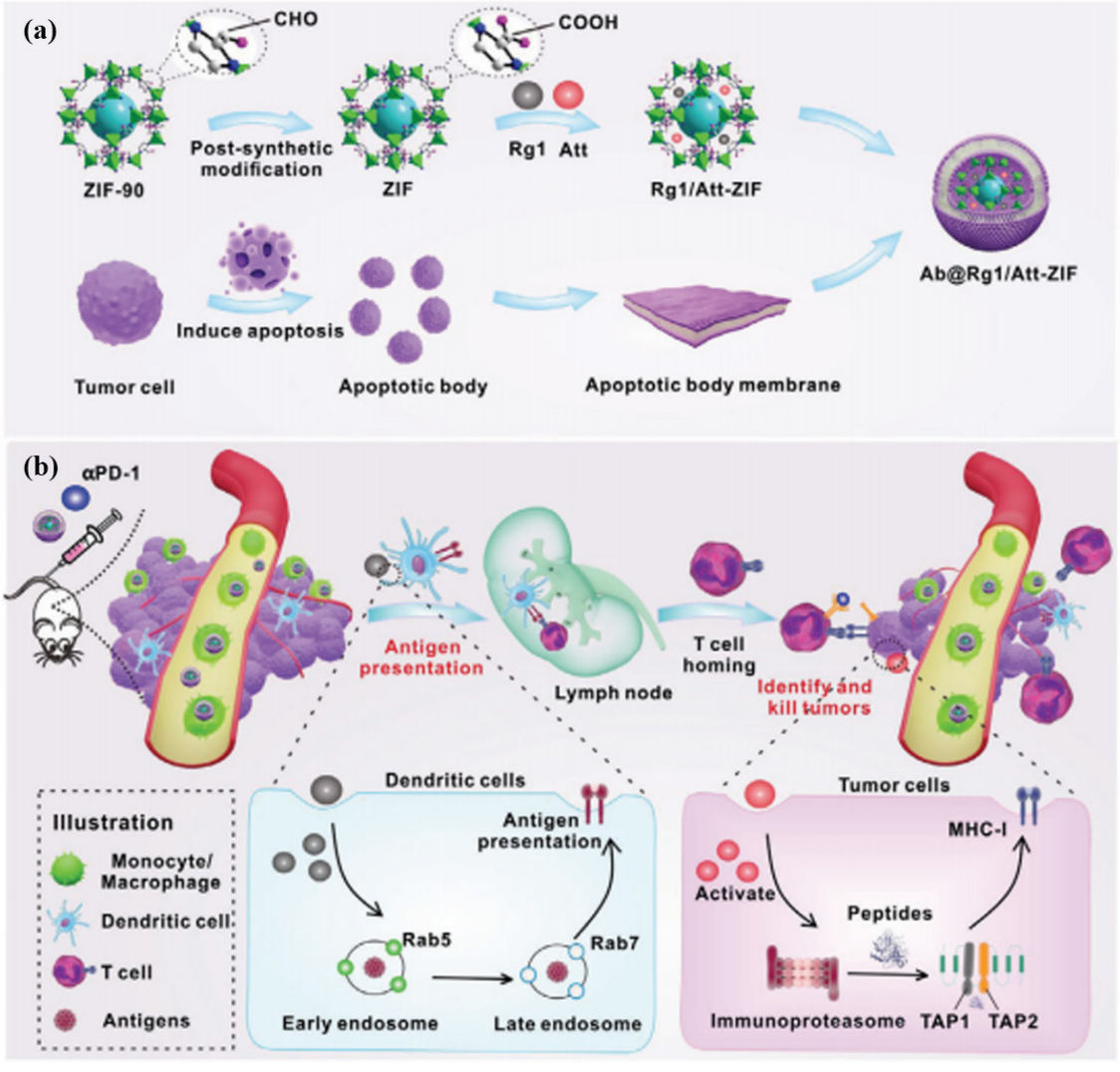

Fig. 6 Schematic diagram of Ab@Rg1/Att-ZIF combined with αPD-1 in MSS. (a) Preparation of Ab@Rg1/Att-ZIF. (b) Following intravenous injection, Ab@Rg1/Att-ZIF was phagocytosed by monocytes/macrophages and delivered to the tumor core. Upon disintegration, it released Rg1 and Att, which enhanced tumor antigen processing in DCs, upregulated MHC-I expression in tumor cells, promoted CTL infiltration, and enabled tumor cell recognition and destruction. The combination with αPD-1 further amplified the therapeutic efficacy against MSS CRC. Reproduced from Ref. [96] ©2024 The Authors.

should focus on optimizing their clinical application, exploring synergies with immunotherapies, and utilizing advanced technologies such as single-cell sequencing and organoid models to better understand their mechanisms of action and guide personalized medicine approaches.

Innovative integration models

The integration of TCM nanoparticles with existing immunotherapy approaches offers a promising strategy to enhance treatment efficacy in gastrointestinal tumors. This combination leverages the immune-boosting properties of TCM and the advanced mechanisms of modern immunotherapies. TCM nanoparticles can complement immune checkpoint inhibitors, cancer vaccines, and cytokine therapies by enhancing immune cell activation, modulating the tumor microenvironment, and overcoming resistance mechanisms [106]. Such combined strategies aim to improve tumor targeting, increase immune cell infiltration, and potentiate the effects of conventional treatments, leading to better overall treatment outcomes [107].

Current preclinical studies show that TCM nanoparticles, when combined with immunotherapies, can enhance anti-tumor immunity and reduce side effects [108]. These studies have demonstrated increased tumor regression and improved survival in animal models [109]. In clinical research, early-phase trials have shown that this combination can be safe and potentially effective, though more extensive trials

Table 2 TCM nanoparticles for GI cancer immunotherapy.

TCM	Immune efficacy	Cancer type	Experimental research	Ref.
Gambogic acid (GA)	Activate dendritic cell maturation, reduce M2 macrophage differentiation, enhance CD8+ T cell activation	Colorectal cancer	*In vivo, in vitro*	[93]
Ursolic acid (UA) and lentinan (LNT)	Dendritic cell maturation and the polarization of tumor-associated macrophages from the pro-tumor M2 phenotype to the anti-tumor M1 phenotype	Colorectal cancer	*In vivo, in vitro*	[94]
Artesunate (AS)	Targeting both tumor cells and M2-like tumor-associated macrophages (TAMs)	Colorectal cancer	*In vivo, in vitro*	[102]
Astragaloside III (As)	Activating NK cells; Enhancing the cytotoxicity of CD8+ T cells; Boosting IFN secretion by immune cells; Increasing the expression of the T-box transcription factor T-bet in T cells	Colon cancer	*In vivo, in vitro*	[92]
Artesunate (AS) and Chloroquine (CQ)	Inhibiting the immunosuppressive phenotype of tumor-associated macrophages (TAMs) and promote the polarization of M2-type TAMs to M1-type TAMs	Colorectal cancer	*In vivo, in vitro*	[102]
Ginseng		Colorectal cancer	*In vivo, in vitro*	[95]
Plumbagin and Dihydrotanshinone I	Inducing immunogenic cell death (ICD) in liver cancer cells, while DIH enhances the ICD effect of PLB through the generation of reactive oxygen species (ROS)	Liver cancer	*In vivo, in vitro*	[103]
Icaritin	Enhancing the induction of immunogenic cell death (ICD) and activating dendritic cells	Hepatocellular carcinoma	*In vivo, in vitro*	[104]
Scutellarin	Reversing the immunosuppressive tumor microenvironment by increasing immunostimulatory cells and reducing immunosuppressive cells	Hepatocellular carcinoma	*In vivo, in vitro*	[105]
α-mangostin and triptolide	Inhibiting the TGF-β/Smad signaling pathway suppresses the activation of tumor-associated fibroblasts (CAFs); reducing the production of extracellular matrix (ECM), improving tumor vascular normalization and enhancing blood perfusion.	Pancreatic cancer	*In vivo, in vitro*	[101]

are needed to confirm these results [107, 110]. Ongoing studies are focusing on optimizing treatment regimens and understanding the best patient populations for this combined therapy (Table 2).

Safety and toxicity assessment

Biocompatibility studies are crucial for assessing the safety of TCM nanoparticles, particularly their potential effects on normal cells and the immune system [111]. These studies aim to evaluate whether the nanoparticles elicit any adverse reactions, such as cytotoxicity or immune system activation, in healthy tissues [112]. Typically, these studies are performed using *in vitro* cell cultures and *in vivo* animal models to ensure that the TCM nanoparticles are safe for human use without causing unintended harm to normal biological functions.

Long-term toxicity studies are essential to evaluate the safety profile of TCM nanoparticles over extended periods. These studies are usually conducted in animal models to assess any potential chronic toxic effects, such as organ damage or systemic toxicity, which may not be apparent in short-term studies [113, 114]. The results from these studies provide valuable insights into the clinical translation potential of TCM nanoparticles, helping to determine whether they can be safely used for long-term treatment without significant side effects or risks to human health [115].

Conclusions

This review underscores the growing significance of TCM nanonization in enhancing the effectiveness of immunotherapy for GI tumors. By transforming TCM compounds into nanoparticles, their bioavailability, target specificity, and therapeutic outcomes can be substantially improved. The integration of TCM nanocarriers with conventional immunotherapies, such as immune checkpoint inhibitors, has shown promising potential in overcoming treatment resistance and boosting immune activation, ultimately improving treatment efficacy.

The combination of TCM nanonization and immunotherapy offers substantial promise in improving patient prognosis for GI cancers. Clinical application prospects are particularly exciting, as this approach could offer more personalized and effective treatment strategies, leading to enhanced patient outcomes. Future applications may involve further optimization of nanoparticle formulations to enhance their targeting capabilities and reduce systemic toxicity. Additionally, continued exploration of synergistic effects between TCM compounds and immunotherapy could unlock novel pathways for enhancing the immune response and overcoming the limitations of current cancer treatments. With further clinical validation and optimization, TCM

nanoparticles combined with immunotherapy have the potential to redefine cancer treatment paradigms, offering a more comprehensive and individualized approach to treating GI cancers. This innovative strategy could not only improve survival rates but also enhance the quality of life for patients, offering a promising direction for future cancer therapies.

CRediT Author Statement

Linjia Peng: conceptualization, writing original manuscript, and editing; **Yanfeng Liang**: visualization, writing review, and editing. **Zixuan Gao, Qiuli Zhang, and Xiaonan Guo**: writing review, and editing. **Daxiang Cui**: investigation, methodology, project administration, and supervision.

Acknowledgements

This work was financially supported by International Cooperation Project of National Natural Science Foundation of China (No. 82020108017), Innovation Group Project of National Natural Science Foundation of China (No. 81921002), the National Key Research and Development Project of China (No. 2017YFA0205301), National Natural Science Foundation of China (No. 82272821), Standard project of Shanghai Science and Technology Commission (21DZ2203200).

Conflict of Interests

The author Daxiang Cui is the EIC for *Nano Biomedicine and Engineering* and was not involved in the editorial review or the decision to publish this article.

References

[1] T.R. de Back, S.R. van Hooff, D.W. Sommeijer, et al. Transcriptomic subtyping of gastrointestinal malignancies. *Trends in Cancer*, 2024, 10(9): 842−856. https://doi.org/10.1016/j.trecan.2024.06.007

[2] P. Sharma, C. Hassan. Artificial intelligence and deep learning for upper gastrointestinal neoplasia. *Gastroenterology*, 2022, 162(4): 1056−1066. https://doi.org/10.1053/j.gastro.2021.11.040

[3] R. Pittayanon, W. Khongka, S. Linlawan, et al. Hemostatic powder vs standard endoscopic treatment for gastrointestinal tumor bleeding: A multicenter randomized trial. *Gastroenterology*, 2023, 165(3): 762−772.e2. https://doi.org/10.1053/j.gastro.2023.05.042

[4] X. Chong, Y. Madeti, J. Cai, et al. Recent developments in immunotherapy for gastrointestinal tract cancers. *Journal of Hematology & Oncology*, 2024, 17(1): 65. https://doi.org/10.1186/s13045-024-01578-x

[5] Q. Gan, Y. Li, Y. Li, et al. Pathways and molecules for overcoming immunotolerance in metastatic gastrointestinal tumors. *Frontiers in Immunology*, 2024, 15: 1359914. https://doi.org/10.3389/fimmu.2024.1359914

[6] K. Miao, W. Liu, J. Xu, et al. Harnessing the power of traditional Chinese medicine monomers and compound prescriptions to boost cancer immunotherapy. *Frontiers in Immunology*, 2023, 14: 1277243. https://doi.org/10.3389/fimmu.2023.1277243

[7] G. Chen, N. Wang, R. Yang, et al. Efficacy and safety of herbal medicines intervention for cachexia associated with cancer: A systematic review and meta-analysis. *Phytotherapy Research*, 2023, 37(11): 5243−5278. https://doi.org/10.1002/ptr.7956

[8] Y. Yan, J. Liu, Y. Pang, et al. Efficacy of Traditional Chinese Medicine Combined Online Group Psychotherapy (TCM-eRhab) on improving quality of life and relieving psychological burden for colorectal cancer survivors: A study protocol for a phase-II randomized controlled trial. *BMC Complementary Medicine and Therapies*, 2024, 24(1): 290. https://doi.org/10.1186/s12906-024-04533-y

[9] X. Feng, Z. Li, W. Guo, et al. The effects of traditional Chinese medicine and dietary compounds on digestive cancer immunotherapy and gut microbiota modulation: A review. *Frontiers in Immunology*, 2023, 14: 1087755. https://doi.org/10.3389/fimmu.2023.1087755

[10] Y.L. Liao, Y. Gui, Q.Z. Li, et al. The signaling pathways and targets of natural products from traditional Chinese medicine treating gastric cancer provide new candidate therapeutic strategies. *Biochimica et Biophysica Acta* (*BBA*) - *Reviews on Cancer*, 2023, 1878(6): 188998. https://doi.org/10.1016/j.bbcan.2023.188998

[11] Y.H. Jin, Y.P. Wang, Y.L. Xie, et al. Research on the development methodology for clinical practice guidelines for organic integration of traditional Chinese and Western medicine. *Military Medical Research*, 2023, 10(1): 45. https://doi.org/10.1186/s40779-023-00481-9

[12] R. Sun, J. Dai, M. Ling, et al. Delivery of triptolide: A combination of traditional Chinese medicine and nanomedicine. *Journal of Nanobiotechnology*, 2022, 20(1): 194. https://doi.org/10.1186/s12951-022-01389-7

[13] K. Jia, Y. Chen, Y. Xie, et al. *Helicobacter pylori* and immunotherapy for gastrointestinal cancer. *The Innovation*, 2024, 5(2): 100561. https://doi.org/10.1016/j.xinn.2023.100561

[14] L. Gervaso, D. Ciardiello, R.A. Oliveira, et al. Immunotherapy in the neoadjuvant treatment of gastrointestinal tumors: Is the time ripe. *Journal for ImmunoTherapy of Cancer*, 2024, 12(5): e008027. https://doi.org/10.1136/jitc-2023-008027

[15] X. Zhu, J. Xue, H. Jiang, et al. CAR-NK cells for gastrointestinal cancer immunotherapy: From bench to bedside. *Molecular Cancer*, 2024, 23(1): 237. https://doi.org/10.1186/s12943-024-02151-3

[16] S. Ai, Y. Li, H. Zheng, et al. Collision of herbal medicine and nanotechnology: A bibliometric analysis of herbal nanoparticles from 2004 to 2023. *Journal of Nanobiotechnology*, 2024, 22(1): 140. https://doi.org/10.1186/s12951-024-02426-3

[17] M. Zheng, K. Liu, L. Li, et al. Traditional Chinese medicine inspired dual-drugs loaded inhalable nano-

therapeutics alleviated idiopathic pulmonary fibrosis by targeting early inflammation and late fibrosis. *J Nanobiotechnology*, 2024, 22(1): 14. https://doi.org/10.1186/s12951-023-02251-0

[18] D. Wei, H. Yang, Y. Zhang, et al. Nano-traditional Chinese medicine: A promising strategy and its recent advances. *Journal of Materials Chemistry B*, 2022, 10(16): 2973−2994. https://doi.org/10.1039/D2TB00225F

[19] Q. Xiang, J. Wang, K. Tao, et al. Optimization of phenolic-enriched extracts from olive leaves *via* ball milling-assisted extraction using response surface methodology. *Molecules*, 2024, 29(15): 3658. https://doi.org/10.3390/molecules29153658

[20] Y. Zhu, T.X. Yang, H. Li, et al. Synergism of jet milling and deep eutectic solvent pretreatment on grapevine lignin fractionation and enhancing enzymatic hydrolysis. *International Journal of Biological Macromolecules*, 2024, 269(pt 2): 132144. https://doi.org/10.1016/j.ijbiomac.2024.132144

[21] J. Wang, Y. Zhao, B. Zhai, et al. Phloretin transfersomes for transdermal delivery: Design, optimization, and *in vivo* evaluation. *Molecules*, 2023, 28(19): 6790. https://doi.org/10.3390/molecules28196790

[22] L. Ke, X. Duan, J. Cui, et al. Research progress on the extraction technology and activity study of Epimedium polysaccharides. *Carbohydr Polym*, 2023, 306: 120602. https://doi.org/10.1016/j.carbpol.2023.120602

[23] G. You, T. Feng, G. Zhang, et al. Preparation, optimization, characterization and *in vitro* release of baicalein-solubilizing glycyrrhizic acid nano-micelles. *International Journal of Pharmaceutics*, 2021, 601: 120546. https://doi.org/10.1016/j.ijpharm.2021.120546

[24] R. Al-Shdefat, M. Hailat, O.Y. Alshogran, et al. Ribociclib hybrid lipid-polymer nanoparticle preparation and characterization for cancer treatment. *Polymers*, 2023, 15(13): 2844. https://doi.org/10.3390/polym15132844

[25] M. Khang, J.H. Lee, T. Lee, et al. Intrathecal delivery of nanoparticle PARP inhibitor to the cerebrospinal fluid for the treatment of metastatic medulloblastoma. *Science Translational Medicine*, 2023, 15(720): eadi1617. https://doi.org/10.1126/scitranslmed.adi1617

[26] A.L. Luss, D.V. Bagrov, A.V. Yagolovich, et al. Toxicity evaluation and controlled-release of curcumin-loaded amphiphilic poly-N-vinylpyrrolidone nanoparticles: *in vitro* and *in vivo* models. *Pharmaceutics*, 2023, 16(1): 8. https://doi.org/10.3390/pharmaceutics16010008

[27] C.R. Liu, B.X. Xu, D.J. McClements, et al. Properties of curcumin-loaded zein-tea saponin nanoparticles prepared by antisolvent co-precipitation and precipitation. *Food Chemistry*, 2022, 391: 133224. https://doi.org/10.1016/j.foodchem.2022.133224

[28] Z.H. Zhang, X.J. Li, S.Y. Sang, et al. Preparation, properties and interaction of curcumin loaded zein/HP-β-CD nanoparticles based on electrostatic interactions by antisolvent co-precipitation. *Food Chemistry*, 2023, 403: 134344. https://doi.org/10.1016/j.foodchem.2022.134344

[29] J. Jing, K.R. Tupally, G.R. Kokil, et al. Development of a hybrid peptide dendrimer micellar carrier system and its application in the reformulation of a hydrophobic therapeutic agent derived from traditional Chinese medicine. *RSC Adv*, 2019, 9(5): 2458−2463. https://doi.org/10.1039/C8RA09606F

[30] W.R. Lee, T.H. Huang, S. Hu, et al. Laser-assisted nanoparticle delivery to promote skin absorption and penetration depth of retinoic acid with the aim for treating photoaging. *International Journal of Pharmaceutics*, 2022, 627: 122162. https://doi.org/10.1016/j.ijpharm.2022.122162

[31] D.V. Bhalani, B. Nutan, A. Kumar, et al. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. *Biomedicines*, 2022, 10(9): 2055. https://doi.org/10.3390/biomedicines10092055

[32] I.D. Boateng. Polyprenols in Ginkgo biloba; a review of their chemistry (synthesis of polyprenols and their derivatives), extraction, purification, and bioactivities. *Food Chemistry*, 2023, 418: 136006. https://doi.org/10.1016/j.foodchem.2023.136006

[33] A. Gul, Fozia, A. Shaheen, et al. Green synthesis, characterization, enzyme inhibition, antimicrobial potential, and cytotoxic activity of plant mediated silver nanoparticle using *Ricinus communis* leaf and root extracts. *Biomolecules*, 2021, 11(2): 206. https://doi.org/10.3390/biom11020206

[34] A. Balčiūnaitienė, P. Štreimikytė, V. Puzerytė, et al. Antimicrobial activities against opportunistic pathogenic bacteria using green synthesized silver nanoparticles in plant and lichen enzyme-assisted extracts. *Plants*, 2022, 11(14): 1833. https://doi.org/10.3390/plants11141833

[35] V. Sakaray, Y.S. Rao, N.V. Naidu. Green synthesis of silver nanoparticles by *Acalypha indica* plant extract and their approach towards multifunctional applications. *Nano Biomedicine and Engineering*, 2024, 16(4): 665−676. https://doi.org/10.26599/NBE.2024.9290064

[36] J. Hawadak, L.P. Kojom Foko, V. Pande, et al. *In vitro* antiplasmodial activity, hemocompatibility and temporal stability of *Azadirachta indica* silver nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology*, 2022, 50(1): 286–300. https://doi.org/10.1080/21691401.2022.2126979

[37] W.J. Feng, Z.Q. Wang, T. Zhang, et al. Biomimetic synthesis of maltodextrin-derived dendritic nanoparticle and its structural characterizations. *Carbohydrate Polymers*, 2023, 312: 120816. https://doi.org/10.1016/j.carbpol.2023.120816

[38] X.Y. Xiao, Y. Zhang, K.D.Sun, et al. Enzymatic and ultrasound assisted β-cyclodextrin extraction of active ingredients from Forsythia suspensa and their antioxidant and anti-inflammatory activities. *Ultrasonics Sonochemistry*, 2024, 108: 106944. https://doi.org/10.1016/j.ultsonch.2024.106944

[39] J. Jeevanandam, S.F. Kiew, S. Boakye-Ansah, et al. Green approaches for the synthesis of metal and metal oxide nanoparticles using microbial and plant extracts. *Nanoscale*, 2022, 14(7): 2534−2571. https://doi.org/10.1039/D1NR08144F

[40] H.G. Lazcano-Ramírez, J.J.O. Garza-García, J.A. Hernández-Díaz, et al. Antifungal activity of selenium nanoparticles obtained by plant-mediated synthesis. *Antibiotics*, 2023, 12(1): 115. https://doi.org/10.3390/antibiotics12010115

[41] M.A. Khan, D. Singh, A. Arif, et al. Protective effect of green synthesized Selenium Nanoparticles against Doxorubicin induced multiple adverse effects in Swiss albino mice. *Life Sciences*, 2022, 305: 120792. https://doi.org/10.1016/j.lfs.2022.120792

[42] Y. Liu, J. Zhang, Y. Tu, et al. Potential-independent intracellular drug delivery and mitochondrial targeting. *ACS Nano*, 2022, 16(1): 1409−1420. https://doi.org/10.1021/acsnano.1c09456

[43] M.M. Agwa, H. Elmotasem, R.I. Moustafa, et al. Advent in proteins, nucleic acids, and biological cell membranes functionalized nanocarriers to accomplish active or homologous tumor targeting for smart amalgamated chemotherapy/photo-therapy: A review. *International Journal of Biological Macromolecules*, 2023, 253: 127460. https://doi.org/10.1016/j.ijbiomac.2023.127460

[44] A. Bandyopadhyay, T. Das, S. Nandy, et al. Ligand-based active targeting strategies for cancer theranostics. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 2023, 396(12): 3417−3441. https://doi.org/10.1007/s00210-023-02612-4

[45] Y.Q. Wang, C. Huang, P.J. Ye, et al. Prolonged blood circulation outperforms active targeting for nanocarriers-mediated enhanced hepatocellular carcinoma therapy *in vivo*. *Journal of Controlled Release*, 2022, 347: 400–413. https://doi.org/10.1016/j.jconrel.2022.05.024

[46] A.S. Postovalova, Y.A. Tishchenko, M.S. Istomina, et al. Comparison of passive targeted delivery of inorganic and organic nanocarriers among different types of tumors. *Nanomedicine: Nanotechnology, Biology and Medicine*, 2024, 59: 102753. https://doi.org/10.1016/j.nano.2024.102753

[47] N. AlSawaftah, W.G. Pitt, G.A. Husseini. Dual-targeting and stimuli-triggered liposomal drug delivery in cancer treatment. *ACS Pharmacology & Translational Science*, 2021, 4(3): 1028−1049. https://doi.org/10.1021/acsptsci.1c00066

[48] M.H. Mohd-Zahid, S.N. Zulkifli, C.A. Che Abdullah, et al. Gold nanoparticles conjugated with anti-CD133 monoclonal antibody and 5-fluorouracil chemotherapeutic agent as nanocarriers for cancer cell targeting. *RSC Advance*, 2021, 11(26): 16131−16141. https://doi.org/10.1039/D1RA01093J

[49] S. Wang, Y. Liu, Q. Sun, et al. Triple cross-linked dynamic responsive hydrogel loaded with selenium nanoparticles for modulating the inflammatory microenvironment *via* PI3K/Akt/NF-κB and MAPK signaling pathways. *Advanced Science*, 2023, 10(31): e2303167. https://doi.org/10.1002/advs.202303167

[50] J. Zhang, L.W. Wei, X.C. Ma, et al. pH-sensitive tumor-tropism hybrid membrane-coated nanoparticles for reprogramming the tumor microenvironment and boosting the antitumor immunity. *Acta Biomaterialia*, 2023, 166: 470–484. https://doi.org/10.1016/j.actbio.2023.05.040

[51] P. Dosta, M.Z. Dion, M. Prado, et al. Matrix metalloproteinase- and pH-sensitive nanoparticle system enhances drug retention and penetration in glioblastoma. *ACS Nano*, 2024, 18(22): 14145−14160. https://doi.org/10.1021/acsnano.3c03409

[52] Z.L. Xu, D. Yang, T. Long, et al. pH-Sensitive nanoparticles based on amphiphilic imidazole/cholesterol modified hydroxyethyl starch for tumor chemotherapy. *Carbohydrate Polymers*, 2022, 277: 118827. https://doi.org/10.1016/j.carbpol.2021.118827

[53] Y.S. Choi, H. Cho, W.G. Choi, et al. Beyond hydrophilic polymers in amphiphilic polymer-based self-assembled NanoCarriers: Small hydrophilic carboxylate-capped disulfide drug delivery system and its multifunctionality and multispatial targetability. *Biomaterials*, 2022, 280: 121307. https://doi.org/10.1016/j.biomaterials.2021.121307

[54] M.F. Wu, Q. Wang, Y.Y. Peng, et al. Enhancing targeted therapy in hepatocellular carcinoma through a pH-responsive delivery system: Folic acid-modified polydopamine-paclitaxel-loaded poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanoparticles. *Molecular Pharmaceutics*, 2024, 21(2): 581−595. https://doi.org/10.1021/acs.molpharmaceut.3c00710

[55] Q. Zhang, G. Kuang, H. Wang, et al. Multi-bioinspired MOF delivery systems from microfluidics for tumor multimodal therapy. *Advanced Science*, 2023, 10(33): e2303818. https://doi.org/10.1002/advs.202303818

[56] S.J. Wang, S.K. Dougan, M. Dougan. Immune mechanisms of toxicity from checkpoint inhibitors. *Trends in Cancer*, 2023, 9(7): 543−553. https://doi.org/10.1016/j.trecan.2023.04.002

[57] M. Oladejo, W. Paulishak, L. Wood. Synergistic potential of immune checkpoint inhibitors and therapeutic cancer vaccines. *Seminars in Cancer Biology*, 2023, 88: 81−95. https://doi.org/10.1016/j.semcancer.2022.12.003

[58] D.T. Le, T.W. Kim, E. Van Cutsem, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. *Journal of Clinical Oncology*, 2020, 38(1): 11−19. https://doi.org/10.1200/JCO.19.02107

[59] H.J. Lenz, E. Van Cutsem, M. Luisa Limon, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: The phase II CheckMate 142 study. *Journal of Clinical Oncology*, 2022, 40(2): 161−170. https://doi.org/10.1200/JCO.21.01015

[60] M.D. Hellmann, L. Paz-Ares, R.B. Caro, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *The New England Journal of Medicine*, 2019, 381(21): 2020−2031. https://doi.org/10.1056/NEJMoa1910231

[61] M. Lei, N.O. Siemers, D. Pandya, et al. Analyses of PD-L1 and inflammatory gene expression association with efficacy of nivolumab ± ipilimumab in gastric cancer/gastroesophageal junction cancer. *Clinical Cancer Research*, 2021, 27(14): 3926−3935. https://doi.org/10.1158/1078-0432.CCR-20-2790

[62] S.Y. Rha, D.Y. Oh, P. Yañez, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial. *The Lancet Oncology*, 2023, 24(11): 1181−1195. https://doi.org/10.1016/S1470-2045(23)00515-6

[63] M. Tampaki, E. Ionas, E. Hadziyannis, et al. Association of TIM-3 with BCLC stage, serum PD-L1 detection, and response to transarterial chemoembolization in patients with hepatocellular carcinoma. *Cancers*, 2020, 12(1): E212. https://doi.org/10.3390/cancers12010212

[64] M. de Miguel, E. Calvo. Clinical challenges of immune checkpoint inhibitors. *Cancer Cell*, 2020, 38(3): 326−333. https://doi.org/10.1016/j.ccell.2020.07.004

[65] P. Sharma, S. Goswami, D. Raychaudhuri, et al. Immune checkpoint therapy-current perspectives and future directions. *Cell*, 2023, 186(8): 1652−1669. https://doi.org/10.1016/j.cell.2023.03.006

[66] S. Mir, A. Venugopalan, J.L. Zhang, et al. Persistence of activated anti-mesothelin hYP218 chimeric antigen receptor T cells in the tumour is associated with efficacy in gastric and colorectal carcinomas. *Clinical and Translational Medicine*, 2024, 14(11): e70057. https://doi.org/10.1002/ctm2.70057

[67] N. Puebla-Osorio N.W., Fowlkes, H.B. Barsoumian, et al. Enhanced tumor control and survival in preclinical models with adoptive cell therapy preceded by low-dose radiotherapy. *Frontiers in Oncology*, 2024, 14: 1407143. https://doi.org/10.3389/fonc.2024.1407143

[68] W. Lam, R. Hu, S.H. Liu, et al. YIV-906 enhances nuclear factor of activated T-cells (NFAT) activity of T cells and promotes immune checkpoint blockade antibody action and CAR T-cell activity. *Frontiers in Pharmacology*, 2022, 13: 1095186. https://doi.org/10.3389/fphar.2022.1095186

[69] A. Guerreiro, I. Compañón, F.S. Lazaris, et al. Non-natural MUC1 glycopeptide homogeneous cancer vaccine with enhanced immunogenicity and therapeutic activity. *Angewandte Chemie*, 2024, 63(49): e202411009. https://doi.org/10.1002/anie.202411009

[70] K.P. Fabian, M.R. Padget, R. Fujii, et al. Differential

combination immunotherapy requirements for inflamed (warm) tumors versus T cell excluded (cool) tumors: Engage, expand, enable, and evolve. *Journal for Immunotherapy of Cancer*, 2021, 9(2): e001691. https://doi.org/10.1136/jitc-2020-001691

[71] L. Huang, Y. Rong, X. Tang, et al. Engineered exosomes as an *in situ* DC-primed vaccine to boost antitumor immunity in breast cancer. *Molecular Cancer*, 2022, 21(1): 45. https://doi.org/10.1186/s12943-022-01515-x

[72] Y. Liu, J. Pagacz, D.J. Wolfgeher, et al. Senescent cancer cell vaccines induce cytotoxic T cell responses targeting primary tumors and disseminated tumor cells. *Journal for Immunotherapy of Cancer*, 2023, 11(2): e005862. https://doi.org/10.1136/jitc-2022-005862

[73] W. Li, Q. Zhou, B. Lv, et al. *Ganoderma lucidum* polysaccharide supplementation significantly activates T-cell-mediated antitumor immunity and enhances anti-PD-1 immunotherapy efficacy in colorectal cancer. *J Agric Food Chem*, 2024, 72(21): 12072−12082. https://doi.org/10.1021/acs.jafc.3c08385

[74] G. Deng, L. Zhou, B. Wang, et al. Targeting cathepsin B by cycloastragenol enhances antitumor immunity of CD8 T cells via inhibiting MHC-I degradation. *J Immunother Cancer*, 2022, 10(10): e004874. https://doi.org/10.1136/jitc-2022-004874

[75] H. Liu, Z.Y. Wang, Y.C. Zhou, et al. Immunomodulation of Chinese Herbal Medicines on NK cell populations for cancer therapy: A systematic review. *Journal of Ethnopharmacology*, 2021, 268: 113561. https://doi.org/10.1016/j.jep.2020.113561

[76] Q. Zeng, Y. Zhang, W. Zhang, et al. Baicalein suppresses the proliferation and invasiveness of colorectal cancer cells by inhibiting Snail-induced epithelial-mesenchymal transition. *Molecular Medicine Reports*, 2020, 21(6): 2544−2552. https://doi.org/10.3892/mmr.2020.11051

[77] S. Xiaodan, C. Ying. Role of ginsenoside Rh2 in tumor therapy and tumor microenvironment immunomodulation. *Biomed Pharmacother*, 2022, 156: 113912. https://doi.org/10.1016/j.biopha.2022.113912

[78] J. Qian, Y. Jiang, H. Hu. Ginsenosides: An immunomodulator for the treatment of colorectal cancer. *Frontiers in Pharmacology*, 2024, 15: 1408993. https://doi.org/10.3389/fphar.2024.1408993

[79] X.H. Wu, J.L. Xia, Z.Q. Wang, et al. Feiyanning downregulating CXCLs/CXCR2 axis to suppress TANs infiltration in the prevention of lung cancer metastasis. *Journal of Ethnopharmacology*, 2022, 295: 115277. https://doi.org/10.1016/j.jep.2022.115277

[80] H. Liu, R. Deng, C.W. Zhu, et al. Rosmarinic acid in combination with ginsenoside Rg1 suppresses colon cancer metastasis *via* co-inhition of COX-2 and PD1/PD-L1 signaling axis. *Acta Pharmacologica Sinica*, 2024, 45: 193−208. https://doi.org/10.1038/s41401-023-01158-8

[81] Y.F. Jiang, Y.E. Hu, Y. Yang, et al. Tong-Xie-Yao-Fang promotes dendritic cells maturation and retards tumor growth in colorectal cancer mice with chronic restraint stress. *Journal of Ethnopharmacology*, 2024, 319: 117069. https://doi.org/10.1016/j.jep.2023.117069

[82] S. Xu, A. Wusiman, Z. Liu, et al. pH-responsive Astragalus polysaccharides-loaded poly(lactic-co-glycolic acid) nanoparticles and their *in vitro* immunogenicity. *International Journal of Biological Macromolecules*, 2019, 125: 865–875. https://doi.org/10.1016/j.ijbiomac.2018.12.156

[83] Y. Liu, L. An, C. Yang, et al. Ginsenoside Rg1 improves anti-tumor efficacy of adoptive cell therapy by enhancing T cell effector functions. *Blood Science* (*Baltimore, Md*), 2023, 5(3): 170–179. https://doi.org/10.1097/BS9.0000000000000165

[84] J. Li, S.P. Fan, H.X. Li, et al. Evaluation of efficacy, safety and underlying mechanism on Traditional Chinese medicine as synergistic agents for cancer immunotherapy: A preclinical systematic review and meta-analysis. *Journal of Ethnopharmacology*, 2025, 338: 119035. https://doi.org/10.1016/j.jep.2024.119035

[85] M.T. Wang, F. Yang, J.W. Kong, et al. Traditional Chinese medicine enhances the effectiveness of immune checkpoint inhibitors in tumor treatment: A mechanism discussion. *Journal of Ethnopharmacology*, 2025, 338: 118955. https://doi.org/10.1016/j.jep.2024.118955

[86] M. De Martino, J.C. Rathmell, L. Galluzzi, et al. Cancer cell metabolism and antitumour immunity. *Nature Reviews Immunology*, 2024, 24: 654−669. https://doi.org/10.1038/s41577-024-01026-4

[87] L. Maiorino, J. Daßler-Plenker, L. Sun, et al. Innate immunity and cancer pathophysiology. *Annual Review of Pathology: Mechanisms of Disease*, 2022, 17: 425−457. https://doi.org/10.1146/annurev-pathmechdis-032221-115501

[88] A. Del Prete, V. Salvi, A. Soriani, et al. Dendritic cell subsets in cancer immunity and tumor antigen sensing. *Cellular & Molecular Immunology*, 2023, 20: 432−447. https://doi.org/10.1038/s41423-023-00990-6

[89] G. Oliveira, C.J. Wu. Dynamics and specificities of T cells in cancer immunotherapy. *Nature Reviews Cancer*, 2023, 23(5): 295−316. https://doi.org/10.1038/s41568-023-00560-y

[90] M. Tsoumakidou. The advent of immune stimulating CAFs in cancer. *Nature Reviews Cancer*, 2023, 23: 258−269. https://doi.org/10.1038/s41568-023-00549-7

[91] D. Galati, S. Zanotta. Dendritic cell and cancer therapy. *International Journal of Molecular Sciences*, 2023, 24(4): 4253. https://doi.org/10.3390/ijms24044253

[92] X. Wu, H. Yang, X. Chen, et al. Nano-herb medicine and PDT induced synergistic immunotherapy for colon cancer treatment. *Biomaterials*, 2021, 269: 120654. https://doi.org/10.1016/j.biomaterials.2021.120654

[93] F. Huang, Q. Zhang, J. Xiao, et al. Cancer cell membrane-coated gambogic acid nanoparticles for effective anticancer vaccination by activating dendritic cells. *International Journal of Nanomedicine*, 2023, 18: 2261−2273. https://doi.org/10.2147/IJN.S408521

[94] Q. Mao, J. Min, R. Zeng, et al. Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Theranostics*, 2022, 12(14): 6088−6105. https://doi.org/10.7150/thno.72509

[95] Y. Lv, M.Y. Li, L. Weng, et al. Ginseng-derived nanoparticles reprogram macrophages to regulate arginase-1 release for ameliorating T cell exhaustion in tumor microenvironment. *Journal of Experimental & Clinical Cancer Research*, 2023, 42(1): 322. https://doi.org/10.1186/s13046-023-02888-7

[96] X. Ye, Y. Liu, L. Wei, et al. Monocyte/macrophage-mediated transport of dual-drug ZIF nanoplatforms synergized with programmed cell death protein-1 inhibitor against microsatellite-stable colorectal cancer. *Advanced Science*, 2024, 11(38): e2405886. https://doi.org/10.1002/advs.202405886

[97] S. Kumagai, S. Koyama, K. Itahashi, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell*, 2022, 40(2): 201−218.e9. https://doi.org/10.1016/j.ccell.2022.01.001

[98] S. Kumagai, S. Koyama, K. Itahashi, et al. Lactic acid supports an immunosuppressive environment and reduces ICB response. *Cancer Discovery*, 2022, 12(4):

OF4. https://doi.org/10.1158/2159-8290.CD-RW2022-020

[99] J. Ye, J.M. Baer, D.V. Faget, et al. Senescent CAFs mediate immunosuppression and drive breast cancer progression. *Cancer Discovery*, 2024, 14(7): 1302−1323. https://doi.org/10.1158/2159-8290.CD-23-0426

[100] C. Ma, C. Yang, A. Peng, et al. Pan-cancer spatially resolved single-cell analysis reveals the crosstalk between cancer-associated fibroblasts and tumor microenvironment. *Molecular Cancer*, 2023, 22(1): 170. https://doi.org/10.1186/s12943-023-01876-x

[101] J.X. Feng, M.J. Xu, J.H. Wang, et al. Sequential delivery of nanoformulated α-mangostin and triptolide overcomes permeation obstacles and improves therapeutic effects in pancreatic cancer. *Biomaterials*, 2020, 241: 119907. https://doi.org/10.1016/j.biomaterials.2020.119907

[102] J. Peng, J. Zhou, R. Sun, et al. Dual-targeting of artesunate and chloroquine to tumor cells and tumor-associated macrophages by a biomimetic PLGA nanoparticle for colorectal cancer treatment. *Int J Biol Macromol*, 2023, 244: 125163. https://doi.org/10.1016/j.ijbiomac.2023.125163

[103] S. Han, S. Bi, T. Guo, et al. Nano co-delivery of Plumbagin and Dihydrotanshinone I reverses immunosuppressive TME of liver cancer. *Journal of Controlled Release*, 2022, 348: 250−263. https://doi.org/10.1016/j.jconrel.2022.05.057

[104] Z. Yu, J. Guo, M. Hu, et al. Icaritin exacerbates mitophagy and synergizes with doxorubicin to induce immunogenic cell death in hepatocellular carcinoma. *ACS Nano*, 2020, 14(4): 4816−4828. https://doi.org/10.1021/acsnano.0c00708

[105] L. Li, Y. Zou, L. Wang, et al. Nanodelivery of scutellarin induces immunogenic cell death for treating hepatocellular carcinoma. *International Journal of Pharmaceutics*, 2023, 642: 123114. https://doi.org/10.1016/j.ijpharm.2023.123114

[106] Y. Cao, Z. Chen, L. Sun, et al. Herb polysaccharide-based drug delivery system: Fabrication, properties, and applications for immunotherapy. *Pharmaceutics*, 2022, 14(8): 1703. https://doi.org/10.3390/pharmaceutics14081703

[107] Z. Wang, S. Fu, Y. Guo, et al. Classification and design strategies of polysaccharide-based nano-nutrient delivery systems for enhanced bioactivity and targeted delivery: A review. *International Journal of Biological Macromolecules*, 2024, 256(pt 2): 128440. https://doi.org/10.1016/j.ijbiomac.2023.128440

[108] C. Yang, H. Ming, B.W. Li, et al. A pH and glutathione-responsive carbon monoxide-driven nano-herb delivery system for enhanced immunotherapy in colorectal cancer. *Journal of Controlled Release*, 2024, 376: 659−677. https://doi.org/10.1016/j.jconrel.2024.10.043

[109] Y.X. Xiong, N. Li, M.M. Han, et al. Rhodiola rosea polysaccharides-based nanoparticles loaded with DOX boosts chemo-immunotherapy for triple-negative breast cancer by re-educating Tumor-associated macrophages. *International Journal of Biological Macromolecules*, 2023, 239: 124110. https://doi.org/10.1016/j.ijbiomac.2023.124110

[110] X. Lang, X. Wang, M. Han, et al. Nanoparticle-mediated synergistic chemoimmunotherapy for cancer treatment. *International Journal of Nanomedicine*, 2024, 19: 4533−4568. https://doi.org/10.2147/IJN.S455213

[111] B. Zhao, H. Lin, X. Jiang, et al. Exosome-like nanoparticles derived from fruits, vegetables, and herbs: Innovative strategies of therapeutic and drug delivery. *Theranostics*, 2024, 14(12): 4598−4621. https://doi.org/10.7150/thno.97096

[112] Q. Yi, Z. Xu, A. Thakur, et al. Current understanding of plant-derived exosome-like nanoparticles in regulating the inflammatory response and immune system microenvironment. *Pharmacological Research*, 2023, 190: 106733. https://doi.org/10.1016/j.phrs.2023.106733

[113] X.D. Wang, J. Fu, C. Jiang, et al. Specific and long-term luminescent monitoring of hydrogen peroxide in tumor metastasis. *Advanced Materials*, 2023, 35(20): 2210948. https://doi.org/10.1002/adma.202210948

[114] J. Zhou, Z. Zhuang, R. Gao, et al. β-Glycosidase sensitive oral nanoparticles for combined photothermal and chemo treatment of colorectal cancer. *Journal of Materials Chemistry B*, 2024, 12(6): 1624−1635. https://doi.org/10.1039/D3TB02393A

[115] S.M. Wei, Y.H. Wang, Z.S. Tang, et al. A novel green synthesis of silver nanoparticles by the residues of Chinese herbal medicine and their biological activities. *RSC Advances*, 2021, 11(3): 1411−1419. https://doi.org/10.1039/D0RA08287B