Review

Precision Delivery of Active Compounds from Edible and Medicinal Plants via Gut Microbiota Targeting: A New Paradigm for Cancer Immunomodulation

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Review

Precision Delivery of Active Compounds from Edible and Medicinal Plants via Gut Microbiota Targeting: A New Paradigm for Cancer Immunomodulation

Lu Peng [1], Long Wang [1], Yingtong Zhao [2], Peng Yu [3,*] and Hongmei Yang [1,*]

[1] Public Experimental Center, Changchun University of Chinese Medicine, 130117, Changchun, China
[2] School of Biological Sciences, University of California San Diego, La Jolla, CA 92093, USA
[3] College of Pharmacy, Changchun University of Chinese Medicine, Changchun, 130117, China
* Correspondence: yupengcczy@163.com (P.Y.); yanghm0327@sina.cn (H.Y.)

Abstract

The immune system plays a critical role in the development and progression of tumors. In recent years, despite the remarkable clinical successes achieved with immunotherapies such as CAR-T cell therapy and checkpoint inhibitors, treatment resistance continues to be a pervasive and critical barrier for a substantial portion of patients. The gut microbiota has been established as a critical determinant of responses to immunotherapy. Enriched with bioactive components such as polysaccharides, polyphenols, and flavonoids, edible and medicinal plants (EMPs) exhibit significant potential to enhance host immunity by reshaping the gut microbiota, increasing the production of microbiota-derived metabolites (e.g., short-chain fatty acids), strengthening the intestinal barrier, and reducing intestinal inflammation. The bioactive components derived from EMPs not only demonstrate substantial pharmacological activities but also serve dual roles: functioning either as inherent drug carriers or as effective modifiers for existing carrier systems, which facilitates targeted drug delivery to specific sites such as the liver and intestinal, enhancing therapeutic efficacy. In summary, this review highlights that bioactive components from EMPs hold significant promise for enhancing cancer immunotherapy by modulating complex interactions with the gut microbiota.

Keywords: cancer immunotherapy; gut microbiota; bioactive components; edible and medicinal plants; drug carriers

1. Introduction

According to the GLOBOCAN 2022 data, approximately 20 million new cancer cases and 9.7 million cancer deaths were reported in world, which show that cancer seriously threaten human health [1]. The conventional treatment for cancer includes surgery, radiotherapy, chemotherapy and targeted therapy. However, the conventional treatment increases tumor recurrence and poor prognosis. Immunotherapy targets immune cells and their interactions with tumor cells [2] and can treat metastatic malignant tumors and prolong the survival time of patients with good prognosis. However, due to the immunosuppressive tumor microenvironment (TME) and the immune escape mechanism of tumor cells, immunotherapy has limited efficacy in tumors [3]. At the same time, in the process of cancer immunotherapy, the emergence of drug resistance, immune-related adverse reactions and heterogeneity make immunotherapy face great clinical challenges.

The gastrointestinal tract contains 60-80% of the body's immune cells and plays a crucial role in maintaining immune homeostasis [4]. Research demonstrates that gut microbiota and metabolites not only modulate intestinal immunity but also play a role in systemic cancer immunomodulation [4,5]. Recent studies show that cancer immunotherapy, including immune checkpoint blockade (ICB), CAR-T and cancer vaccines, seems to have different therapeutic effects in different individuals, which

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is related to the gut microbiome [6–10]. Therefore, gut microbiota, as the "second genome" of the human body, represents a highly promising target for precision cancer immunotherapy.

Edible and medicinal plants (EMPs), as an indispensable and important part of traditional Chinese medicine, have functions of both nutritional and pharmacological. Due to high safety, minimal side effect, abundant functional components including polysaccharides, flavonoids, and saponins and multi-pathway pharmacological, EMPs display unique advantages in the field of cancer treatment, improving quality of life for patients [11]. Emerging evidence demonstrates that EMPs can modulate antitumor immune responses through gut microbiota regulation [12]. In this review, we emphasize the crosstalk among the active compounds from EMPs, gut microbiome, cancer immune response, and cancer immunotherapy, providing insights for the development of novel immunotherapeutic strategies. Furthermore, the article examines current research advancements in utilizing active compounds from EMPs to engineer drug delivery systems for tumor therapy, offering translational insights for clinical applications.

2. Bioactive Compounds from EMPs and Regulation of Gut Microbiome

EMPs have been widely utilized in China, Korea, Japan, and other countries for treating various diseases, including cancer [13], inflammatory disorders [14], and neurodegenerative disease [15,16]. According to chemical structures, bioactive compounds from EMPs are categorized as polysaccharides, flavonoids, saponins, and polyphenols, alkaloids, terpenoid, phenolic compounds, coumarin, essential oil and volatile oil. Extensive research has shown that polysaccharides, saponins, and polyphenols found in MFH plants enhance anti-tumor immunity by directly or indirectly modulating immune cell activity and the gut microbiota [12,17–19] (Figure 1).

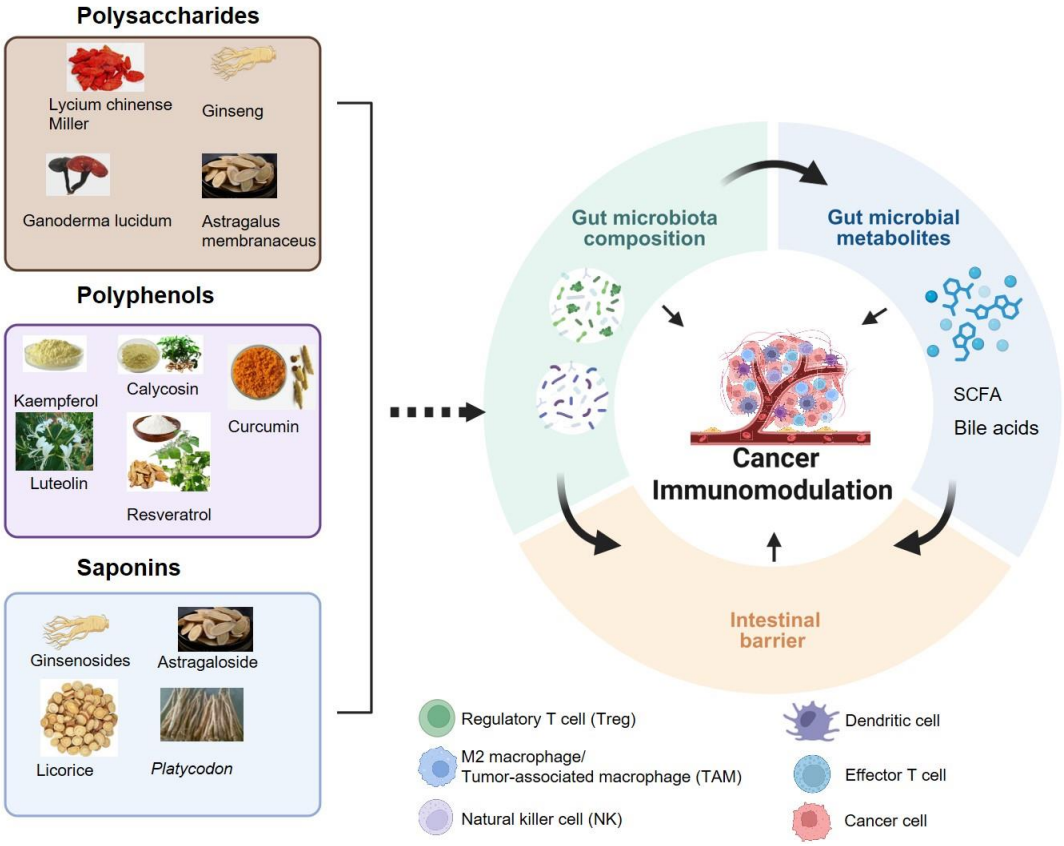

Figure 1. The Interaction between bioactive compounds from edible and medicinal plants and gut microbiota in cancer immunomodulation. Created with biorender.com.

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2.1. Polysaccharides

Polysaccharides are a class of natural bioactive compounds abundantly present in EMPs, including *Astragalus membranaceus* [20], *Panax ginseng C. A. Meyer* [21,22], and *Lycium chinense* Miller [23,24], demonstrating unique anti-tumor activities. Increasing evidence demonstrates that polysaccharides can effectively regulates both the structural composition and metabolic activities of gut microbiota, maintaining microbial homeostasis, preserving intestinal barrier integrity, and ultimately enhancing gut immunity [25,26]. Ginseng polysaccharides (GPs), bioactive components of *Panax ginseng*, enhanced PD-1 blockade therapy by increasing the microbial metabolites valeric acid and decreasing the ratio of Kyn/Trp, which collectively increased CD8+ T cell recruitment while inhibiting Treg-mediated immunosuppression. Furthermore, GPs modulated gut microbial metabolism and composition, particularly by promoting the abundance of Parabacteroides distasonis and Bacteroides vulgatus, key bacterial genus involved in ginsenoside biotransformation, which was significantly associated with therapeutic response and prognosis. Clinical investigations have demonstrated that GPs improves therapeutic response to PD-1 checkpoint blockade, potentially overcoming immunotherapy resistance [27]. The water-soluble polysaccharides extracted from the spore bodies of Ganoderma lucidum polysaccharides (GLP) inhibit the TLR4/MyD88/NF-κB signaling pathway, improving the microbial flora imbalance induced by AOM/DSS, increasing the production of short-chain fatty acids, and alleviating endotoxemia. In addition, GLP can significantly improve the intestinal barrier function, inhibit the infiltration of macrophages, and suppress colonic inflammation and tumor occurrence [22]. In addition, emerging research indicates that polysaccharides such as *Lycium barbarum* polysaccharides[28], *Lentinan edodes* polysaccharides [29] and *Astragalus* polysaccharides (APS) [30] modulate gut microbiota and their derived metabolites, promoting the restoration of immune function. These findings demonstrate that polysaccharides can serve as adjuvants to improve intestinal and immunosuppression.

2.2. Polyphenols

Polyphenols, known for their potent antioxidant and anti-inflammatory properties, are one of the most important and widely occurring bioactive components in EMPs. Flavonoids, phenolic acids, lignans, and stilbenes are the four major classes of polyphenols [31]. Among these, flavonoids are the most abundant, followed by phenolic acids.

Flavonoids exhibit diverse biological activities and pharmacological effects, including potent antioxidant, anti-inflammatory, and anti-tumor effects. Based on their core structures and substituents, flavonoids can be classified into isoflavones, neoflavonoids, flavones, flavonols, flavanones, flavanonols, flavanols, chalcones [32]. Accumulating research suggests that flavonoids extracted from EMPs, such as kaempferol (a flavonol) and calycosin (an isoflavone from *Astragalus membranaceus*), can enhance cancer immunotherapy by activating antitumor immune responses through remodeling the gut microbial diversity and modulating microbial metabolites [33–35]. Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disorder with the potential to progress to colorectal cancer (CRC) [36]. Luteolin, a bioactive flavonoid derived from EMPs such as *honeysuckle* (*Lonicera japonica*), *astragalus* (*Astragalus membranaceus*), and *angelica* (*Angelica sinensis*), demonstrates significant therapeutic effects against IBD [37,38]. Its mechanisms of action include: (1) modulating T-cell subset differentiation [39], (2) downregulating pro-inflammatory mediators, (3) activating antioxidant pathways [40,41], (4) enhancing gut microbiota composition [42,43], and (5) restoring intestinal mucosal barrier function through specific molecular signaling pathways [44]. These multifaceted actions collectively ameliorate IBD symptoms and consequently suppress CRC development. However, the majority of polyphenols that escape absorption in the upper gastrointestinal tract travel directly to the colon, where they are metabolized by gut microbiota into a spectrum of smaller phenolic acids. These metabolites exhibit greater biological activity and higher absorption efficiency. For example, ellagic acid is converted into urolithins, which significantly enhance gut barrier function, reduce inflammation, and create a systemically favorable environment for antitumor immunity [45]. Furthermore, resveratrol, a natural stilbenes compound, enhance

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antitumor immune responses by modulating the abundance and diversity of gut microbiota, which contributes to improve the efficacy of tumor immunotherapy [46].

Additionally, other polyphenolic compounds such as curcumin can remodel the gut microbiota composition by enriching beneficial bacteria, which are closely associated with the maintenance of intestinal barrier integrity, anti-inflammatory effects, the production of beneficial metabolites and tumor microenvironment remodeling [47–49].

2.3. Saponins

Saponins are a class of bioactive compounds ubiquitously present in EMPs. These structurally complex phytochemicals exhibit diverse biological activities attributable to their intricate chemical architectures, including immunomodulation [50,51], cardiovascular protection [52,53], antioxidant effects [54,55], and antitumor properties[56–58]. Based on their aglycone structures, saponins are primarily classified into two major categories: triterpenoid saponins (such as *ginseng*, *licorice*, *astragalus*, and *platycodon*) and steroidal saponins (like *ophiopogon japonicus* and *Chinese yam*). Among these, triterpenoid saponins are particularly notable for their immunomodulatory and antitumor activities, such as ginsenoside and astragaloside. Emerging evidence suggests that multiple ginsenosides (such as Rh2 [59], Rg1 [60] and Rk3 [61]) regulate gut microbial diversity and promote anti-tumor immune responses, inhibiting tumor growth. For example, Rk3 ameliorates gut microbiota dysbiosis by enriching beneficial bacteria such as Akkermansia muciniphila and Barnesiella intestinihominis while eliminating pathogenic Desulfovibrio species, restoring intestinal barrier integrity. Mechanistically, Rk3 modulates chemokine and inflammatory cytokine production through regulation of innate lymphoid cells and T helper 17 (Th17) cell signaling pathways, significantly suppressing colonic tumorigenesis [61]. Moreover, recent studies revealed that Astragaloside IV(AS-IV) exhibit potent immunomodulatory and gastrointestinal protective effects by alleviating mucosal inflammation and restoring intestinal barrier integrity during different stages of inflammatory bowel disease (IBD) progression to colorectal cancer. AS-IV exerts their therapeutic effects through multiple mechanisms, including targeting key immune signaling pathways (e.g., NF-κB and PPAR) and promoting M1 macrophage polarization, suppressing tumor growth and metastasis via multi-targeted actions, which offers novel strategies for future drug development [62].

3. Synergistic Effects of the Bioactive Compounds from EMPs on Immunotherapy via Gut Microbiota Modulation

To counteract tumor immune evasion during cancer progression, various immunotherapies have been developed [2]. However, tumor immunotherapy faces substantial limitations and challenges. Immune checkpoint blockade therapies, particularly PD-1/PD-L1 inhibitors, demonstrate clinical efficacy in only approximately <30% of patients, with a subset of responders eventually experiencing disease recurrence [63]. Meanwhile, chimeric antigen receptor (CAR) T-cell therapy exhibits limited therapeutic potential against solid tumors [64]. Furthermore, immunotherapeutic approaches are frequently associated with severe immune-related adverse events and the development of treatment resistance. In recent years, accumulating evidence from both preclinical and clinical research highlights the crucial role of the gut microbiota in modulating patient response to immunotherapy [8,65,66]. Research indicates that the gut microbiome-derived metabolites and secreted molecules enhance immunotherapy efficacy [67,68]. With advantages including natural derivation, multi-target modulation, and low toxicity, bioactive compounds from EMPs can synergize with immunotherapy by modulating gut microbiota, which reduces treatment toxicity while improving antitumor efficacy, leading to better patient outcomes. Emerging research reveals that active ingredients from medicinal foods potentiate cancer immunotherapy via modulating gut microbiota composition, promoting the production of beneficial metabolites such as short-chain fatty acids (SCFAs) (Figure 2), and improving intestinal barrier function to reduce inflammation (Figure 3).

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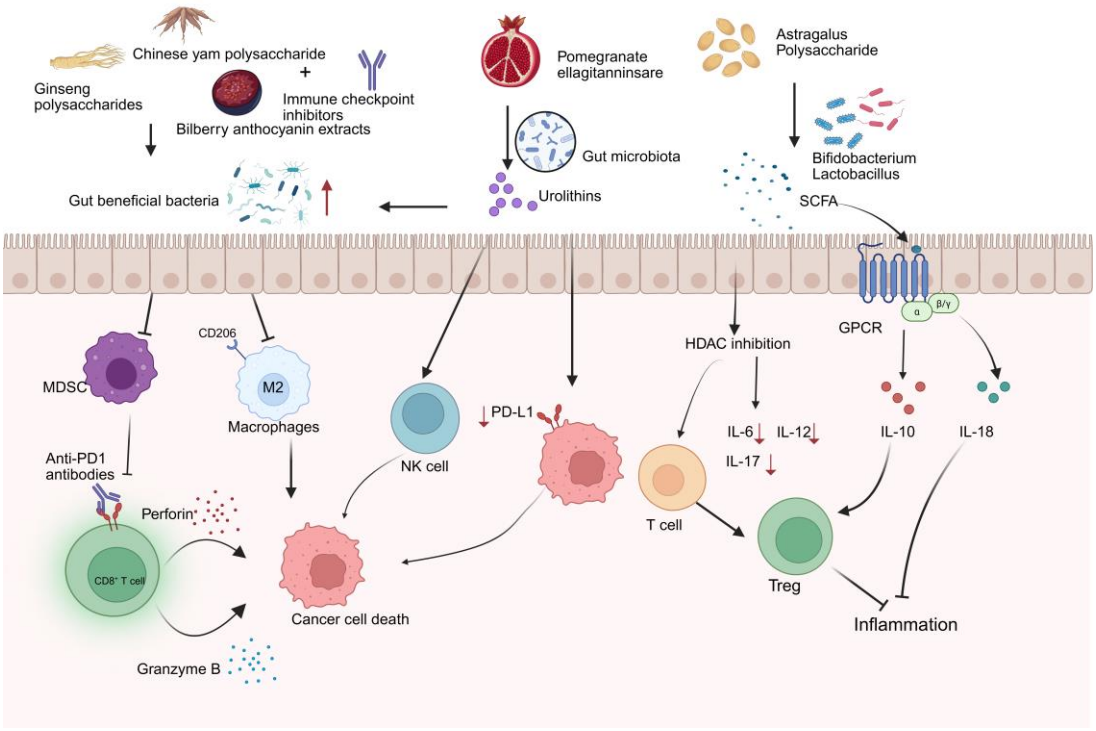

Figure 2. The interaction bioactive compounds from edible and medicinal plants and gut microbiota in cancer immune response. Created with biorender.com.

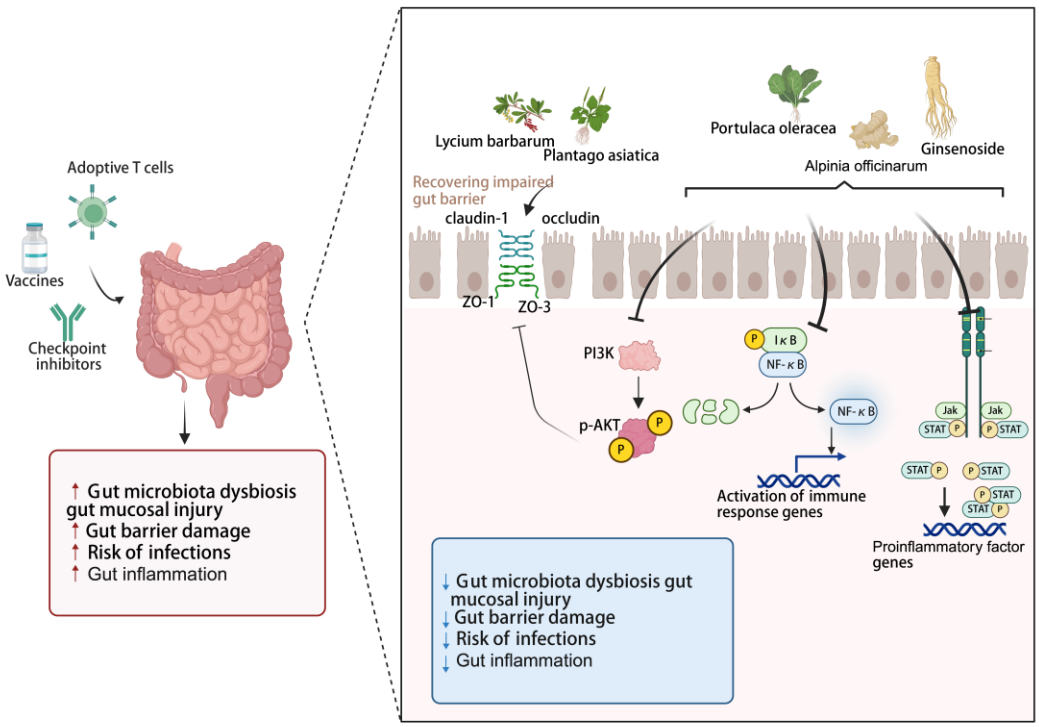

Figure 3. Natural bioactive compounds from edible and medicinal plants improve intestinal barrier dysfunction and alleviate intestinal inflammation in cancer immunotherapy. Created with biorender.com.

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3.1. Gut Microbiota Composition Remodeling

Emerging evidence suggests that specific gut bacteria, notably Bacteroides fragilis, Bacteroides thetaiotaomicron, Bifidobacterium species, Akkermansia muciniphila, and Faecalibacterium spp., may enhance the efficacy of cancer immunotherapy, as observed in preclinical studies and patient cohorts [8,9,69,70]. Consequently, therapeutic strategies targeting gut microbiota modulation have been proposed to enhance treatment efficacy in oncology. Immune checkpoint inhibitors (ICIs) represent the most extensively studied form of immunotherapy [71–73]. However, their low response rates in cancer patients remain a major therapeutic challenge.

As the dominant effector population in anti-tumor immunity, CD8+ T cells have shown remarkable therapeutic efficacy in various immunotherapeutic strategies. Anti-PD-1 antibodies blockade activated CD8+ T cells to secrete perforin and granzyme B, mediating tumor cell death [74,75]. Bioactive compounds from EMPs have been shown to modulate the microbiota-immune axis, ultimately enhancing the efficacy of ICIs. For instance, GPs can enhance immune surveillance by increasing the abundance of Lachnospiraceae bacteria, which in turn suppresses myeloid-derived suppressor cells (MDSCs) and promotes the infiltration and activation of $CD8^+$ T cells [76,77]. Furthermore, when combined with αPD-1 monoclonal antibody (mAb) therapy, GPs reshape the gut microbiota and improve the sensitivity of non-small cell lung cancer (NSCLC) patients to anti-PD-1 immunotherapy [27]. In addition, recent research showed that Chinese yam polysaccharide (CYPs), derived from medicinal food plants, exhibit immunomodulatory and antitumor properties. 16S rRNA sequencing revealed that combined treatment with CYPs and αPD-1 monoclonal antibody (mAb) enriched beneficial bacteria (e.g., *Clostridium_UCG-014* and Actinobacteria) while reducing pathogenic taxa (including Enterobacteriaceae and Desulfovibrionaceae). Furthermore, this combination therapy remodeled the tumor microenvironment (TME) by suppressing immunosuppressive M2 macrophages (CD206+ subset) and enhancing cytotoxic CD8+ T-cell infiltration, improving the response to anti-PD-1 immunotherapy in CRC patients [78]. Bilberry anthocyanin extracts significantly increased the relative abundance of Clostridia and Lactobacillus johnsonii while enhancing effective microbial community diversity, consequently improving the efficacy of ICIs [79].

Based on the above research, it is suggested that bioactive compounds from EMPs can enhance the efficacy of tumor immunotherapy and inhibit tumor progression by modulating the composition of the gut microbiota (promoting the abundance of beneficial bacteria while suppressing harmful bacteria) and regulating the tumor immunosuppressive microenvironment. This highlights the potential of bioactive compounds from EMPs in immune modulation for microbiota-targeted cancer therapies.

3.2. Microbial Metabolites

Gut microbiota-derived metabolites modulate the development and function of various immune cells while reshaping the tumor microenvironment [80–82]. Immunotherapy combined with microbial metabolites can effectively activate the immune system, eliminate tumor cells and overcome drug resistance, mitigating severe treatment-related side effects [83]. Therefore, targeting gut microbiota-derived metabolites represents a promising therapeutic strategy to enhance tumor immunotherapy response rates in patients.

Research indicates that non-digestible bioactive compounds from EMPs, such as polysaccharides, are fermented by specific gut microbiota (e.g., Bifidobacterium and Lactobacillus), leading to the production of short-chain fatty acids (SCFAs) like propionate and butyrate [84–86]. SCFAs regulate immune cells function to augment antitumor immune responses and maintain intestinal homeostasis through mechanisms involving the activation of G-protein-coupled receptors (GPRs) and inhibition of histone deacetylases (HDAC) [87–90]. In addition, polyphenols-EMPs components, such as pomegranate ellagitanninsare, are metabolized by gut microbiota into ellagic acid and further converted into urolithins that can reshape the gut microbiota and modulate the tumor microenvironment. Moreover, when combined with anti-PD-1 antibody therapy, they have

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been shown to inhibit the growth of colon cancer, thereby supporting more effective anticancer treatment [91,92]. Together, these findings reveal how interactions between gut microbiota and EMPs may offer novel strategies for developing natural adjuvants to enhance cancer immunotherapy.

3.3. Intestinal Barrier Dysfunction and Intestinal Inflammation

Cancer immunotherapy, particularly ICIs, frequently induces immune-related adverse events (irAEs), many of which are strongly linked to both gut microbiota dysbiosis gut mucosal injury, intestinal barrier damage, bacterial translocation resulting from increased gut permeability and systemic inflammation [93–96]. A healthy gut microbiome and an intact intestinal barrier are essential for maintaining immune homeostasis [97,98]. Once the barrier is compromised, systemic chronic inflammation is triggered, which promotes the expansion of immunosuppressive cells—such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). This process fosters an immunosuppressive TME, ultimately leading to either primary or adaptive resistance to ICIs [99–101]. Therefore, targeting the intestinal barrier and inflammation represents a viable strategy for sensitizing tumors to immunotherapy.

The intestinal barrier acts as a crucial frontline defense against external pathogens and toxins [102]. It is well established that numerous components from EMPs directly or indirectly contribute to the intestinal barrier integrity [103–105]. Polysaccharides, known for their favorable safety profile, are effective in reducing inflammation and suppressing the growth of malignant tumors, which represent a promising adjuvant therapy for a variety of disorders associated with intestinal barrier injury [104]. Numerous bioactive polysaccharides, including those derived from Plantago asiatica [106], Lycium barbarum [107] and Spirulina [108] have been shown to modulate the expression of tight junction proteins (including occludin, claudin-1, ZO-1, and ZO-3), which collectively contribute to the amelioration of epithelial barrier dysfunction.

Additionally, Studies indicate that approximately 60% of cancer patients treated with ICIs develop severe treatment-limiting toxicities [109,110], which are closely associated with inflammation-related adverse events induced during the therapy [111–113]. Colitis is a common and severe adverse effect of ICIs therapy. Therefore, developing targeted therapeutic strategies for intestinal inflammation—aimed at effectively managing toxicity while preserving or even enhancing the antitumor efficacy of ICIs—represents a promising approach. As potent natural anti-inflammatory agents, various bioactive compounds from EMPs serve such as astragalosides [114], curcumin [115,116], ginsenoside Rh2 [117], *Alpinia officinarum* Hance polysaccharides [118], and Portulaca oleracea L. polyphenols [119], work synergistically through multiple targets and pathways, precisely modulating key signaling pathways associated with intestinal inflammation, including PI3K/AKT, NF-κB, MAPK, and JAK/STAT—thereby effectively alleviating gut barrier disruption and reducing intestinal inflammation. Clinical studies have also shown that certain medicinal food homologous ingredients, such as curcumin, can serve as an adjunctive therapy to significantly improve the clinical remission rate and endoscopic improvement scores in patients with mild to moderate ulcerative colitis [120].

Based on these findings, it has been elucidated that natural bioactive compounds from EMPs can enhance tumor immunotherapy by modulating the gut microbiota composition, regulating microbial metabolites, improving intestinal barrier dysfunction, and alleviating intestinal inflammation, which work synergistically to mitigate adverse effects induced by immunotherapy, increase patient response rates, and improve overall treatment efficacy.

4. Construct DDS Based on Components from EMPs

EMPs compounds including polysaccharides, polyphenols, flavonoids and saponins exhibit considerable potential in enhancing tumor immunotherapy by modulating the gut microbiota–immune axis. However, their widespread clinical translation and application are substantially limited by inherently low bioavailability, which results from poor water solubility, chemical instability, and inefficient intestinal absorption. Recent studies have confirmed that advanced drug delivery systems

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(DDS) strategies, such as nanotechnology, targeted delivery systems, and biotransformation, can significantly enhance the anti-tumor efficacy of EMPs bioactive compounds [121–123]. These approaches not only reduce side effects and improve patient compliance but also hold great promise for developing these compounds into effective adjuvant interventions for tumor immunotherapy. However, DDS still face numerous challenges and problems. EMPs components are now being extensively explored as "smart materials" for constructing or functionalizing drug delivery systems (DDS), rather than merely serving as the encapsulated "cargo," owing to their inherent bioactivity, excellent biocompatibility, and unique physicochemical properties [124,125]. Additionally, their ability to modulate immune cell function enables an integrated strategy of "delivery and therapy in one.

4.1. Advantages of Bioactive Compounds from EMPs for DDS Carriers

An ideal DDS should be capable of precisely delivering drugs to the diseased site. Nevertheless, Dai et al. revealed that due to target heterogeneity, the delivery efficiency of nanoparticles to cancer cells is abysmally low, with only approximately 0.0014% of the ligand-modified nanoparticles successfully binding to them [126]. Utilizing the inherent targeting capabilities of natural plant active ingredients such as polysaccharides, or further functionalizing them, constructed novel DDS, which significantly enhance drug targeting precision and increase drug accumulation at the site of disease. For example, Liu et al. developed a novel nanocarrier material, AA/ASP-AZO-Fc, by leveraging the intrinsic liver-targeting property of Angelica sinensis polysaccharide (ASP). The resulting polymeric micelle system effectively delivered curcumin to hepatic tissues, demonstrating a targeted therapeutic strategy for hepatocellular carcinoma [127]. Furthermore, nanotechnology can be integrated with immunotherapy to enhance tumor-targeted treatment [128]. Liu et al. designed novel methotrexate (MTX)-modified PPT nanoparticles loaded with Astragalus polysaccharide micelles. This system can safely and effectively target ovarian cancer cells and achieve precise drug release. Additionally, it exerts immunomodulatory effects on tumor-associated macrophages to combat tumor cells, thereby enhancing the efficacy of immunotherapy for ovarian cancer [129].

Indeed, the long-term biosafety of many nanocarrier materials remains to be fully elucidated. Nel et al. highlighted that the intrinsic properties of nanomaterials could lead to adverse consequences, primarily through harmful interactions with biological systems and the environment, potentially resulting in toxicity [130]. Among these, liposomes have been successfully utilized as nanocarriers in drug delivery systems. With various formulations available, they have entered clinical applications for targeted cancer therapy [131,132]. However, clinical studies have revealed that the application of liposomes often results in low targeting efficiency and elevated systemic toxicity, resulting in adverse side effects [133–136]. Natural biopolymers are recognized for their established safety profile, excellent biodegradability, non-toxic degradation products and favorable tolerability, make them promising candidates for replacing synthetic materials in DDS [125,137]. The enhancement of the physicochemical properties of DDS by bioactive compounds such as ginsenosides can increase the bioavailability of active pharmaceutical ingredients, potentiating their antitumor therapeutic effects [125,138]. For instance, ginsenoside Rh2-liposomes can replace cholesterol to enhance stability and reduce potential side effects, while significantly prolonging their circulation time in vivo. Their key advantages include active targeting of tumor cells, promoted drug accumulation at tumor sites, and effective remodeling of the TME to reverse immunosuppression, potently inhibiting tumor growth [139]. Bioactive food-derived components serving as DDS carriers offer a multifunctional and innovative platform for anticancer drug delivery.

4.2. Intestinal-Targeting Release of the Medication

Oral administration is the most preferred route of drug delivery due to its convenience and high patient compliance [140]. However, the highly acidic environment of gastric acid can lead to its inactivation, degradation by gastrointestinal enzymes may reduce its bioavailability, and its premature release in non-target areas could potentially cause systemic side effects [141]. In order to

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achieve efficient and precise delivery of these active ingredients to specific intestinal sites and control their release behavior, colon targeted drug delivery have emerged and become a research hotspot in the field of pharmaceutics. It is crucial for treating inflammatory bowel disease (IBD) and colon cancer, as well as for enhancing the bioavailability of easily degradable drugs for systemic absorption, making it a vital approach [142,143]. Delivery systems utilizing edible bioactive compounds which offer excellent biocompatibility, biodegradability, low toxicity, and ease of functional modification have emerged as ideal carriers for colon-targeted drug delivery [143]. Edible bioactive ingredients exhibit diverse responsive properties, allowing them to be naturally engineered to respond to specific intestinal conditions such as pH and microbial enzymes, enabling targeted drug release at disease sites. Due to their high safety profile, structural versatility, and the fact that they can only be degraded by specific enzymes produced by colonic microbiota after reaching the intestine, natural polysaccharides are widely used in the construction of oral colon-specific drug delivery systems for targeted colonic release of therapeutics [144]. In addition, leveraging the pH sensitivity of polysaccharides, nano-sized polysaccharide-based drug carriers can be utilized to construct pH-responsive delivery systems, enabling targeted intestinal drug release and controlled therapeutic delivery [145]. Moreover, orally administered nano-drugs, constructed from bioactive components of EMPs, enter the systemic circulation via the colon and exert antitumor effects by directly killing tumor cells and modulating the gut microbiota [146]. Based on EMPs compounds, natural, safe, and robust delivery systems are expected to lead the field of oral drug delivery into a new era characterized by sustainability, precision, and personalization, thereby offering innovative solutions for nutritional intervention and disease treatment.

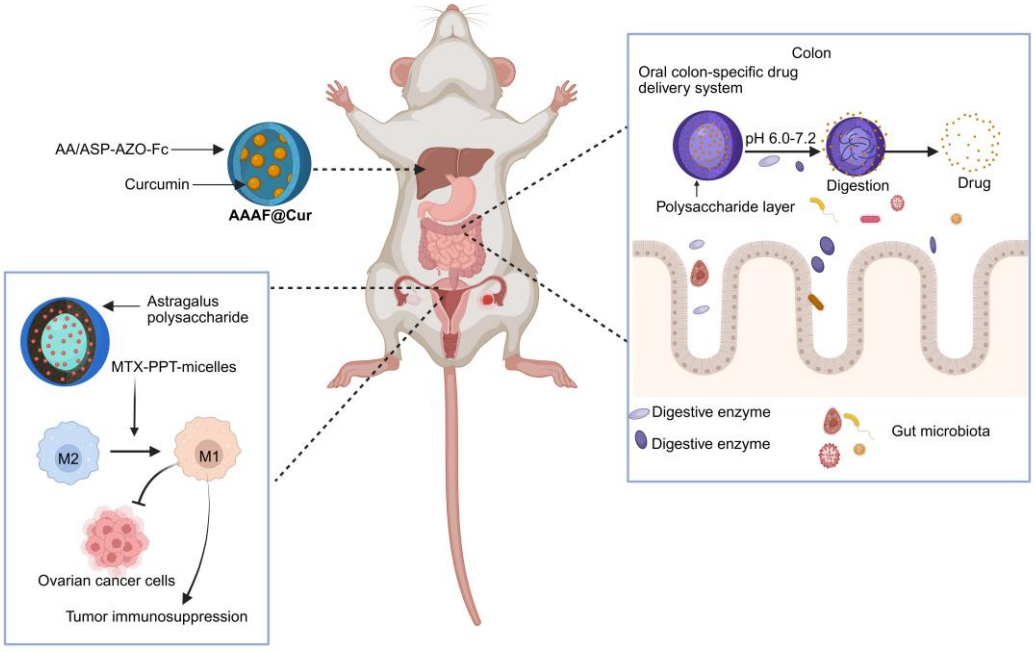

Figure 4. Drug delivery systems constructed from bioactive components of medicinal-edible plants enable precise drug release at specific sites and modulate immune responses against cancer. Created with biorender.com.

5. Conclusions

In recent years, cancer immunotherapy, particularly ICBs, has become a hotspot in cancer treatment. However, during immunotherapy, due to tumor heterogeneity and inter-patient variability, irAEs might arise, including issues such as drug resistance and poor prognosis. Gut

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microbiota and their metabolites can modulate tumor immune responses. In turn, cancer can reshape the gut microbial composition, leading to the modulation of TME and the promotion of immune suppression [147]. This review has detailed that EMPs, which are abundant in polysaccharides, polyphenols, and saponins (exemplified by traditional sources like ginseng, astragalus, angelica, and turmeric), exhibit favorable characteristics: high safety, stability, low toxicity, and multi-targeting capability. Notably, EMPs can enhance anti-tumor immune responses and synergize with cancer immunotherapy via bidirectional interactions with the gut microbiota, constituting a highly promising interdisciplinary research field. Beyond their direct use as anti-cancer agents, the bioactive compounds of EMPs can also participate in the assembly of drug delivery systems, which enables targeted transport of therapeutic agents to specific sites, facilitating precise cancer treatment. Additionally, DDS assembled from EMPs compounds offer a promising alternative to synthetic materials, mitigating the long-term toxicity concerns associated with their use, while also boosting the bioavailability and anti-tumor potency of the therapeutic agents. Nevertheless, substantial challenges persist in effectively translating these findings into clinical practice. The inherent variability in the origin, processing, and extraction of EMPs leads to significant inconsistencies in the composition and concentration of their bioactive compounds, resulting in poor reproducibility and unstable research outcomes. This complexity is compounded by the fact that, unlike single-compound drugs, their extracts are multi-component mixtures, making it difficult to determine whether their overall interaction with cancer immunotherapy is synergistic or antagonistic. Taken together, these advancements underscore the substantial potential of leveraging the interplay between bioactive components from EMPs and the gut microbiota to enhance the efficacy of cancer immunotherapy.

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