REVIEW

Natural products and their derivatives: Promising modulators of tumor immunotherapy

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Abstract
A wealth of evidence supports the role of tumor immunotherapy as a vital therapeutic option in cancer. In recent decades, accumulated studies have revealed the anticancer activities of natural products and their derivatives. Increasing interest has been driven toward finding novel potential modulators of tumor immunotherapy from natural products, a hot research topic worldwide. These works of research mainly focused on natural products, including polyphenols (e.g., curcumin, resveratrol), cardiotonic steroids (e.g., bufalin and digoxin), terpenoids (e.g., paclitaxel and artemisinins), and polysaccharide extracts (e.g., lentinan). Compelling data highlight that natural products have a promising future in tumor immunotherapy. Considering the importance and significance of this topic, we initially discussed the integrated research progress of natural products and their derivatives, including target T cells, macrophages, B cells, NKs, regulatory T cells, myeloid-derived suppressor cells, inflammatory cytokines and chemokines, immunogenic cell death, and immune checkpoints. Furthermore, these natural compounds inactivate several key pathways, including NF-κB, PI3K/Akt, MAPK, and JAK/STAT pathways. Here, we performed a deep generalization, analysis, and summarization of the previous achievements, recent progress, and the bottlenecks in the development of natural products as tumor immunotherapy. We expect this review to provide some insight for guiding future research.

KEYWORDS
cardiotonic steroids, polyphenolics, polysaccharides, terpenoids, Tregs, tumor immunotherapy

1 | INTRODUCTION

It is considered that 18,100,000 new cancer cases and 9,600,000 cancer deaths reported worldwide in 2018.1 In recent years, unsatisfactory results in cancer treatment have been partly due to a condition of systemic immune unresponsiveness or immunosuppression against cancers.2,3 Many immune cells, including macrophages, CD4+ T cells, CD8+ cytotoxic T cells (CTLs), NKs, B cells, CD4+CD25+Foxp3+ regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs) play key roles in the pathologic process of tumor growth and development, as well as in response to chemotherapies.2,3 In addition to these immune cells, several other inflammatory cytokines and chemokines, such as TGF-β, ILs (e.g., IL-10), IFN-γ, and TNF-α, can be triggered, enhanced, or reduced.2,4-6 Moreover, immune checkpoints pathways, such as programmed cell death-1 (PD-1) and CTLA-4, and several key pathways including the NF-κB, PI3K/Akt, MAPK, and JAK/STAT pathways, are associated with anticancer effects of immune system.7-12 The main function of immune system in tumor...
microenvironment (TME) is to monitor tissue homeostasis, protect against invading pathogens, and interfere with the detection and clearance of malignant cells. However, immune system dysfunction in tumors results in malignant cells escaping immune surveillance, immune recognition, and eradication. As a developing approach, tumor immunotherapy has transferred focus from tumor itself to the host’s immune system, mobilizing immune cells, recognizing and eventually destroying the tumor cells. 

Recently, the role of several immune checkpoint inhibitors targeting tumor immunity has become increasingly important, for example, programmed death ligand-1 (PD-L1) inhibitor durvalumab and CTLA4 inhibitor ipilimumab. High-dose IL-2 and IFN-α-2b have been used to treat multiple advanced cancers. Adoptive T cell therapy has been investigated in several kinds of solid tumors. However, these tumor immunotherapies also result in unique adverse effects owing to their mechanisms of actions, distinct from those caused by other cancer therapies, such as the organ-specific inflammatory side effects (or immune-related adverse events), cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome. The management of these adverse effects often requires close monitoring and specific treatment, including steroids and immunoregulatory therapy, thus further reducing the patient’s quality of life and increasing their financial burden. Therefore, tumor immunotherapy needs to be explored from a novel perspective.

Natural products and their derivatives possess characteristics of structural diversity, diverse biologic activities, low toxicity and side effects, and availability of a wide range of sources; their role in the development of new anticancer drugs and lead drug compounds is increasing in importance. Notably, there has been a growing interest for discovering novel natural product-derived potential modulators of tumor immunotherapy, a hot research topic worldwide. In fact, several well-known natural products including polyphenols (e.g., curcumin, resveratrol), cardiotonic steroids (e.g., digoxin and bufalin), terpenoids (e.g., paclitaxel, artemisinin, and triptolide), polysaccharides (e.g., lentil), saponins, and capsaicin have potential immunomodulatory effects. In this review, we aimed to summarize the integrated research progress of several representative classes of natural products on tumor immunotherapy and key intracellular pathways, highlighting the increased potential of natural products in immunotherapy.

2 | MOLECULAR MECHANISMS ON NATURAL PRODUCTS IN TUMOR IMMUNOTHERAPY

2.1 | Polyphenols

Polyphenols are a large group of compounds, possessing more than 8000 structural variants. Most polyphenols contribute to pharmacologic activities, such as anti-inflammatory, immunomodulatory, and anticancer actions. For instance, curcumin, resveratrol, apigenin, wogonin, epigallocatechin-3-gallate, and icariin have demonstrated efficacy as anticancer compounds. Polyphenols are commonly found in vegetables, fruits, and cereals as glycoside esters or free aglycones; they are mainly classified into two groups: nonflavonoids and flavonoids.

### 2.1.1 | Nonflavonoids

Nonflavonoids include phenolic acids (e.g., curcumin), stilbenoids (e.g., resveratrol), and phenolic amides. The medicinal nonflavonoids mainly comprise phenolic acids and stilbenes. Hence, we only reviewed the role of curcumin and resveratrol in tumor immunity.

**Curcumin**

Curcumin (Fig. 1) is abundantly present in the plant Curcuma longa. Curcumin has a long history of use as an edible spice and in the medical treatment of inflammatory diseases. Here, we summarized previous achievements in the development of curcumin as a modulator of the tumor immune system. The plasticity, polarization, and function of tumor-associated macrophages (TAMs), modulation of Tregs, and modulation of the immunogenicity of dying cancer cells, along with the TME in response to curcumin, have provided a wealth of knowledge on the tumor immunotherapy potential of curcumin against various cancers. Recently, Hung et al. demonstrated that TNF-α triggered cancer immunosuppression through CSN5-mediated stabilization of PD-L1, which can be inhibited by curcumin in several types of cancer cells. Moreover, curcumin alone or in combination with anti-CTLA4 therapy effectively suppressed tumor growth in 4T1 breast cancer, B16 melanoma, and CT26 colon cancer, which could be attributed to the decrease of CSN5-mediated stabilization of PD-L1, inhibition of PD-L1 expression through the NF-κB pathway, and the increase of CD8+ T cell population. Immune dysfunction, such as the depletion of T cells, and a switch from Th1 to Th2 response, along with augmentation of CD4+CD25+Fox3+ Tregs population, was restored by curcumin in tumor-bearing hosts. Furthermore, curcumin prevented tumor-induced inhibition of T cell proliferation, suppressed Tregs activity by inhibiting TGF-β and IL-10, as well as enhanced the ability of T cells to eliminate tumor cells. Similarly, curcumin treatment improved the antitumor immune response in Cal 27 and FaDu oral cancer cells in vitro and a 4-nitroquinoline-oxide-induced mouse model in vivo, accompanied by the inhibition of PD-L1 and p-STAT3 expression, increased of CD8+ T cells, and decreased Tregs and MDSCs. Curcumin also acts as an immunorestore to protect against thymic atrophy in tumor-bearing mice, as evidenced by the neutralization of tumor-induced oxidative stress and restoration of NF-κB activity, along with the reformation of the TNF-α signaling pathway. These evidences indicate that curcumin can successfully reverse tumor-induced immunosuppression. Hou et al observed that curcumin inhibited tumor growth in a Lewis lung carcinoma isogenic tumor model by suppressing MDSCs, which is characterized by a decrease of MDSCs in the spleen and tumor tissues, promotion of MDSCs maturation, and differentiation, and down-regulation of ARG1, reactive oxygen species (ROS), and IL-6 in tumor-bearing mice. Notably, curcumin at a dose of 100 mg/kg/d was less effective...
but decreased T cells in 3LL tumor-bearing mice. Interestingly, 50 mg/kg curcumin significantly inhibited tumor growth by promoting the cytotoxicity of CD8+ T cells against tumor cells and IFN-γ secretion.49 Thus, curcumin dose should be carefully considered when used as an immunomodulator. Evidence of the immune modulation properties of curcumin in vitro and in vivo is summarized in Table 1.

Curcumin derivatives, such as hydrazinocurcumin encapsulated nanoparticles or dendrosomal curcumin, have been found to exert
immunomodulatory effects via macrophages. Curcumin derivatives induced TAMs repolarization from tumor-promoting M2 phenotype toward the more antitumor M1 phenotype by inhibiting STAT3 when cocultured with 4T1 cells, and subsequently inhibiting breast tumor growth, angiogenesis, and metastasis, as well as prolonging tumor-bearing mice survival in vivo. Recently, novel drug loading strategies were applied to increase the efficiency of tumor immunotherapy. For example, a lipid-encapsulated formulation of curcumin caused tumor remission in 50% of GL261-implanted glioblastoma mice through changing the polarity of tumor-associated microglia, inhibiting the tumor-promoting Arginase1high, iNOSlow M2-type tumor-associated microglia population while activating the Arginase1low, iNOShigh M1-type tumoricidal microglia. The combination immunotherapy strategy containing curcumin efficiently induced the immunogenic cell death (ICD) of residual cancer cells, and consequently enhanced the tumor immunoactivity and sensitized the tumor to antitumor T cell immunity. Another effective antitumor immunotherapy involved a core-shell structural nanodrug, loading NF-κB inhibitor curcumin, and anti-PD-1 antibody, which was pH-sensitive, which markedly improved the antitumor immunotherapeutic effect both in vitro and in vivo.

**Resveratrol**

Resveratrol (Fig. 1) exists in a variety of plants, such as berries, grapes, mulberries, and pomegranates. Several review articles have described the antitumor potential of resveratrol in preclinical and clinical studies against various cancers, such as leukemia, breast and lung cancer, and hepatocellular carcinoma, as well as the anti-tumor mechanisms of resveratrol, including induction of apoptosis and autophagy, cell cycle disruption, inhibition of angiogenesis, and epithelial-mesenchymal transition. Although the utility of resveratrol as tumor immunotherapy has been reported in several published reviews, we reviewed the relevant studies of considerable significance in recent years. As the PD-1/PD-L1 signaling pathway plays a significant role in immune tumor evasion, new inhibitors of the PD-1/PD-L1 signaling pathways are urgently needed. Menendez’s group demonstrated that resveratrol enhanced cytotoxic T lymphocytes against tumor cells, probably by targeting the N-linked glycan decoration of PD-L1 through GSK3β activation. In their research, resveratrol was predicted to bind PD-L1 dimerization using molecular docking and molecular dynamics simulations. However, direct evidence of the interaction between resveratrol and PD-L1 dimerization is lacking, such as a co-crystallization of resveratrol directly bound to PD-L1 dimerization. Elmets’s group observed that the TLR4 activation plays a protective role in 7,12-dimethylbenz(a)anthracene-induced cutaneous carcinogenesis, which can be prevented by resveratrol via TLR4 targeting to enhance the cell-mediated immune response.

The above conclusion could be assumed owing to the fewer tumors formed, smaller tumor size, and higher levels of IFN-γ and IL-12 in the TLR4 competent mice treated with resveratrol, and not TLR4 deficient mice. Additionally, resveratrol inhibited angiogenesis and increased the cell-mediated immune response to a considerable extent in the TLR4 competent mice than in TLR4 deficient mice. In EG7 tumor-bearing C57BL/6 mice, resveratrol treatment induced changes in the Tregs population and tumor-associated immunomodulatory cytokines, as evidenced by the decrease of the CD4+CD25+ cell population among CD4+ cells, FoxP3 expression, as well as secretion of TGF-β ex vivo and in vivo, and the increase of IFN-γ expression in CD8+ T cells ex vivo and in vivo. Xiong et al. observed that the inhibition of Renca tumor growth by resveratrol depended on CD8+ T cells. Resveratrol switched the expression of Th2 cytokines (e.g., IL-6 and IL-10) to Th 1 cytokines with modulation of Fas expression through IFN-γ and inhibited angiogenesis via the decreased level of vascular endothelial growth factor (VEGF) in the TME. Additionally, resveratrol, at low and noncytotoxic doses for immune cells, efficiently inhibited tumor growth and lung metastasis in 4T1 tumor-bearing mice through the inactivation of STAT3, as well as by preventing the generation and function of regulatory B cells (tBregs). Furthermore, resveratrol inhibited TGF-β production from tBregs. Similarly, in a mouse lung cancer xenograft, STAT3 inactivation was also observed in resveratrol inhibited M2 polarization. Interesting, low doses of resveratrol treatment (50 μM) up-regulated the expression of Rab 4B, resulting in increased HLA class II protein recycling and presentation, as well as restoring the CD4+ T cell recognition of B-cell lymphomas, indicating that resveratrol can be used for restoring the immune defense to prevent cancer recurrence. Similar to levamisole, resveratrol also demonstrated potent immune enhancing activity through the activation of NF-κB in immunosuppressive mice. Evidence of the immune modulation properties of resveratrol in vitro and in vivo is summarized in Table 1 and Figure 2.

**2.1.2 Flavonoids**

Most plant-based foods are rich in flavonoids, especially the dark fruits and vegetables, as well as dark chocolate, red wine, and tea. They consist of 15 carbon atoms, 2 phenyl rings, and 1 heterocyclic ring. Flavonoids such as flavones (e.g., apigenin, wogonin, baicalein, and baicalin), flavanones (e.g., catechins), flavonoids (e.g., icariin), flavanones (e.g., naringenin), isoflavones, and anthocyanidins (procyanidin) have anti-inflammatory effects and anticancer activities. Wogonin (Fig. 1) is one of the main flavonoids in the extract of Scutellaria baicalensis Georgi. It possesses antioxidant, anti-inflammatory, immunomodulatory, and antitumor activities. Wogonin can reverse the viability of chronic lymphocytic leukemia cells in vitro and prevent the development of leukemia in mice after the adoptive transfer of Eμ-
| Cell type | Natural products       | Dose                        | Experimental model                                  | Type of cancer   | References |
|-----------|------------------------|-----------------------------|-----------------------------------------------------|------------------|------------|
| T cells   | Curcumin               | 50 mg/kg, every alternate day, p.o. | Tumor-bearing Swiss albino mice, healthy human volunteers | Any tumor        | 45         |
|           |                        | /                           | 4-nitroquinoline-oxide-induced C57BL/6 mice         | Tongue carcinoma | 46         |
|           |                        | 5, 10 μM                    | Cal 27 and FaDu cell lines                          |                  |            |
|           |                        | 25, 50, or 100 mg/kg/d × 10 d, i.p. | 3LL tumor-bearing C57BL/6 or nude mice             | Lewis lung carcinoma | 49         |
|           |                        | 0.8 mg/mice                 | fLuc-4T1 tumor-bearing BALB/c mice                  | Breast cancer    | 50         |
|           |                        | 1, 5, 10, 20, 40 μM         | 4T1 cells                                           |                  |            |
|           |                        | 2 mg/kg at days 6, 9, 12, 15 | B16F10 tumor-bearing C57BL/6 mice                  | Melanoma         | 51         |
|           | Resveratrol            | 100 μM                      | JIMT-1 cells                                       | Breast cancer    | 52         |
|           |                        | 10 μmol/mouse, paint        | γC3H/HeN and γC3H/HeJ mice                          | Lymphoma         | 53         |
|           |                        | 4 mg/kg, i.p.               | EG7 tumor-bearing C57BL/6 mice                     |                  |            |
|           |                        | 1, 2.5, 5 mg/kg, i.p.       | Renca tumor-bearing γBALB/c mice                   | Renal cell carcinoma | 55         |
|           |                        | 50 μM                       | Nalm-6,DR4 and Ramos,DR4 cells                     | Lymphoma         | 56         |
|           | HS-1793                | 0.5, 1.5 mg/kg, i.p.        | FM3A tumor-bearing γC3H/He mice                    | Breast cancer    | 57         |
|           |                        | 0.3–2.5 μM, 72 h            | Tumor-bearing mice isolated splenocytes            | Breast cancer    | 58         |
|           | Scutellaria ocmulgeen leaf extract | 100 mg/kg, p.o.             | F98 tumor-bearing F344 rats                         | Malignant gliomas | 59         |
|           | Apigenin               | 25 mg/kg, i.p.              | TC-1 tumor-bearing γC57BL/6 mice                   | Cervical cancer  | 60         |
|           | Baicalein              | 50 mg/kg                    | H22 tumor-bearing γBALB/c mice or BALB/c-nu/nu mice | Hepatocellular carcinoma | 61         |
|           | Baicalin               | 80 mg/kg                    | H22 tumor-bearing γBALB/c mice or BALB/c-nu/nu mice | Hepatocellular carcinoma | 61         |
|           | EGCG                   | -                           | γSKH-1 hairless mice                               | Cutaneous carcinogenesis | 62         |
|           |                        | 3 mg/mouse/200 μL acetone   | γC3H/HeN mice                                      | Cutaneous carcinogenesis | 63         |
|           |                        | 0.1, 0.5, or 2.5 mg/mL      | TC-1 tumor-bearing γC57BL/6 mice                   | Cervical cancer  | 64         |
|           | Naringenin             | 200 mg/kg p.o.              | 4T1 tumor-bearing γBALB/c mice                     | Breast cancer    | 65         |
|           | Procyanidin            | 1.2 mg/mice                 | B16F10 tumor-bearing γC57BL/6 mice                 | Melanoma         | 66         |
|           | Digoxin                | 2 mg/kg, i.t.               | B16F10 tumor-bearing γC57BL/6 mice                 | Melanoma         | 67         |
|           | Telocinobufagin        | 5, 25, 125 mg/L             | 2BALB/c mice isolated lymphocyte cell             |                  | 68         |
|           | Cinobufagin            | 0.5, 1, 2.5 mg/L            | 2BALB/c mice isolated lymphocyte cell             |                  | 69         |
|           | Gamabufotalin          | 8, 16 ng/mL                 | Human peripheral blood mononuclear cells           | Glioblastoma and pancreatic cancer | 70         |
|           | Paclitaxel             | 0.04, 0.4, 4, 40 nM         | OVCAR-3 cells                                      | Ovarian carcinoma | 71         |
|           |                        | 5 mg/kg, i.p.               | MCA102 tumor-bearing γC57BL/6 mice                 | Fibrosarcoma     | 72         |
|           |                        | 135 mg/m2, i.v.             | Patients                                           | Cervical cancer  | 73         |
|           | Artemether             | 10 mg/kg, i.p.              | Spontaneous mouse mammary tumor (SMMT)-bearing γBALB/c mice | Breast cancer    | 75         |
|           | Dihydroartemisinin     | 12.5, 25, 50,100, 200 mM   | SW1990, BxPC-3, PANC-1 cells                       | Pancreatic cancer | 76         |
|           | Artesunate             | 0.03125, 0.125, 0.5, 2, 8 mg/L | HepG2 cells                                        | Hepatocellular carcinoma | 77         |
|           | Artemisinin            | 100 mg/kg, i.p.             | 4T1 tumor-bearing γBALB/c mice                     | Breast cancer    | 78         |
|           | Triptolide             | 100 nM                      | U251-MG, T98G, U87-MG, A172, LN229 and LN18 cells  | Gioma            | 79         |

(Continued on next page)
| Cell type | Natural products | Dose | Experimental model | Type of cancer | References |
|-----------|-----------------|------|--------------------|----------------|------------|
| B cells   | Resveratrol     | 20, 50 mg/mouse, i.p. | 4T1 tumor-bearing BALB/c mice | Breast cancer | 87         |
| MDSC<sub>3</sub> | Curcumin | 50 mg/kg | LLC cells tumor-bearing C57BL/6 mice | Lewis lung carcinoma | 48         |
| NKs       | Asiatonic acid  | 10 mg/kg, i.p. | B16F10 ang LCC tumor-bearing C57BL/6 mice | Melanoma and Lung carcinoma | 91         |
|            | Naringenin       | 50 mg/kg, i.p. | B16F10 ang LCC tumor-bearing C57BL/6 mice | Melanoma and Lung carcinoma | 91         |
| Macrophages | Hydrazinocurcumin | 100 μM 3 d intervals × 5 times, i.v. | 4T1 tumor-bearing BALB/c mice | Breast cancer | 96         |
| DCs       | Paclitaxel      | 75 mg/m2 | Patients | Prostate cancer | 104        |
| POL-P3b   | Capsaicin       | 50, 100, 200 mg/kg | CT26 tumor-bearing mice | Colon cancer | 101        |
| DCs       | Paclitaxel      | 25 mg/kg, i.v. | 4T1.2 tumor-bearing BALB/c mice | Breast cancer | 108        |
| Cytokines | Wogonin         | 100 μM | Mouse gastric carcinoma MFC cells tumor-bearing mice | Gastric carcinoma | 109        |
| Immune checkpoints | EGCG | 0.3% in drinking water | 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone treated A/J mice | Nonsmall-cell lung cancer | 110        |
| Splenocytes | Resveratrol | 15, 30, 60 mg/kg | Specific-pathogen-free mice | / | 111        |

Note: oral administration, p.o.; intratumoral injection, i.t.
FIGURE 2 Proposed models for the molecular mechanisms of immunomodulatory effects by natural productions. Inhibitory effects of natural products on tumors through enhancing the cytotoxic function of effect T cells and NKs, attenuating CD4+CD25+Foxp3+ regulatory T cells (Tregs), reducing myeloid-derived suppressor cells, decreasing TGF-β, IL-10, IL-5, indoleamine 2,3-dioxygenase, ARG1 levels, inducing IL-12, IFN-γ, and TNF-α/β production, and preventing cell-cell interaction of Tregs via the inhibition of CTLA-4 and PD-L1.

T-cell leukemias cells through the regulation of TNF-α-induced NF-κB activity. Wogonin demonstrated a strong antitumor immune effect in vivo by inducing the ROS-mediated endoplasmic reticulum stress response, and then activated the PI3K pathway to induce the translocation of calreticulin (CRT) and annexin A1, along with the release of high-mobility group protein 1 and ATP. It has also been reported that wogonin can reverse tumor-induced immune inhibition through the suppression of Treg cell function, as evidenced by the decreased secretion of TGF-β1 and IL-10 in Tregs culture, and activation of p38 MAPK pathway. In vivo studies have shown that wogonin has a significant inhibitory effect on early chronic lymphoid leukemia, mouse gastric cancer xenografts, and gliomas.

Apigenin (Fig. 1), is a bioavailable flavonoid, derived from a variety of fruits, vegetables, and drinks. Apigenin has anti-inflammatory, antioxidant, and anticancer characteristics. Apigenin also inhibited the expression of IFN-L1-induced PD-L1 protein in breast cancer patients, inhibited the phosphorylation of STAT1 tyrosine 701 site to inhibit the up-regulation of IFN-L1 induced PD-L1, and induced more effective T cells killing, or apoptosis of human cervical cancer cells induced by the p53 dependent pathway. In vivo studies have shown that it has a significant inhibitory effect against A375 melanoma xenografts. Similarly, baicalein and baicalin inhibited STAT3 activity, down-regulated PD-L1 expression, and enhanced the killing ability of T cells. Furthermore, apigenin enhanced the anticancer effect toward cervical cancer in vitro and in vivo, by enhancing the ability of HPV DNA vaccination to trigger IFNγ-inducing CD8+ T cell.

**Flavanes**

Flavanes, also named catechins, are the major constituents of green tea, such as (−)-Epicatechin-3-gallate (EGCG, Fig. 1), (−)-Epigallocatechin, and (−)-Epicatechin, exerting anticancer activities in various tumors. Flavanes These effects are partially attributed to their antioxidant, antiangiogenic and antimutagenic effects, as well as their anti-inflammatory activities. Reportedly, in an in vivo tumor model, increased numbers of CD8+ T cells were observed in (−)-epigallocatechin-3-gallate-treated tumors when compared with the non-EGCG-treated tumors. Katiyar et al. reported that EGCG increased the number of CD8+ CTLs infiltrating the TME, inducing a direct cytotoxicity on tumor cells, enhancing the release of IL-12, and thereby inducing a Th1 response against tumors. EGCG also improved the antitumor effects of DNA vaccination through the enhanced tumor-specific T cell immune response, as evidenced by a significant increase in E7-specific CD8+/CD4+ T cell-mediated immune responses when co-treated with Sig/E7/LAMP-1 DNA vaccination and EGCG. EGCG restored the killing ability of T cells by suppression of immune checkpoint PD-L1/PD-1 signaling and, finally,
inhibition of lung cancer growth. The underlying mechanisms include IFN-γ, EGF, and JAK2/STAT1 signaling. In colorectal cancer cells, EGCG down-regulated the expression and enzymatic activity of IFN-γ-induced indoleamine 2,3-dioxygenase (IDO) through the suppression of STAT1 activation.

### Flavonoids

Icarin (Fig. 1) is isolated from Epimedium plants and possesses anti-inflammatory effects, immunologic regulation, and anticancer potency. Furthermore, it has immunoadjuvant effects on enhancing the Th1-immune response, suggesting that icarin may serve as an adjuvant for tumor immunotherapy. Icarin could increase the CTLs response toward the P815AB peptide in tumor-bearing DBA/2J mice. Reportedly, icarin and its derivative reduced the proportion of MDSCs in the spleen of tumor-bearing mice, decreased the production of NO and ROS, and finally delayed the development of tumors.

### Flavanones

Naringenin (Fig. 1), mainly isolated from citrus, functions as an effective inhibitor of Smad3 and potential immunomodulator. Treatment with asiatic acid and naringenin generated a synergistic effect on the inactivation of TGF/Smad3 signaling, suppressed melanoma, and lung carcinoma growth by enhancing NKs killing against cancer via a mechanism associated with Id2 and IRF2. Naringenin administration decreased the number of MDSCs in the spleen and lungs of tumor-bearing 4T1/TGF-β1 mice overexpressing the immunosuppressive TGF-β1 cytokine. Furthermore, naringenin increased the level of activated T cells. Additionally, procyanidin and silibinin enhances the function of T cells and reduces the number of circulating MDSCs in mice bearing cancer cells, respectively.

### Cardiac glycosides (CGs)

CGs are compounds containing a steroid-like structure and an unsaturated 5- or 6-membered lactone ring as the common parent nucleus, including one or more sugar moieties located at C3 (Fig. 1). Usually, CGs are divided into two main categories: bufadienolides bearing the lactone 2-furanone at C17 (e.g., ouabain, digitoxin, and digoxin) and cardenolides bearing the lactone 2-pyrone at C17 (e.g., ouabain, digitoxin, and digoxin). Most CGs have been isolated from plants, including Digitalis purpurea, Digitalis lanata, Strophantus gratum, Kalanchoe, Helleborus, Cotyledon, and Nerium oleander. Additionally, some CGs have also been observed in amphibians (e.g., Bufoanidae) and snakes (e.g., Rhadophis tigrinus). Traditionally, CGs (e.g., digitoxin and digoxin) have been approved by the FDA for the treatment of heart failure and atrial arrhythmias (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/default.htm). The specific inhibition of the Na+/K+-ATPase pump is the mechanism by which CGs affect myocardial contraction. Recently, preclinical experiments revealed that CGs (e.g., bufalin and digoxin) exhibited potent anticancer effects. Additionally, the Huachansu injection containing bufadienolides (e.g., bufalin, cinobufagin, cinobufotalin, and resibufogenin) was approved by the Chinese FDA to treat cancer, and several CGs (e.g., Digitalis, Anvirzel and UNBS1450) entered clinical trials for the treatment of solid tumors, such as liver, lung, and breast cancer (see http://clinicaltrials.gov/ and the literature).

#### Cardenolides

An ICD inducer is a compound that possesses cytotoxicity while triggering an immune response toward dead cell-associated antigens. To identify novel inducers of ICD, Kroemer’s group used a fluorescence microscopy platform to screen the U.S. FDA-approved 120 anticancer drugs and a library encompassing 879 chemicals in human osteosarcoma U2OS cells. They identified cardenolides, including digoxin, digitoxin, ouabain, and digitoxigenin as potent ICD inducers. They found cardenolides (e.g., digoxin and digitoxin)-induced ICD was associated with the suppression of Na+ /K+-ATPase in cell membranes. In immunocompetent mice, digoxin enhanced the antitumor effect of DNA-damaging agents cisplatin and mitomycin C. A retrospective analysis (145 cancer patients treated with digoxin and 290 cancer patients untreated with digoxin) demonstrated an improved 5 yr survival rate in patients treated with digoxin. Huang et al. reported that the combination strategy of cisplatin prodrug coadministration with digoxin effectively induced ICD by promoting DC maturation, activating CD8+ T cell responses, and completely eradicating residual tumors in B16F10 tumor-bearing mice. Furthermore, these two research groups demonstrated that tumor cells succumbing to chemotherapeutic drugs (cisplatin and cisplatin prodrug) and digoxin could vaccinate syngeneic mice against the subsequent challenge with living cells of the same type in vivo. These combination strategies suggest that digoxin can ameliorate the efficacy of nonimmunogenic anticancer therapies and generate vaccine-like functions for improved immunochemotherapy.

#### Bufadienolides

For the past few years, several researchers have focused on the anticancer effects of bufadienolides, partly by enhancing the immune system function. For example, Chung’s group observed that both cardenolide ouabain and bufadienolide bufalin promoted immune responses in murine WEHI-3 leukemia cells in mice in vivo, evidenced by the decreased liver and spleen weights, modulation of immune-associated leukocyte markers, such as CD3 (T cells), CD19 (B cells), Mac-3 (macrophages), and CD11b (monocytes), restoration of glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and lactate dehydrogenase levels, and the activation of macrophage phagocytosis. Furthermore, telocinobufagin and cinobufagin activated the immunologic system in vitro, including stimulate splenocyte proliferation, enhance the activation of NKs and the phagocytosis ability of macrophage, and increase the percentage of CD4+/CD8+ cells in splenocytes and the ratio of Th1/Th2 (the levels of Th1 cytokines such as IL2, IL12, IFN-γ, and TNF-α are up-regulated while the levels of Th2 cytokines such as IL4 and IL10 are down-regulated after these two agents treatment). Moreover, ybutofolin, at a concentration of 8 ng/mL (IC50 value in human pancreatic cancer cell line SW1990), almost nontoxic to peripheral blood mononuclear cells.
(PBMCs) (IC\textsubscript{50} value is 44.1 ± 2.4 ng/mL), efficiently decreased the ratio of CD4\textsuperscript{+}CD25\textsuperscript{+}Foxp3\textsuperscript{+} Tregs in mitogen-stimulated PBMCs, suggesting that bufotalin not only exerts a killing effect on tumor cells, but also enhances the antitumor immunity by inhibiting the expansion and function of Tregs.\textsuperscript{70} In addition to the immunomodulatory effects mentioned earlier, Yang et al. reported that bufalin inhibited the proliferation and migration of HCC Bel-7404 and SK-Hep1 cells, which may be attributed to its ability to suppress the APOBEC3F-induced intestinal immune network.\textsuperscript{151}

2.3 Terpenoids

Terpenoids are a class of compounds derived from mevalonic acid, possessing a basic carbon structure with two or more isoprene units (C5 units), such as monoterpenes (comprised of 10 carbon atoms, C10), sesquiterpenes (C15), diterpenes (C20), and so on. It is widely present in plants and has extensive pharmacologic actions, including anti-inflammatory, immunomodulatory, antibacterial, antitumor, and neuroprotective effects.\textsuperscript{152} These natural compounds are widely used in medicine, for example, paclitaxel and its derivatives as common anti-tumor drugs were used for the treatment of nonsmall-cell lung cancer, ovarian cancer, and breast cancer.\textsuperscript{153} Artemisinin and its derivatives are currently the most effective treatments for malarial parasite infection.\textsuperscript{154} Here, we highlighted the role of these compounds in tumor immunity.

2.3.1 Paclitaxel

Paclitaxel (Taxol, Fig. 1) is a well-known natural anticancer drug in clinical use. It is a tricyclic diterpenoid compound, isolated from the bark and needles of Taxus brevifolia.\textsuperscript{153} There have been several published reviews on the antitumor effects of paclitaxel and its analogs, as well as its role in tumor immunotherapy.\textsuperscript{153,155,156} Tumor-infiltrating DCs are considered potent antigen-presenting cells. DCs can activate the CTLs or tolerogenic DCs to suppress the immune reaction against tumor cells to escape. Reportedly, a low and nontoxic concentration of paclitaxel stops the pre-DCs to be tolerogenic DCs and maintain DC functions, thus suppressing the immune reaction against tumors to escape.\textsuperscript{71} Moreover, DCs can induce antigen-specific CTLs, and an injection of paclitaxel induces tumor-specific cytotoxic T lymphocyte response and acquisition of prolonged tumor immunity.\textsuperscript{72} Jordanova et al. showed that paclitaxel treatment lead to a markable reduction in proliferating (Ki67\textsuperscript{+}) CD3\textsuperscript{+}CD8\textsuperscript{+} T cells and Foxp3\textsuperscript{+} (CD3\textsuperscript{+}CD8\textsuperscript{+}) Tregs, with increased rates of CTLs, providing a theoretical basis for paclitaxel in the treatment of tumor stroma.\textsuperscript{73} In chemotherapy, a high concentration of paclitaxel is used for antitumor treatment but is toxic to immune cells. Therefore, many vectors have been used to study the reduction of paclitaxel toxicity. Many studies demonstrated that systemic delivery of paclitaxel using a nanocarrier or receptor resulted in a significantly improved antitumor response.\textsuperscript{108,157} For example, paclitaxel derivative-loaded nanoparticles showed lower cytotoxicity toward bone marrow-derived macrophages (BMDMs) than free paclitaxel, up-regulating the CD11b expression in BMDMs. This nanoparticle polarized macrophages toward M1 and inhibited their M2 differentiation, both on phenotypic and functional levels. Accordingly, they also observed similar results in B16F10 melanoma tumor inhibition in vivo, which was associated with immune system stimulation.\textsuperscript{158} Moreover, paclitaxel is used not only as a chemotherapeutic agent for the treatment of tumors, but also in combination with immunotherapeutic agents, such as IL-2, IDO inhibitor NLG919, and a DC-based cancer vaccine.\textsuperscript{74,104,159} Recently, novel drug loading strategies were applied to increase the efficiency of tumor immunotherapy. For example, an effective antitumor immunotherapy composed of a nanodrug loading paclitaxel and anti-PD-1 antibody, which was pH and matrix metalloproteinase dual sensitive, markedly improved the antitumor immunotherapeutic effect both in vitro and in vivo.\textsuperscript{160} Although the direct anticancer effects of paclitaxel on various cancer cells remain well known, paclitaxel also acts as an adjuvant drug to regulate immune cells, and its mechanism of action is becoming increasingly evident. However, cancer is difficult to cure as the tumor-associated microenvironment is an extremely complicated system that involves several kinds of multifunctional immunizing cells and molecules, as well as tumor cells. The function of paclitaxel alone or in combination with other immunotherapies in tumor interventions need to be further investigated.

2.3.2 Artemisinins

Artemisinin (Fig. 1) is a natural compound derived from the Chinese herb Artemisia annua, also known as Qinghao or sweet wormwood. Artemisinin and its synthetic derivatives (e.g., dihydroartemisinin, arteunate, artemether, artemether) have demonstrated immunotherapeutic effects against a range of cell lines and are also effective against drug-resistant cancer cell lines.\textsuperscript{161,162} Artemisinin enhanced the human NK cell line NK-92MI, and primary NK cell cytotoxicity against leukemia K562 cells via the stimulation of granule exocytosis, mediated by the activation of Vav-1 and ERK1/2 signaling.\textsuperscript{93} In addition to NKs killing and lymphocyte proliferation, the antitumor mechanisms of artemesinate in vitro also involved blocking the secretion of immunosuppressive factors, such as TGF-β1 and IL-10, in colorectal cancer colon26 (murine) and RKO (human) cells.\textsuperscript{84} Artemether not only promoted the delayed-type hypersensitivity (DTH) response and hemagglutination antibody production in normal mice, but also inhibited tumor growth in spontaneous mouse mammary tumor-bearing BALB/c mice, which may be attributed to the depletion of immunosuppressive cells CD4\textsuperscript{+}CD25\textsuperscript{+}Foxp3\textsuperscript{+} Tregs in the spleen.\textsuperscript{75} The enhanced DTH response was also observed in dihydroartemisinintreated BALB/c mice against sheep red blood cells.\textsuperscript{163} γδ T cells play an important role in the antitumor activity of dihydroartemisinin and artemesinate against pancreatic cancer cells (SW1990, BxPC-3, and PANC-1) and liver cancer cells (HepG2), respectively.\textsuperscript{164,165} Mechanistically, dihydroartemisinin increased the expression of intracellular perforin, granulase B, and the production of IFN-γ, and then enhanced the γδ T cell-mediated killing activity.\textsuperscript{164} In contrast, elevating the expression of GraB and Fas, as well as reducing the secretion of TGF-β1, may be important artemesinate mechanisms promoting the antitumor activity of γδ T cells.\textsuperscript{165} Furthermore, artemisinin enhanced
the antitumor immune response in 4T1 breast cancer cells in vivo by promoting T cell function and quelling immunosuppression from Tregs and MDSCs in the tumor.\textsuperscript{78} A recent study has also shown that the topical administration of artemisinin could suppress contact the hypersensitivity response and Con A-induced T cell proliferation.\textsuperscript{166} Notably, a novel immune regulatory function of dihydroartemisinin involves the reciprocal regulation of Th and Tregs generation by modulating mTOR signal.\textsuperscript{167} Furthermore, artesunate, a semisynthetic analog of artemisinin, demonstrated potent apoptosis-inducing effects across a broad range of B-cell lymphoma cell lines in vitro, and prominent antilymphoma activity in vivo, indicating its relevance for the treatment of B cell lymphoma.\textsuperscript{88}

2.3.3 Triptolide

Triptolide (Fig. 1) is a biologically active diterpene triepoxide extracted from Celastraceae, and possesses antiproliferative properties against several types of cancers.\textsuperscript{168} Recently, a study demonstrated that triptolide may be used to reverse CD4\textsuperscript{+} T cell inhibition caused by glioma cells and is an alternative candidate for targeting PD-L1, one of the checkpoint inhibitors for the treatment of glioma.\textsuperscript{79} Triptolide treatment also induces the down-regulation of CD4\textsuperscript{+}CD25\textsuperscript{+}Foxp3\textsuperscript{+} Tregs, and up-regulation of IL-10, TGF-\textbeta, and VEGF in melanoma-bearing mice.\textsuperscript{80} Interestingly, triptolide can treat tumors, as well as cancer-related pain by regulating the functions of other immune cells, such as T cells.\textsuperscript{81,169}

2.4 Saponins

Saponin is a type of glycoside whose aglycon is a triterpene or a spiran sterane compound. It is mainly distributed in higher terrestrial plants and is also observed in small amounts in marine organisms, such as starfish and sea cucumber.\textsuperscript{170} Saponin exhibits a wide range of biologic and pharmacologic properties, including analgesic, antipyretic, anti-inflammatory, immunomodulatory, and antitumor activities.\textsuperscript{170} Saponin mainly includes steroidal saponin and triterpenoid saponin, of which triterpenoid saponin plays an important role in tumor immunotherapy. Reportedly, quillaja saponin-21, a highly purified saponin extracted from the Chilean tree Quillaja saponaria Molina, is among the most potent immunologic adjuvants.\textsuperscript{171} It has been shown that saponin-based ISCOMATRIX vaccines could treat tumors by activating the immune response of CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells.\textsuperscript{172,173} The saponin-based vaccine, chitosan hydrogel, generated effector CD8\textsuperscript{+} T cells in a mouse model. Additionally, other triterpenoid saponins also have tumor immunotherapeutic effects.\textsuperscript{174} Platycodin D, a triterpenoid saponin isolated from Platycodon grandiflorus (Jacq.) A., triggered the extracellular release of PD-L1 and PD-treated cancer cells, restoring Jurkat T cells activation.\textsuperscript{82} Ginsenoside F1, a triterpenoid saponin component of ginseng, enhanced NK function and may possess chemotherapeutic potential in NK-based immunotherapy.\textsuperscript{95}

2.5 Other natural products

In addition to the earlier mentioned natural products, there are some several others that have not mentioned, such as polysaccharides (e.g., mushroom extract), anthracyclines, polysaturated fatty acids, ginseng, which have been previously described.\textsuperscript{16,27} Here, the parent review just briefly summarized part natural products, reported in previous reviews.

2.5.1 Polysaccharides

Polysaccharides are a kind of polymers formed by the connection of aldose or ketose through glycoside bonds and are found mainly in plants, animals, and microorganisms. Studies have shown that polysaccharides have a wide range of pharmacologic activities, such as antitumor, immune regulation, antiviral, antiaging, hypoglycemic, and blood lipid activities, especially in antitumor immunity with minimal adverse reactions.\textsuperscript{175-178} For example, Partulaca oleracea L. polysaccharides (POL-P3b), derived from the monodendate plant, demonstrated tumor growth inhibition and immunoregulation, and can be used for treating cervical cancer and for enhancing immunity.\textsuperscript{83,105} As a biologic response regulator, polysaccharides promote cellular humoral and immune responses to inhibit and eliminate tumor cells. POL-P3b can increase the level of TH1-type cytokines (IL-12) and decrease the level of TH2-type cytokines (IL-10).\textsuperscript{83} Additionally, POL-P3b can also induce apoptosis of intestinal DC by stimulating the TLR4-PI3K/AKT-NEF-\textbeta signaling pathway. In vivo studies have shown that POL-P3b possess a significant inhibitory effect on cervical cancer xenografts.\textsuperscript{105} Xie’s group reported the immunoregulatory activity of the polysaccharide from Ganoderma atrum (PGA) in CT26 and S180 tumor-burdened mouse models, as evidenced by the activation of macrophage phagocytosis and inhibition of tumor growth by PGA through the inhibition of the MAPK signal pathway, induced by TLR4.\textsuperscript{101,102} Several studies indicated that the antitumor immune mechanism of lentinan polysaccharide, especially p-glucans, is associated with immune cells, activating immune cells through signaling pathways, such as CR3-Syk-PI3K signaling, and NF-\textbeta, to enhance the antitumor activity, as well as cytokines (e.g., IFN-\gamma).\textsuperscript{179-184} The immunomodulatory mechanisms of these compounds are also summarized in reviews.\textsuperscript{185,186} Furthermore, clinical studies indicated that lentinan showed effective tumor growth inhibition in gastric, nonsmall-cell lung cancer, ovarian, or colorectal cancers.\textsuperscript{187-189} Reportedly, polysaccharides from Plantago asiatica, aloe, ginseng, and achyranthes also improved the immune cell activity in tumor-bearing mice.\textsuperscript{190}

2.5.2 Vitamin E succinate (VES)

VES is one of the eight isomers of vitamin E.\textsuperscript{191} and possesses strong anticancer properties, including inhibition of tumor cell proliferation, the introduction of apoptosis, as well as suppression of tumor progression in tumor-bearing mice in multiple malignant tumors, such as prostate, breast and gastric cancer, and melanoma, lymphoma, and leukemia.\textsuperscript{192-197} VES selectively stimulates the expression of TRAIL and TRAIL receptors in human CD4\textsuperscript{+} T cells and enhances the expression of TRAIL in nonstimulated CD4\textsuperscript{+} T cells. The binding of VES to human CD4T cells enhances the anticancer effect of VES on Human gastric cancer cell line MKN28.\textsuperscript{194} Vitamin E demonstrated potent antitumor effects against the HPV16 E7-expressing TC-1 tumor model by
reducing the immunosuppression mediated by MDSCs and CD8+ T cells. Moreover, vitamin E therapy can be combined with the active immunity of antigen-specific tumor vaccine, resulting in a strong antitumor effect.85 Furthermore, the effect of natural vitamins, such as vitamins A–E have been systematically reviewed.28,198

2.5.3 | Capsaicin

Capsaicin (Fig. 1), a derivative of vanillyl amide, is the pungent component of red peppers.199 The pharmacologic effects of capsaicin include enhancing immunity, resisting inflammation, lowering blood pressure, reducing excessive blood coagulation, and lowering blood sugar levels.200 Capsaicin could target TAMs, accompanied by the apoptosis and destruction of tumor-associated stromal cells, which is tumor-specific T cells dependent, depleting the immunosuppressive host cell population at the tumor site, and thereby altering the cytokine profile at the microenvironment.103 Another mechanism by which tumors escape the body’s immune attack is by increasing the intratumoral population of Tregs and depleting CD8+ CTLs. Intratumoral administration of capsaicin has been shown to increase the CTL population while decreasing the numbers of Tregs. Furthermore, capsaicin demonstrated in vivo inhibition in the Meth A fibrosarcoma and CT26 xenograft tumors.86 In human osteosarcoma cells, capsaicin can induce the translocation of a large quantity of CRT from intracellular compartments to the cell surface. Additionally, CRT on the human OS cell surface can be used as specific signaling molecules to promote the phagocytosis of tumor cells, thereby mediating tumor cell immunogenic death.105 Capsaicin induced the pre- and early apoptotic cell surface exposure of CRT, HSP90, and HSP70, as well as ATP release.201

3 | CONCLUSION AND FUTURE PERSPECTIVE

Compared with tumor immunity targeted therapies, such as durvalumab and ipilimumab, natural products (e.g., polysaccharide) have an extensive range of immunomodulatory activities, abundant sources, and fewer adverse reactions. In the last decades, series of studies have revealed that natural products exert anticancer activities based on immunoregulation in vitro and in vivo. Most recently, some natural product derivatives with enhanced stability and efficacy have been developed through chemical modification, indicating an attractive prospect for the development of natural products as novel tumor immunotherapy. For example, natural vitamins C, D, and E have been tested in clinical trials. Curcumin alone is not clinically effective due to its absorption and metabolism issues, but its derivatives (e.g., demethoxycurcumin, bis-demethoxycurcumin) are undergoing clinical trials evaluations. Currently, more than 100 ongoing trials on resveratrol are listed on www.clinicaltrials.gov. These findings provide a new approach for the development of novel and effective tumor immunotherapies. Moreover, the combination of natural products with traditional antitumor therapies targeting tumor cells can further exert their advantages in targeted therapies, with synergistic effects and reduced toxicity. They could provide a safer and more effective strategy for clinical interventions. It is expected that natural products will demonstrate promising breakthroughs in tumor immunotherapy in the future.

The immunoregulation mechanisms of natural products are complex and involve multiple signal transduction pathways. Although natural products and their derivatives, as modulators of tumor immunotherapy have made encouraging progress and appear promising in vitro and in vivo preclinical studies in this review, the following problems still exist in this field: (i) Due to the characteristics of individual patient differences, tumor heterogeneity, and TME differences, the overall effective rate of tumor immunotherapy is still relatively low, and the target population is relatively small. (ii) Most natural products possess extensive pharmacologic effects, but their targets and molecular mechanisms have not been fully elucidated, especially those related to tumor immunity, and there is still a considerable lag in developing natural products as tumor immunotherapy.

AUTHORSHIP

J.-X.C. and L.-J.D. designed the manuscript. L.-J.D., M.Q., and N.L. drafted the manuscript. Y.-H.L. and D.-M.Z. participated in the procedures. J.-X.C. and D.-M.Z. helped to design the manuscript and with its revision. Li-Juan Deng, Ming Qi, and Nan Li contributed equally to this work.

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DISCLOSURES

The authors declare no conflicts of interest.

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