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Novel natural product therapeutics targeting both inflammation and cancer

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Abstract

Inflammation is recently recognized as one of the hallmarks of human cancer. Chronic inflammatory response plays a critical role in cancer development, progression, metastasis, and resistance to chemotherapy. Conversely, the oncogenic aberrations also generate an inflammatory microenvironment, enabling the development and progression of cancer. The molecular mechanisms of action that are responsible for inflammatory cancer and cancer-associated inflammation are not fully understood due to the complex crosstalk between oncogenic and pro-inflammatory genes. However, molecular mediators that regulate both inflammation and cancer, such as NF-κB and STAT have been considered as promising targets for preventing and treating these diseases. Recent works have further demonstrated an important role of oncogenes (*e.g.,* NFAT1, MDM2) and tumor suppressor genes (*e.g.,* p53) in cancer-related inflammation. Natural products that target these molecular mediators have shown anticancer and anti-inflammatory activities in preclinical and clinical studies. Sesquiterpenoids (STs), a class of novel plant-derived secondary metabolites have attracted great interest in recent years because of their diversity in chemical structures and pharmacological activities. At present, we and other investigators have found that dimeric sesquiterpenoids (DSTs) may exert enhanced activity and binding affinity to molecular targets due to the increased number of alkylating centers and improved conformational flexibility and lipophilicity. Here, we focus our discussion on the activities and mechanisms of action of STs and DSTs in treating inflammation and cancer as well as their structure-activity relationships.

Keywords

Cancer; Inflammation; Sesquiterpenoid; MDM2; p53; NF-κB

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Introduction

There is an increasing interest in investigation of the relationships between inflammation and cancer. We and others have proposed to dually target molecules involved in both inflammation and cancer as a novel approach to cancer prevention and treatment. Inflammation is the body's protective response to microbial infection and other environmental stimuli, which usually cause tissue damage. Consequently, infection-triggered inflammatory response causes the destruction of damaged tissues and stimulates its regeneration [1–2]. It has been recognized that acute inflammation contributes to tumor regression while chronic inflammation plays a crucial role in tumor initiation and progression [3–4]. Indeed, more than one fifth of human cancers are associated with chronic and dysregulated inflammation [4]. Chronic inflammation is commonly featured by the persistent activation of immune system, which inevitably results in the accumulation of genetic and epigenetic aberrations, and consequently leads to malignant transformation [4–5]. During this procedure, many molecular mediators, including cytokines [*e.g.,* tumor necrosis factor (TNF)-α and interleukins (ILs)], transcription factors [*e.g.,* nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3)], tumor suppressor genes (*e.g.,* p53) and oncogenes [*e.g.,* murine double minute 2 (MDM2)] are involved in the tumor inflammatory microenvironment; most of the mediators (Fig. 1) have been extensively discussed in recent reviews [5–7]. Here, we focus on the recently uncovered mediators that are involved in inflammation and cancer as well as the changing paradigms in the field.

NF-κB and STAT are well-documented pro-inflammatory transcription factors that play critical roles in inflammation and cancer [8–9]. After activation by pro-inflammatory stimuli, NF-κB regulates the transcription of most of the genes related to inflammation [*e.g.,* TNF, ILs, chemokines, and cyclooxygenase 2 (COX-2)] as well as survival genes in cancer cells [*e.g.,* c-Myc, cyclinDl, and B-cell lymphoma-extra large (Bcl-xl)] [8]. STAT activation contributes to parts of IL-6's functions and promotes cancer cell proliferation and tumorigenesis [9]. Recent studies have indicated that NF-κB and STAT3 collaboratively control the communication between cancer cells and inflammatory cells [9]. Nuclear factor of activated T-cells (NFAT), which was initially discovered in human T cells, has been demonstrated to play an important role in the regulation of inflammatory response, development and metastasis of cancer, and other biological events in the human body [10–11]. Hypoxia-inducible factor 1 (HIF1) exerts a well-established role in cancer initiation and progression and is essential for the execution of an optimal inflammatory response [12]. The complex cross-talks (Fig. 1) among NF-κB, STAT3, NFAT, and HIF1 in immune cells and tumor cells have yet to be fully comprehended. All of these transcription factors have been demonstrated as promising targets for the treatment of inflammation and cancer.

The MDM2 oncogene and the p53 tumor suppressor gene continue to hold interest as therapeutic targets in human cancers [13–14]. Many MDM2 inhibitors and p53 activators have been developed for the treatment and prevention of human cancers; several of them have currently entered clinical trials [13–16]. Recent studies have shown that MDM2 plays an important role in inflammation and inflammatory diseases via both p53-dependent and p53-independent mechanisms (Fig. 1) [17–21]. MDM2 inhibitors have also been reported to exert potent anti-inflammatory effects in tissue injury by inhibiting NF-κB [17, 21–23]. Because both

p53 and NF-κB p65 exert their transactivation activities by interacting with p300/CREB-binding protein (CBP), there is a competitive relationship between p53 and NF-κB p65 [24–26]. Overexpression and activation of either p53 or NF-κB p65 inhibit the activity but not the expression of another protein [27]. Moreover, MDM2 induces NF-κB p65 expression at the transcriptional level, independent of p53 [28–29]. MDM2 directly binds to the first two Sp1-binding sites in the p65 promoter, increases p65 expression, and activates p65-mediated gene expression [28–29]. Recent studies have also uncovered that the nucleotide-binding oligomerization domain (NOD)-like receptors and Src kinase have multiple regulatory roles and have been proposed as molecular targets for treating both chronic inflammation and cancer [30–32].

Natural products are still a major chemical resource for anti-inflammatory and anticancer drug discovery [33–36]. Sesquiterpenoids (STs) are a large class of plant-derived secondary metabolites that exhibit diverse biological activities and have been implicated in traditional medicine against inflammation and cancer [37–38]. This class of natural products show 'drug-like' chemical properties, including alkylating center reactivity, lipophilicity, and molecular geometry and electronic features [37–38]. Several STs in clinical trials, including the derivatives of thapsigargin (**1**), parthenolide (**2**), and artemisinin (**3**), have been comprehensively discussed in the recent reviews [37–40]. We have summarized these clinical studies in Table 1. Recent advances have indicated that dimeric sesquiterpenoids (DSTs) exert enhanced anti-inflammatory and anticancer activities due to the increased binding affinity to molecular targets [41–42]. In this review, we will focus our discussion on representative STs and DSTs that have shown potent anti-inflammatory and anticancer activities (Fig. 2 and Table 2) as well as their characterization, molecular target(s), mechanism(s) of action, and structure-activity relationships.

Dual Effects of STs and DSTs on Inflammation and Cancer

Inulanolide A, japonicone A, lineariifolianoid A, and their analogs—The *Inula* plants have a long history of use in traditional Chinese medicine for treating inflammation and cancer [52]. Monomeric STs are characterized as one of the main chemical constituents of *Inula* plants [52], and have shown chemical diversity [53–55] and excellent pharmacological activities [56–63]. These ST monomers have always been considered as the major bioactive constituents until the discovery of novel DSTs, including inulanolide A (InuA, **4**) and its analogs from *Inula Britannica* [64]. These DSTs have exhibited potent anti-inflammatory activities by inhibiting NF-κB activation and decreasing the production of nitric oxide (NO) and TNF-α in lipopolysaccharide (LPS)-stimulated RAW264.7 cells [64]. Their activities are significantly stronger than the previously identified ST monomers from the same plant [64]. These results have prompted phytochemists to isolate and identify new DSTs with greater biological activities and better drug-like properties, leading to the isolation and characterization of japonicone A (JapA, **5**), lineariifolianoid A (LinA, **6**) and their analogs [65–69]. All these dimers have exhibited strong inhibitory effects against LPS-induced NO production in RAW264.7 cells [65–69].

Hu *et al.* have further investigated the molecular mechanisms that are responsible for the anti-inflammatory activities of JapA and characterized this compound as a novel TNF-α

antagonist [70]. JapA has been found to directly bind to TNF-α and selectively inhibit the interaction between TNF-α and tumor necrosis factor receptor 1 (TNFR1). However, JapA does not show significant effects on the binding of TNF-α to TNFR2. Consequently, the compound blocks TNF-α-TNFRl-mediated multiple signaling pathways *via* inhibition of TNF-α-induced NF-κB activation as well as the expression of adhesion molecules [intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1)] and chemokine [monocyte chemoattractant protein-1 (MCP-1)] in the endothelial cells. In the *in vivo* studies, JapA protects mice from acute hepatitis without compromising the host's defense against the virus [70].

These DSTs have shown promising anticancer activity in preclinical studies. JapA has been screened in a wide spectrum of human normal and cancer cell lines and exhibits a selective cytotoxicity against human lymphoma cells with IC_{50} values at sub-micromole levels, but has no apparent effect on normal cells [71]. Li *et al.* have reported that JapA inhibits the proliferation of lymphoma cells, arrests the cell cycle in G_2-M phase, and induces cell apoptosis *in vitro,* and suppresses the growth and metastasis of lymphoma *in vivo*. JapA's anti-lymphoma activities have been attributed to its inhibitory effects on TNF-α-TAK1 (TGF-beta activated kinase 1)-IKK (IκB kinase)-NF-κB signaling axis and TNF-α-induced NF-κB activation and nuclear translocation, which lead to the downregulation of NF-κB target genes that regulate cancer cell growth (cyclin D1 and c-Myc) and apoptosis [B-cell lymphoma 2 (Bcl-2), Bcl-xL, X-linked inhibitor of apoptosis protein (XIAP), TNF receptor-associated factor 2 (TRAF2)] [71].

During our studies on the search for novel dual MDM2 and NFAT1 inhibitors for cancer prevention and therapy, we have identified several STs and DSTs, including JapA, InuA, and LinA [72–75]. JapA has been shown to selectively inhibit breast cancer cell growth without affecting normal breast cells, regardless of p53 status [72]. JapA has also been found to inhibit breast cancer cell proliferation and colony formation, arrest cells in G2-M phase, induce cell apoptosis, and suppress breast tumor growth and metastasis in dose-dependent and p53-independent manners. We have discovered that JapA directly binds to MDM2 protein and induces its autoubiquiti-nation and proteasomal degradation [72]. It has been further found that JapA also inhibits NFATl-mediated *MDM2* transcription by inhibiting NFAT1 protein stability and nuclear translocation and disrupting the interaction between NFAT1 DNA binding domain and *MDM2* P2 promoter [73]. The importance of NFAT1 and MDM2 for JapA's anticancer activity has been validated using NFAT1-MDM2 overexpression and knockdown in breast cancer cell lines. InuA and LinA have also exhibited potent anti-breast cancer activity *in vitro* and *in vivo* by targeting NFAT1 and MDM2 [74–75].

Artemisinin and its derivatives, dimers, and conjugates—Artemisinin (**3**) is isolated from the medical plant *Artemisia annua* L. and identified as a sesquiterpenoid bearing a peroxide bridge [76]. Artemisinin and its derivatives artesunate (**7**), dihydroartemisinin (**8**), artemether, and arteether are clinically used antimalarial drugs without host toxicity and have been considered as the most effective drugs in the treatment of cerebral malaria and chloroquine resistant falciparum malaria [77]. In addition to the antimalarial activities, artemisinin and its derivatives have recently been reported to possess

anti-inflammatory activity. Wang *et al.* have demonstrated the anti-inflammatory activity of artemisinin in tet-radecanoylphorbol acetate (TPA)-induced skin inflammation in mice [78]. Artemisinin has further been found to inhibit TNF-α-induced phosphorylation and degradation of inhibitor of kappa B alpha (IκBα) as well as the nuclear translocation of NF-κB p65, resulting in inhibition of the expression of NF-κB target genes [78]. Artemisinin also inhibits reactive oxygen species (ROS) production and phosphorylation of p38 and extracellular signal-regulated kinase (ERK), without affecting the phosphorylation of c-Jun N-terminal kinase (JNK) [78].

Xu *et al.* have reported that artesunate inhibits the secretion of IL-1β, IL-6, and IL-8 from TNF-α-stimulated human rheumatoid arthritis fibroblast-like synoviocytes (RAFLS) by inhibiting the nuclear translocation of NF-κB and its DNA-binding and transcriptional activities and preventing Akt phosphorylation [79]. The same group has further found that artesunate inhibits the secretion of vascular endothelial growth factor (VEGF) and IL-8 as well as the expression of HIF-1α in RAFLS by inhibiting phosphoinositide 3-kinase (PI3K)/Akt activation [80]. Both studies have indicated that artesunate may have therapeutic potential for human arthritis and have been further validated using the K/BxN mouse model of rheumatoid arthritis and the rat model of Freund's complete adjuvant-induced arthritis [81–82]. These studies have been comprehensively discussed in recent reviews [40, 77]. Dihydroartemisinin has also recently been observed to inhibit the onset of experimental autoimmune encephalomyelitis (EAE) and ameliorate this disease in EAE-inflicted mice by inhibiting the mammalian target of rapamycin (mTOR) pathway [83]. This compound also suppresses ovalbumin (OVA)-induced chronic airway inflammation in mice by inhibiting ERK, p38 mitogen-activated protein kinase (MAPK) phosphorylation, IκBα phosphorylation, and NF-κB activation [84]. Further studies have indicated that dihydroartemisinin protects rats against bleomycin-induced pulmonary fibrosis and alcoholic liver injury by inhibiting the mRNA and protein expression of transforming growth factor beta 1 (TGF-β1), TNF-α, alpha-smooth muscle actin (α-SMA), and NF-κB and activating farnesoid X receptor (FXR), respectively [85–86].

There is an increasing interest in repurposing artemisinin, artesunate and other derivatives for treating human cancers [reviewed in refs [87–88]]. Accumulating evidence has indicated that artemisinin and its derivatives possess potent *in vitro* and *in vivo* activities against various types of human cancer. Because these compounds have shown excellent drug-like properties and safety profiles, repurposing artemisinin and its derivatives as anticancer drugs can significantly reduce the costs during drug development and clinical trials, therefore lowering investment risk and accelerating development process. Currently, artesunate and artemether are under evaluation for their anticancer activity in clinical trials. The detailed information has been summarized in Table 1. Mechanistically, the peroxide bridge of artemisinin and its derivatives is vital for their anticancer activities and can react with the ferrous atom and produce free radicals or ROS, inducing cancer cell apoptosis and oxidative DNA damage [89–91]. Qian *et al.* have found that dihydroartemisinin induces transferrin receptor-1 internalization, decreases iron uptake, and disturbs iron homeostasis in cancer cells, which are at least partially responsible for the anticancer activity of the compound [92]. Nakase *et al.* have prepared a series of artemisinin-transferrin conjugates, which exhibit stronger cytotoxicity against prostate cancer cells and induce more cell apoptosis than the

parent drug in a transferrin receptor-dependent manner [93]. Artemisinin and its derivatives have been reported to inhibit liver cancer cell growth and proliferation, arrest cell cycle at G_1 phase, and induce cell apoptosis *in vitro* by down-regulating MDM2 expression and modulating the expression of proteins associated with cell cycle progression and apoptosis, independent of p53 [94]. Artemisinin and dihydroartemisinin also inhibit xenograft tumor growth and sensitize liver cancer to the treatment of a chemotherapeutic agent, gemcitabine *in vivo* [94]. Similar results have been observed in ovarian cancer cells *in vitro* and *in vivo* [95]. This group has also demonstrated the potential embryotoxicity of dihydroartemisinin in the embryos of wild-type and TG (flk1: GFP) transgenic zebrafish [96].

Recently, there have been several reports of the potent antitumor activities of artemisinin-derived dimers. Jeyadevan and co-workers have synthesized a series of artemisinin dimers with a different linker group at C-10 [97]. Two phosphate ester dimers of artemisinin, compounds 14a (**9**) and 14b (**10**) possess more potent anticancer activity than dihydroar-temisinin and doxorubicin [97]. The same group has further designed and synthesized the second generation trioxane dimers of artemisinin [98]. The lead compounds phthalate dimer 5 (**11**) and bis-benzyl alcohol dimer 7 (**12**) selectively induce human cervical cancer cell death without significant cytotoxicity against normal cervical cells [98]. Saikia *et al.* have designed and synthesized nine artemisinin-derived triazole dimers and evaluated their anticancer activity in leukemia, colon, lung, and liver cancer cells. However, none of them exhibits more significant activities than artemisinin [99].

Interestingly, a recent study has reported the preparation of artemisinin-chemotherapeutic agent conjugates as well as the preclinical assessment of their efficacy and safety in human ovarian cancer models [100]. ARS4 (**13**), a dihydroar-temisinin-melphalan conjugate exhibits stronger anti-ovarian cancer activity than its parent drugs *in vitro* and *in vivo*, without inducing apparent host toxicity. Its anticancer activities have been attributed to ARS4-mediated MDM2 inhibition and its modulatory effects on various proteins that regulate cell cycle progression, apoptosis, and epithelial-mesenchymal transition (EMT), which are consistent with the mechanisms of action of its parent drugs dihydroartemisinin and melphalan [100]. However, further evaluation of these conjugates in more clinically-relevant cancer models is still needed.

Ainsliadimer A and ainsliatrimer A—The genus *Ainsliaea* has been reported to be a rich source of natural STs, especially guaianolides, which have shown diverse biological activities [101–102]. Several *Ainsliaea* species have been used in traditional Chinese medicine for the treatment of angina and rheumatoid arthritis, such as *Ainsliaea macrocephala* [101–102]. In a recent study for isolation and characterization of novel bioactive compounds from *A. macrocephala,* ainsliadimer A (**14**), a novel guaianolides-type DST with an unprecedented carbon skeleton has been discovered and shown remarkable inhibitory effects on the production of NO [102]. Li *et al.* have studied the biomimetic total synthesis of ainsliadimer A, which has finally been accomplished in 14 steps [103]. Dong *et al.* have further investigated its biological activities and have characterized this compound as a potent inhibitor of the NF-κB pathway [104]. They have found that ainsliadimer A selectively binds to IKKα/β via the conserved cysteine 46 residue and allosterically inhibits its activities,

resulting in the marked inhibition of NF-κB signaling pathway as well as the induction of cancer cell death *in vitro* and the repression of xenograft tumor growth *in vivo* [104].

Another study for identifying novel anticancer natural products from *Ainsliaea* plants has been performed; a novel trimeric guaianolides, named ainsliatrimer A (**15**) has been identified from *Ainsliaea fulvioides*, which has been used in Chinese folk medicine for the treatment of rheumatism, traumatic injuries, edema, stomachache, and anorexia [105]. Ainsliatrimer A and its analogs exhibit potent cytotoxicities against human leukemia (CEM) and colon cancer (LOVO) cell lines with IC_{50} values in a sub-micromolar range [105]. Li *et al*. have further accomplished the biomimetic synthesis of ainsliatrimer A and demonstrated that this compound induces cancer cell apoptosis [106]. To further identify the molecular target of ainsliatrimer A, Li *et al*. have synthesized a biotin-labeled ainsliatrimer A and revealed that peroxisome pro-liferator-activated receptor gamma (PPARγ) is a major cellular target for this compound [107]. Ainsliatrimer A directly binds to PPARγ and activates its transcriptional activity, leading to the expression of PPARγ target gene (*e.g.,* COX-2) and cancer cell death [107].

Others DSTs—As a continuation of work for identifying bioactive constituents from *Artemisia* plants, a guaianolide-type DST, artemilinin A (**16**), and a sesquiterpenoid-monoterpenoid dimer, isoartemisolide (also named DSF-52, **17**) are isolated from *Artemisia argyi* [108]. Neither compound shows significant cytotoxicity against cancer cell lines. Isoartemisolide exhibits potent inhibitory effects on the production of NO, pros-taglandin E2 (PGE2) and TNF-α in LPS-stimulated BV-2 microglial cells, which have been attributed to its targeting effects on NF-κB, JNK/p38 MAPKs, and Janus kinase 2 (Jak2)/Stat3 pathways I[108–109]. Another guaianolide-type DST, named DSF-27 (**18**) from the same medical plant has also shown inhibitory effects on LPS-induced microglial activation, protecting neurons from microglia-mediated neuro-inflammatory injury by inhibiting the spleen tyrosine kinase (Syk)/NF-κB and Jak2/Stat3 signaling pathways [110].

The medicinal plant *Eupatorium perfoliatum* L. has traditionally been used as an anti-fever, anti-malarial, and anti-inflammatory agent [111]. Mareike and coworkers have evaluated the anti-inflammatory effects of the crude extracts of *E. perfoliatum* L as well as the defined lead compounds from this plant, including a novel DST, diguaiaperfolin (**19**). This compound exhibits a strong inhibition of NO production and inducible nitric oxide synthase (iNOS) expression in LPS-stimulated RAW264.7 macrophages without significant cytotoxicity against RAW264.7 macrophages [111]. Another DST, shizukaol B (**20**) from *Chloranthus japonicas* has been reported to inhibit ICAM-1/lymphocyte function-associated antigen 1 (LFA-1)-mediated cell aggregation and monocyte adhesion to human umbilical vein endothelial cells (HUVEC) by inhibiting the expression of ICAM-1, VCAM-1, and E-selectin in human promyelocytic HL-60 cells, which suggests that the compound may be a potential anti-atherosclerotic drug [112]. Shizukaol B also possesses potent inhibitory effects on NO production in LPS-stimulated BV-2 cells and may be used as an anti-neuroinflammatory agent as well [113].

The dimeric sesquiterpene thioalkaloid, 6-hydroxythiobi-nupharidine (**21**) from the rhizome of *Nuphar pumilum* has been observed to inhibit anti-sheep erythrocyte plaque forming cell

formation without causing any apparent cytotoxicity against mouse spleen cells [114]. The same group has further reported that 6-hydroxythiobinupharidine possesses potent immunosuppressive activity [115]. 6-Hydroxythiobinupharidine and its analogs exhibit anti-melanoma activity by inhibiting melanoma cell growth, inducing apoptosis, and inhibiting cell invasion *in vitro* and suppressing the lung metastasis of B16 melanoma cell in mice *in vivo* [116–117]. This compound has also been found to exert its anticancer activity by inhibiting NF-κB pathways and inducing cleavage of PARP [118–119].

Microlenin (**22**), a novel guaianolide-type DST from *Helenium microcephalum*, has shown excellent anticancer activity in Ehrlich ascites carcinoma cell via inhibition of DNA and protein synthesis [120–122]. Another DST, meiogynin A (**23**) has been isolated from the bark of *Meiogyne cylindrocarpa* and identified as a novel inhibitor of Bcl-xL/Bcl-2 antagonist killer 1 (Bak) binding with a K_i value of 10.8 μmol·L^{-1} [123–124]. This compound also has inhibitory effects on myeloid cell leukemia-1 (Mcl-1)/BH3 interacting domain death agonist (Bid) binding with a K_i value of 5.2 μmol·L^{-1} [125]. The dual targeting effects by meiogynin A result in cancer cell death and apoptosis [123, 126–127]. Parviflorene F (**24**), an un-symmetrical DST from *Curcuma parviflora,* has been reported to cause cancer cell death and apoptosis via increasing the expression level of TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) [128–130]. Cryptoporic acid E (**25**) from the fungus *Cryptoporus volvatus* has been characterized as an inhibitor of superoxide anion radical release and shown potent inhibitory effects on okadaic acid-stimulated tumor promotion in mouse skin, N-Methyl-N-Nitrosourea-induced colon carcinogenesis in rats, and 1, 2-dimethylhydrazine-caused colon carcinogenesis in mice [131–132].

Despite a tremendous increase in the identification of novel DSTs from natural source, most of the studies just reported the characterization and initial screening for their anti-inflammatory and anticancer activities [41]. Further detailed investigation is required for determining their *in vivo* efficacy, toxicity, molecular targets, and mechanisms of action.

Structure–Activity Relationships of STs and DSTs for Their Anti-inflammatory and Anticancer Activities

It has been widely accepted that several chemical properties are critical for the anticancer and anti-inflammatory activities of STs and dimeric DSTs: (1) alkylating centers, (2) oligomerization of sesquiterpenoids, and (3) lipophilicity. All the chemical features (Fig. 3) will be discussed in the following sections.

Alkylating centers—The α, β-unsaturated moieties (Fig. 3A), *e.g.,* α-methylene-γ-lactone and α, β-unsubstituted cyclopentenone are typical alkylating centers in STs and DSTs and are critical for the biological activities of this class of compounds [37, 58, 63]. STs and DSTs bearing α, β-unsaturated moieties often exert more potent anticancer and anti-inflammatory activities than the compounds without these functional moieties [58, 63]. Mechanistically, the α, β-unsaturated moiety functions as a reactive Michael acceptor, which forms a covalent bond with biological nucleophiles, especially with the proteins harboring cysteine residues [37, 104]. The formation of stable drug-protein adducts may finally lead to the inactivation of the target proteins by inducing protein conformational changes, inhibiting

protein-protein interaction or protein-DNA interaction, blocking the biological functions, and/or promoting their degradation [72–73, 104]. In addition, the peroxide bridge (Fig. 3A) in artemisinin and its analogs and dimers may also be considered as a precursor of an alkylating center [40]. Heme or free iron-induced breaking of the peroxide bridge causes degradation of artemisinin, resulting in the formation of nucleophilic radical metabolites [40]. These metabolites then act as alkylating agents by binding to target proteins containing electrophilic moieties, leading to the inactivation of these target proteins [40]. Moreover, the number of alkylating centers in the STs and DSTs is an important factor for the activities of these compounds. DSTs often contain more than two alkylating centers, causing more potent anticancer and anti-inflammatory activities than their monomers [41–42].

Oligomerization of sesquiterpenoids—Polyvalency effect is a common biological event, which always gives rise to enhanced binding affinity of small ligands to target proteins and increased steric stability of lig- and-receptor complex [42]. We and other investigators have recently discovered that oligomerization, especially dimerization and trimerization of STs can have increased binding affinities that are greater than monomeric STs, leading to enhanced anticancer and anti-inflammatory activities [63, 72–73, 104]. This phenomenon may be attributed to the increased number of alkylating centers as well as the conformational flexibility due to the novel linkage modes between the monomers. Due to the dimerization and trimerization of STs, each dimer and trimer may bear two or three alkylating centers and become bifunctional and trifunctional alkylating agents, *e.g.,* phthalate artemisinin dimer 5 and microlenin (Fig. 3B), often resulting in more than a hundred-fold increase in the binding affinity to a protein target [70, 72, 104]. Furthermore, the linker between the ST monomers is crucial for the conformational flexibility of the oligomers, *e.g.,* JapA (Fig. 3B). More flexible oligomers are often observed to exert more potent activities against inflammation and cancer [41].

Lipophilicity and others—Lipophilicity is a critical factor which controls cell penetrating ability of small molecules [133]. Generally, the presence of lipophilic moieties (*e.g.,* ester group) in STs and DSTs results in enhanced penetration through cell membrane and increased biological activities, whereas the presence of hydrophilic groups (*e.g.,* hydroxyl group) show contrasting results [58, 63, 66]. However, in *in vivo* studies, high lipophilic STs and DSTs always have very low bioavailability, which finally causes moderate *in vivo* efficacy (Fig. 3C) [37, 39]. In addition, the biological activities of STs and DSTs are also affected by other factors, including the size and position of lipophilic groups and the number of hydrogen-bond donors and receptors [37, 39]. Many studies have shown that only the addition of the ‘size optimum’ functional groups increases the activity while the presence of oversized or undersized functional groups even reduces the penetrating ability, thereby decreasing their activities [37]. The addition of functional moieties to inappropriate positions may cause steric hindrance to alkylating centers, reducing its binding affinity to the protein target [63, 72–73, 104]. The introduction of hydrophilic groups, *e.g.,* hydroxyl groups to STs and DSTs may not only reduce their penetrating ability, but also increases the number of hydrogen-bond receptors (Fig. 3C). These moieties can form hydrogen-bonds with amino acid residues on target proteins and then enhance the drug-protein binding, leading to enhanced anticancer and anti-inflammatory activities [70, 72, 104].

Discussion and Future Directions

There is increasing evidence demonstrating the correlation between inflammation and cancer [134–135]. The critical mediators of chronic inflammation contribute to cancer initiation and progression, as well as resistance to chemotherapy [6]. Overexpression and activation of oncogenes and mutation and deletion of tumor suppressor genes have recently been observed to play a crucial role in cancer-related inflammation [17–21]. In light of the accumulating reports referring to the critical role of these molecules in inflammation and cancer, the spotlight in this field has been shifted to the identification of pharmacological inhibitors and activators for prevention and treatment of cancer-related and inflammation-related diseases. Natural products hold great promise for anti-inflammatory and anticancer drug discovery because of their excellent chemical properties and promising activities [33–36].

Intense research efforts during recent years have resulted in the discovery of several novel STs and DSTs with potent activities against inflammation and cancer and some of them are undergoing clinical evaluation. STs and DSTs are promising drug candidates for the treatment of inflammation and cancer owing to several favorable features: 1) diverse chemical structures; 2) potent *in vitro* and *in vivo* activity; and 3) high binding affinity to molecular targets. However, some drawbacks of this class of compounds limit their development as therapeutics in the clinic. First, most of these STs and DSTs are isolated from plants and/or other natural resources with low yield and content. Second, this class of compounds often has a hydrophobic characteristic, which may result in poor bioavailability and moderate *in vivo* efficacy. Third, some STs and DSTs have been reported to have low selectivity index and exert cytotoxicity against both normal and cancer cells, which may cause unexpected adverse effects.

To facilitate the transition of STs and DSTs from laboratory to the clinic, the pharmacokinetic properties, especially oral bioavailability should be extensively evaluated and optimized. As summarized in Table 1, most of the STs and DSTs in clinical trials have been optimized for improved water-solubility and bioavailability. Furthermore, the pharmacological and toxicological profiles of STs and DSTs need to be examined, which can help determine the appropriate dose schedules for robust activity but manageable toxicity in the future clinical studies. In addition, optimal drug delivery systems for STs and DSTs can also be utilized to improve the pharmacokinetic profiles and reduce the adverse effects. Because the major molecular targets of STs and DSTs, including NF-κB, MDM2, and STAT3 play important roles in chemoresistance, the drug combination studies of STs and DSTs with chemotherapeutic agents and other targeted therapeutics should be carried out in the future. It is known that acquired resistance to therapeutic agents is one of the major clinical challenges in drug development. The STs and DSTs, *e.g.,* JapA and InuA have shown multi-targeting pharmacological properties, which may be developed as effective agents to overwhelm such resistance.

In conclusion, we deem that STs and DSTs represent a novel class of natural products possessing many advantages over other compounds as anticancer and anti-inflammatory agents, However, to facilitate their transition from bench to clinic, further studies are still

needed to focus on pharmacological and toxicological profiles, molecular targets and mechanisms of action, biomimetic synthesis and SAR, optimal drug delivery system, and drug combination studies with other therapeutic agents.

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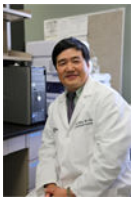
Biography



Ruiwen ZHANG, M.D., Ph.D., D.A.B.T., FAAAS

Professor ZHANG has a longstanding research interest in the field of translational biomedical research, particularly in translational medicine, cancer therapy and prevention, clinical pharmacology and therapeutics, pharmacogenomics, pharmaceutical and toxicological researches. Thanks to continuously funding from NIH and other governmental and private agencies, Dr. Zhang has maintained a strong research program, making significant contributions to several research fields, including pharmacogenomics of anticancer agents, oncogene and tumor suppressor, molecular targeted cancer therapy, dietary and chemical cancer prevention, drug discovery and development, preclinical and clinical pharmacology, toxicology, and cancer biomarkers. For his outstanding contributions to sciences, Dr. Zhang was elected as a Fellow of American Association for the Advancement of Science (AAAS) in 2009. He has published more than 220 papers, 2 books, and more than 50 invited reviews/book chapters; his publications have been cited more than 10500 times, with an H-index of 55 and an i10-index of 165. He has been invited to give more than 190 presentations in prestigious universities, institutions, and organizations. Dr. Zhang has been a certified toxicologist by the American Board of Toxicology (D.A.B.T.) since 1999 and served on Board of Directors of ABT between 2009 and 2013. He has been an FDA advisory committee member and served as a study section member for NIH, DoD, CDC, FDA, and NIOSH and other international panels. Dr. Zhang is Editor-in-Chief of *Current Cancer Drug Targets,* Associate Editor-in-Chief of *Chinese Journal of Natural Medicines,* and also an associate editor, senior editorial board member, or editorial board member of more than 20 scientific journals. He has been an honorary professor of seven universities.

Abbreviations

α-SMA	Alpha-smooth muscle actin
Bak	Bcl-2 antagonist killer 1
Bcl-2	B-cell lymphoma-2
Bcl-xl	B-cell lymphoma-extra large
Bid	BH3 interacting domain death agonist
CBP	CREB-binding protein
COX-2	Cyclooxygenase 2
DSTs	Dimeric sesquiterpenoids
EAE	Experimental autoimmune encephalomyelitis
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal–regulated kinase
FXR	Farnesoid X receptor
HIF1	Hypoxia-inducible factor 1
HUVEC	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule 1
IκBα	Inhibitor of kappa B alpha
IKK	IκB kinase
ILs	Interleukins
iNOS	Inducible nitric oxide synthase
InuA	Inulanolide A
Jak2	Janus kinase 2
JapA	Japonicone A
JNK	c-Jun N-terminal kinase
LFA-1	Lymphocyte function-associated antigen 1
LinA	Lineariifolianoid A
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
Mcl-1	Myeloid cell leukemia-1

MCP-1	Monocyte chemoattractant protein-1
MDM2	Murine double minute 2
mTOR	Mammalian target of rapamycin
NFAT	Nuclear factor of activated T-cells
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NOD-like	Nucleotide-binding oligomerization domain
receptors	like receptors
OVA	Ovalbumin
PGE2	Prostaglandin E2
PI3K	Phosphoinositide 3-kinase
PPARγ	Peroxisome proliferator-activated receptor gamma
RAFLS	Rheumatoid arthritis fibroblast-like synoviocytes
ROS	Reactive oxygen species
STAT	Signal transducer and activator of transcription
STs	Sesquiterpenoids
Syk	Spleen tyrosine kinase
TAK1	TGF-beta activated kinase 1
TGF-β1	Transforming growth factor beta 1
TNF-α	Tumor necrosis factor alpha
TNFR	Tumor necrosis factor receptor
TPA	Tetradecanoylphorbol acetate
TRAF2	TNF receptor-associated factor 2
TRAIL-R2	TNF-related apoptosis-inducing ligand receptor 2
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
XIAP	X-linked inhibitor of apoptosis protein

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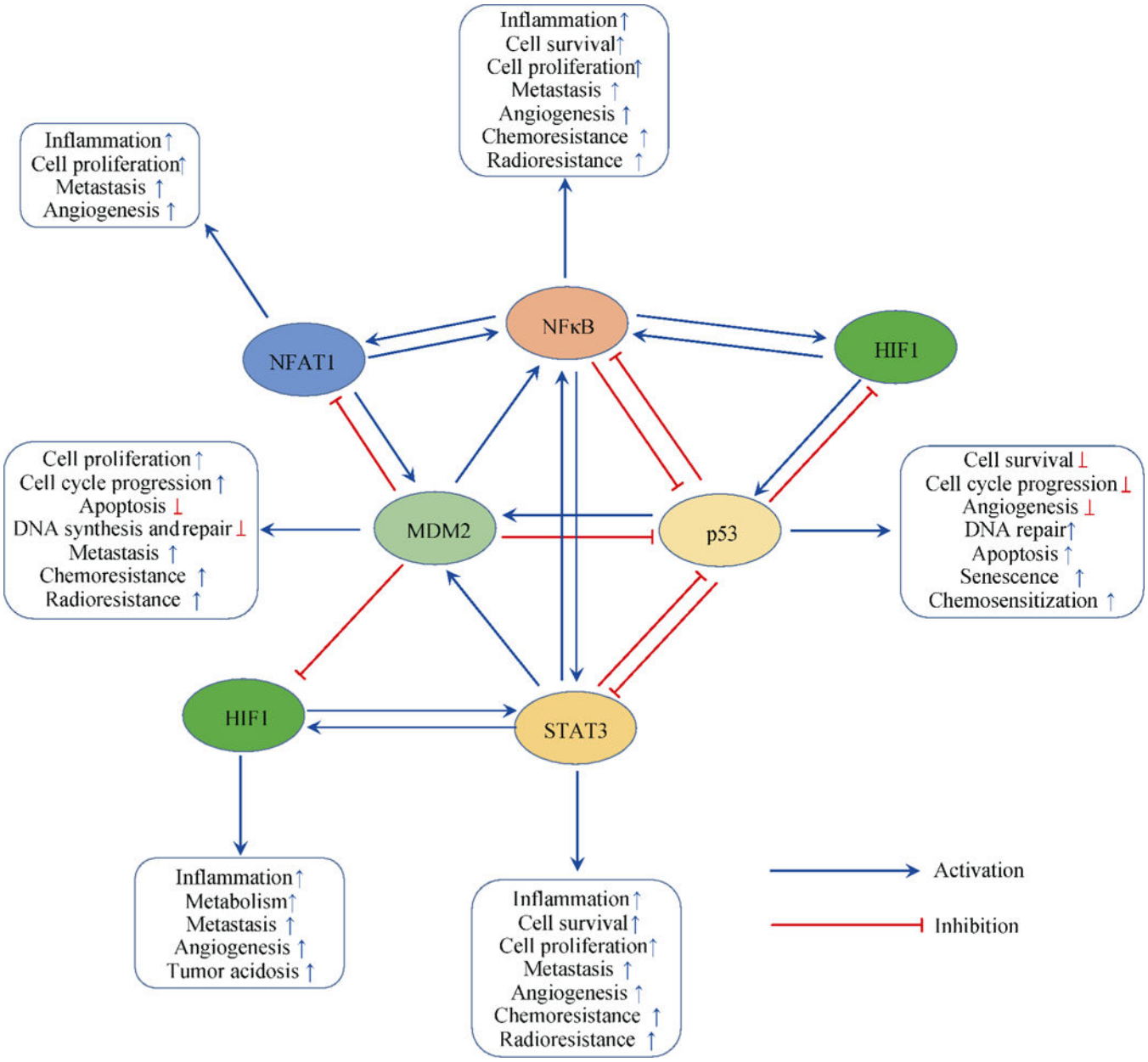


Fig. 1.

Key mediators of inflammation and cancer that are targeted by STs and DSTs

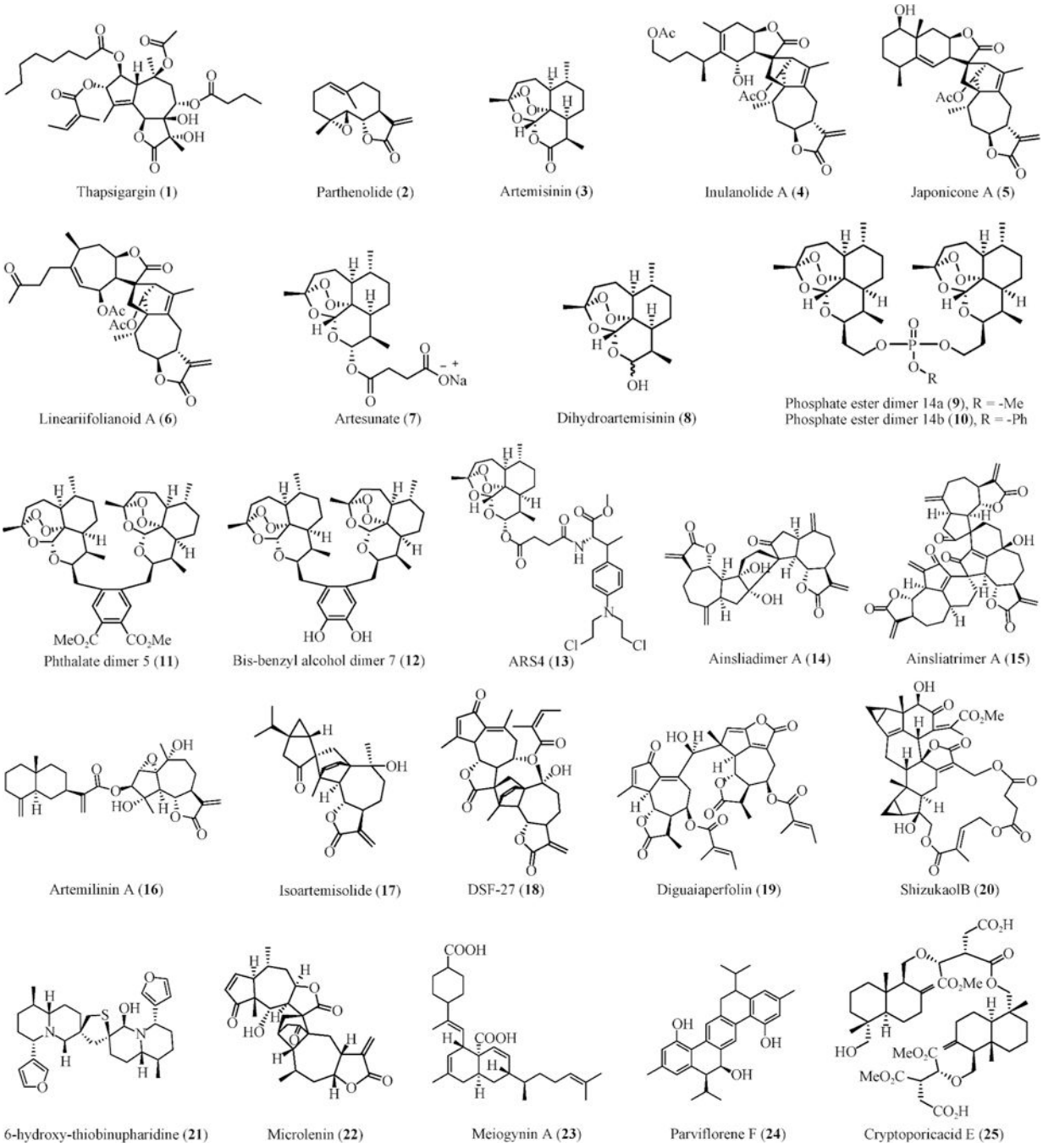


Fig. 2.

Chemical structures of STs and DSTs with potent anti-inflammatory and anticancer activities

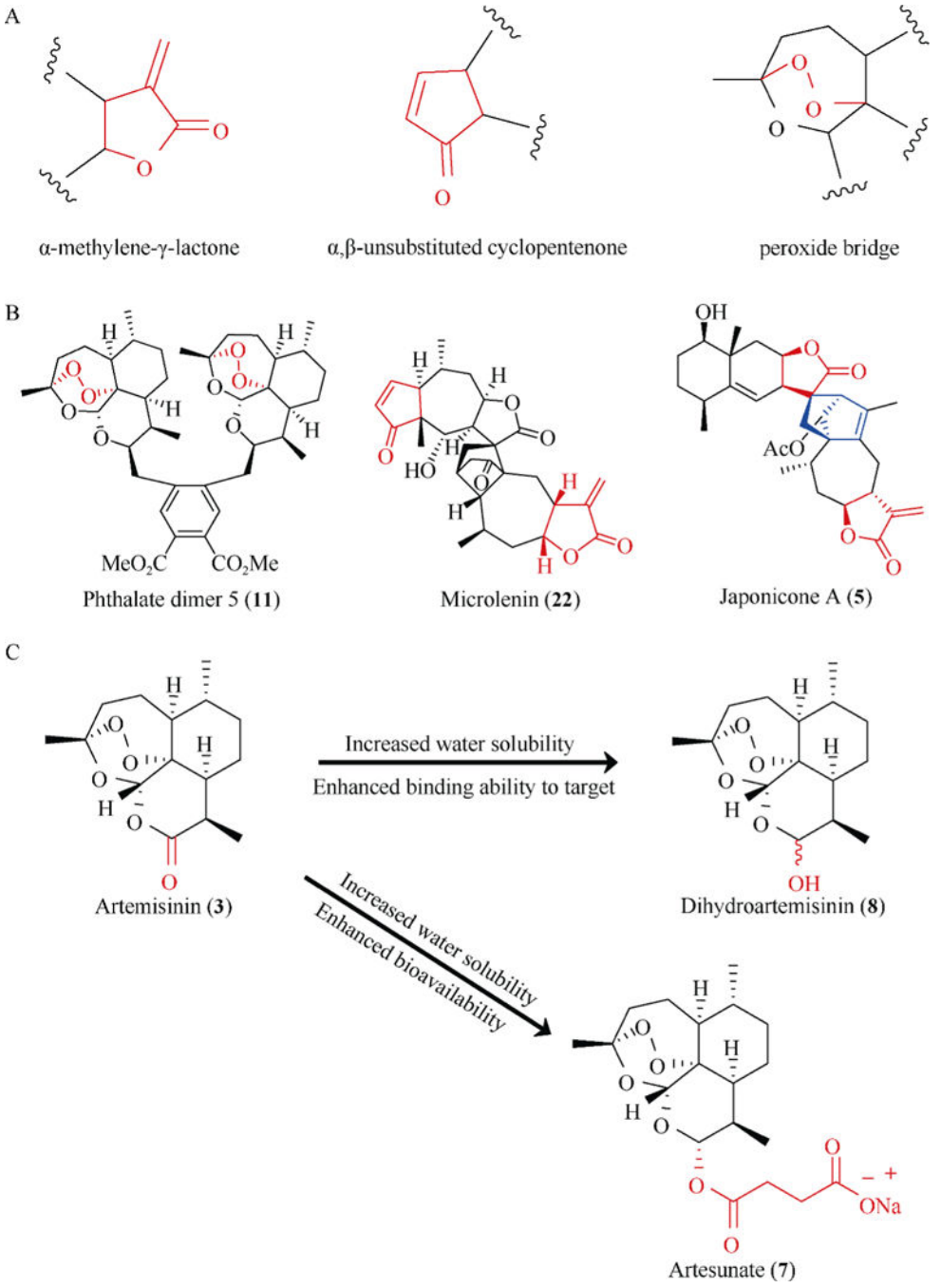


Fig. 3.

Chemical features of STs and DSTs related to anti-inflammatory and anticancer activities. (A) The common alkylating centers of STs and DSTs are highlighted in red. (B) DSTs often contain more alkylating centers (in red) and a novel linker between the monomers (in blue). (C) The introduction of hydroxyl group and other functional moieties may affect the target binding ability and bioavailability of STs and DSTs

Table 1

STs and DSTs in human clinical trials

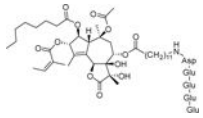
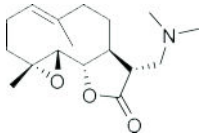
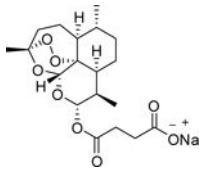
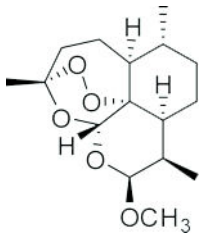
Compounds	Chemical Structures	Clinical trial phase	Disease	Sponsor	References
Mipsagargin (G-202)	 A soluble prodrug of thapsigargin	Phase 1	Advanced solid tumors	GenSpera, Inc.	[43]
		Phase 2	Chemotherapy-naive metastatic castrate-resistant prostate cancer	GenSpera, Inc.	[44]
DMAPT (or LC-1)	 A water-soluble analog of parthenolide	Phase 1	Acute myeloid leukemia	Leuchemix Inc.	[45]
Artesunate	 A semi-synthetic derivative of Artemisinin	Phase 1	Hepatocellular carcinoma	University Hospital, Ghent	[46]
		Phase 1	Solid tumors	Georgetown University	[47]
		Phase 1	Cervical intraepithelial neoplasia grade 2/3, high-risk HPV (any strain)	Sidney Kimmel Comprehensive Cancer Center	[48]
		Phase 2	Colorectal cancer, bowel cancer	St George's, University of London	[49]
		Phase 1	Metastatic breast cancer, locally advanced breast cancer	Heidelberg University	[50]
Artemether	 A semi-synthetic derivative of Artemisinin	Phase 1; Phase 2	Solid tumors	LondonPharma Ltd.	[51]

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Table 2

Summary of representative STs and DSTs with anti-inflammatory and anticancer activity and their mechanisms of action

Compounds	Source	Anti-inflammatory activity	Anticancer activity	Molecular mechanisms	References
Inulanolide A (4)	*I. britannica*, *I. japonica*	Inhibits the production of NO and TNF-α in LPS-stimulated RAW264.7 cells	Inhibits cell proliferation, arrests cells in G2-M phase, induces cell apoptosis, suppresses cell migration and invasion in breast cancer cells *in vitro*, independent of p53 Suppresses breast tumor growth and metastasis *in vivo*, independent of p53	Inhibits NF-κB activation Inhibits NFAT1-MDM2 pathway, independent of p53 Modulates the expression of proteins related to cell proliferation, cell cycle progression, apoptosis, and DNA damage	[64, 74]
Japonicone A (5)	*I. japonica*	Inhibits TNF-α-mediated cytotoxicity in L929 cells Inhibits TNF-α-induced endothelial cell activation Reduces TNF-α-induced hepatic injury in d-GalN sensitized mice	Inhibits cell proliferation, arrests cells in G2-M phase, and induces cell apoptosis in breast cancer cells *in vitro*, independent of p53 Suppresses breast tumor growth and metastasis *in vivo*, independent of p53	Binds to TNF-α and selectively inhibits the interaction between TNF-α and TNFR1 Inhibits TNF-α-TAK1-IKK-NF-κB signaling axis and TNF-α-induced NF-κB activation and nuclear translocation and downregulates NF-κB target genes Binds to MDM2 and induces MDM2 degradation Inhibits NFAT1 and NFATl-mediated MDM2 transcription	[65, 70–73]
Lineariifolianoid A (6)	*I. lineariifolia*	Has no significant effect on TNF-α-mediated L929 cytotoxicity	Inhibits cell proliferation, arrests cells in G2-M phase, induces cell apoptosis, suppresses cell migration and invasion in breast cancer cells *in vitro*, independent of p53	Inhibits NFAT1-MDM2 pathway, independent of p53 Modulates the expression of proteins related to cell proliferation, cell cycle progression, apoptosis, and DNA damage	[68, 75]
Artemisinin (3)	*A. annua*	Exerts anti-inflammatory activity in TPA-induced skin inflammation in mice	Inhibits cancer cell growth and proliferation, arrests cell cycle at G1 phase, and induces cell apoptosis *in vitro* Suppresses xenograft tumor growth and sensitizes cancer cells to chemotherapy *in vivo*	Inhibits TNF-α-induced phosphorylation and degradation of IκBα, nuclear translocation of NF-κB p65, and expression of NF-κB target genes Reacts with the ferrous atom and produces free radicals or ROS Inhibits MDM2 expression, independent of p53 Modulates the expression of proteins associated with cell cycle progression and apoptosis, independent of p53	[78, 89, 92–94]
Artesunate (7)	synthetic derivative	Exerts anti-arthritis activity in K/BxN mouse model of rheumatoid arthritis and rat model of Freund's complete adjuvant-induced arthritis	Induces cancer cell apoptosis	Inhibits nuclear translocation NF-κB and its transcriptional activity Inhibits PI3K/Akt activation Reacts with the ferrous atom and produces free radicals or ROS	[79–82, 89, 90]
Dihydroartemisi-nin (8)	synthetic derivative	Inhibits onset of EAE and ameliorates this disease in EAE-inflicted mice Inhibits OVA-induced chronic airway inflammation in mice Protects rats against bleomycine-induced pulmonary	Inhibits cancer cell growth and proliferation, arrests cell cycle at G1 phase, and induces cell apoptosis *in vitro* Suppresses xenograft tumor growth and sensitizes cancer cells to chemotherapy *in vivo*	Inhibits mTOR pathway Inhibits phosphorylation of ERK, p38 MAPK and IκBα, and activation of NF-κB Inhibits mRNA and protein expression of TGF-β1, TNF-α, α-SMA, and NF-κB Activates FXR Reacts with the ferrous atom and produces free radicals or ROS Induces transferrin	[83-86, 89,91, 92, 95, 96]

Compounds	Source	Anti-inflammatory activity	Anticancer activity	Molecular mechanisms	References
		fibrosis and alcoholic liver injury		receptor-1 internalization, decreases iron uptake, and disturbs iron homeostasis Inhibits MDM2 expression, independent of p53 Modulates the expression of proteins associated with cell cycle progression and apoptosis	
Phosphate ester dimer 14a (9)	synthetic derivative	Not reported	Inhibits cancer cell growth and induces apoptosis	Not reported	[97]
Phosphate ester dimer 14b (10)	synthetic derivative	Not reported	Inhibits cancer cell growth and induces apoptosis	Not reported	[97]
Phthalate dimer 5 (11)	synthetic derivative	Not reported	Inhibits cervical cancer cell growth without apparent cytotoxicity against normal cervical cells	Not reported	[98]
Bis-benzyl alcohol dimer 7 (12)	synthetic derivative	Not reported	Inhibits cervical cancer cell growth without apparent cytotoxicity against normal cervical cells	Not reported	[98]
ARS4 (13)	synthetic derivative	Not reported	Inhibits cancer cell growth and proliferation, arrests cells in S phase, induces cell apoptosis, and prevents cell migration in ovarian cancer cells *in vitro* Suppresses xenograft tumor growth and metastasis *in vivo*	Inhibits MDM2 expression, independent of p53 Modulates the expression of proteins related to cell cycle progression, apoptosis, and EMT	[100]
Ainsliadimer A (14)	*A. macrocephala*	Inhibits NO production in LPS-stimulated RAW264.7 cells	Inhibits cancer cell growth *in vitro* Represses xenograft tumor growth *in vivo*	Binds to IKKα/β and allosterically inhibits its activities, resulting in inhibition of NF-κB signaling pathway	[102, 104]
Ainsliatrimer A (15)	*A. fulvioides*	Not reported	Inhibits cancer cell growth and induces apoptosis *in vitro*	Binds to PPARγ and activates its transcriptional activity	[105–107]
Artemilinin A (16)	*A. argyi*	Not reported	Weak cytotoxicity	Not reported	[108]
Isoartemisolide (DSF-52, 17)	*A. argyi*	Inhibits the production of NO, PGE_2 and TNF-α in LPS-stimulated BV-2 microglial cells	Weak cytotoxicity	Inhibits NF-κB, JNK/p38 MAPKs, and Jak2/Stat3 pathways	[108, 109]
DSF-27 (18)	*A. argyi*	Inhibits LPS-induced microglial activation and protects neurons from microglia-mediated neuro-inflammatory injury	Not reported	Inhibits the Syk/NF-κB and Jak2/Stat3 signaling pathways	[110]
Diguaiaperfolin (19)	*E. perfoliatum*	Inhibits NO production and iNOS expression in LPS-stimulated RAW264.7 macrophages	Not reported	Not reported	[111]
Shizukaol B (20)	*C. japonicas*	Inhibits ICAM-1/LFA-1-mediated cell aggregation and	Not reported	Inhibits the expression of ICAM-1, VCAM-1 and E-selectin	[112, 113]

Compounds	Source	Anti-inflammatory activity	Anticancer activity	Molecular mechanisms	References
		monocyte adhesion to HUVEC in human promyelocytic HL-60 cells Inhibits the NO production in LPS-stimulated BV-2 cells			
6-hydroxy-thiobi nupharidine (21)	*N. pumilum*	Inhibits anti-sheep erythrocyte plaque forming cell formation Possesses potent immunosuppressive activity	Inhibits cancer cell growth, induces apoptosis, and inhibits cell invasion *in vitro* Suppresses lung metastasis of B16 melanoma cell in mice *in vivo*	Inhibits NF-κB pathways and induces cleavage of PARP	[114–119]
Microlenin (22)	*H. microcephalum*	Not reported	Induces Ehrlich ascites carcinoma cell death	Inhibits DNA and protein synthesis	[120–122]
Meiogynin A(23)	*M. cylindrocarpa*	Not reported	Induces cancer cell death and apoptosis	Inhibits Bcl-xL/Bak binding and Mcl-1/Bid binding	[123–127]
Parviflorene F (24)	*C. parviflora*	Not reported	Induces cancer cell death and apoptosis	Increases the expression levels of TRAIL-R2	[128–130]
Cryptoporic acid E (25)	*C. volvatus*	Not reported	Prevents okadaic acid-stimulated tumor promotion in mouse skin Prevents N-Methyl-N-Nitrosourea-induced colon carcinogenesis in rats Prevents 1,2-dimethylhydrazine-caused colon carcinogenesis in mice	Inhibits superoxide anion radical release	[131, 132]