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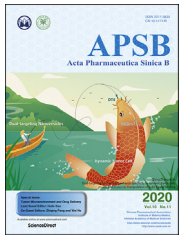

REVIEW

Natural products remodel cancer-associated fibroblasts in desmoplastic tumors

Rujing Chen[a], **Leaf Huang**[b,*], **Kaili Hu**[a,*]

[a]*Murad Research Center for Modernized Chinese Medicine, Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*
[b]*Division of Pharmacoengineering and Molecular Pharmaceutics, Center for Nanotechnology in Drug Delivery, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

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Abstract Desmoplastic tumors have an abundance of stromal cells and the extracellular matrix which usually result in therapeutic resistance. Current treatment prescriptions for desmoplastic tumors are usually not sufficient to eliminate the malignancy. Recently, through modulating cancer-associated fibroblasts (CAFs) which are the most abundant cell type among all stromal cells, natural products have improved chemotherapies and the delivery of nanomedicines to the tumor cells, showing promising ability to improve treatment effects on desmoplastic tumors. In this review, we discussed the latest advances in inhibiting desmoplastic tumors by modeling CAFs using natural products, highlighting the potential therapeutic abilities of natural products in targeting CAFs for cancer treatment.

*Corresponding authors.
E-mail addresses: leafh@email.unc.edu (Leaf Huang), kaili-hu@163.com (Kaili Hu).

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1. Introduction

The tumor microenvironment consists of stromal cells (*e.g.*, endothelial cells, immunological cells, stromal macrophages, pericytes and fibroblasts) and the acellular compartments including extracellular matrix (ECM) and cytokines, supporting and promoting tumor progression (Fig. 1)[1]. Desmoplastic tumors, such as breast cancer[2], pancreatic ductal adenocarcinoma (PDAC)[3], prostate cancer (PC)[4] and cholangiocarcinoma[5], that are aggressive with very poor prognosis, are usually characterized with high levels of stromal cell density and ECM concentrations. Among all the stromal cells, cancer-associated fibroblasts (CAFs) are the most abundant cell type. The rapidly proliferating cancer cells, CAFs and ECM fibers (such as collagen and hyaluronan) in desmoplastic tumors with the surrounding normal tissue[6] form a highly complex and heterogeneous tumor microenvironment, causing intratumoral solid stresses gathering, vessel constricting and hypoperfusion[7]. The highly complex and heterogonous pathophysiology limits the effective delivery of drugs to tumors[8].

There are both quiescent and activated fibroblasts in the tumors. Activated fibroblasts related to cancer have been termed CAFs or tumor-associated fibroblasts[9]. The α-smooth muscle actin (α-SMA) has been regarded as the most reliable marker of activated fibroblasts[10]. The CAFs can be developed from several cell types, including resident tissue fibroblasts, epitheliums *via* epithelial-to-mesenchymal transition (EMT), endothelial cells *via* endothelial-to-mesenchymal transition, bone marrow-derived cells (BMDCs), adipose cells and stellate cells[10]. Through expressing a series of proteins such as α-SMA, tenascin and collagen, the CAFs enhance the complexity and heterogeneity of pathophysiology in tumor microenvironment, causing physiological abnormalities[11]. In desmoplastic tumor microenvironment, solid stress, winding and leaky blood vessel networks, collapsed and nonfunctional lymphatic vessels and highly dense ECM accumulation are the major physiological abnormalities[12], compromising the main important process for efficient molecular transports: vascular transport, transvascular transport, interstitial transport, and cellular uptake (Fig. 1)[13]. Due to these transport barriers, most anticancer drugs cannot reach the effective dose in the cancer site as they have poor distribution and penetration into desmoplastic tumors. Therefore, chemotherapy and nanotherapy many times fail to treat desmoplastic tumors even if they are potent enough to kill cancer cells *in vitro*.

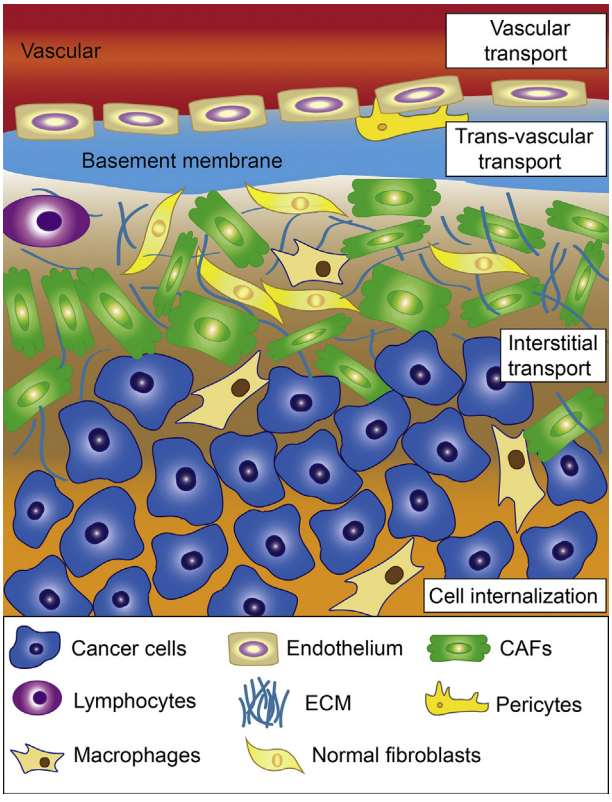

Figure 1 Desmoplastic tumor microenvironment. Desmoplastic tumor microenvironment is characterized with the whole noncancer components around tumor cells, including fibroblasts, macrophages, lymphocytes, extracellular matrix and intertwined blood vessels composed of endothelial cells and pericytes.

Besides, CAFs are the dominant component of the tumor stroma, where they produce a wide range of mediators including transforming growth factor-β (TGF-β)[14], interleukin 6 (IL-6), matrix metalloproteinases (MMPs)[15] vascular endothelial growth factor (VEGF)[16] hepatocyte growth factor (HGF)[17], stromal cell-derived factor 1 (SDF-1)[18], hypoxia-inducible factor-1 (HIF-1)[19] and tissue inhibitors of metalloproteinases (TIMPs)[20], etc. These secreted mediators are receptor ligands overexpressed by other cell types in the tumor microenvironment, which cause intercellular crosstalk, resulting in cancer progression and metastasis. What's more, desmoplasia results in high activity of CAFs and the accumulation of stromal components around tumors. CAFs further talk with different stromal components in the desmoplastic tumor microenvironment. By activating various pathways such as TGF-β[14], CAFs can affect the angiogenesis and the ECM of the desmoplastic tumor stroma, as well as affect the invasion, proliferation and migration of cancer cells. By remodeling the ECM, CAFs may be involved in the generation and maintenance of the desmoplastic tumor stem cell niche[21]. By affecting WNT signaling, they can also induce cancer cell drug resistance[22]. Therefore, CAFs play an important role in the initiation, development and metastasis of desmoplastic tumors.

Recently, the study of Ligorio et al.[23] also found that CAFs influenced tumor architecture by changing the intrinsic patterns of tumor glands in human PDAC, which further demonstrated the importance of tumor-stroma interaction in desmoplastic tumor treatment. More and more scientists realized the importance of CAFs in the treatment of desmoplastic tumors, and attempted to target them to improve desmoplastic tumor therapy[24], such as directly depleting CAFs and normalizing CAFs. Ji et al.[25] designed an MMP-2 responsive peptide-hybrid liposome to down-regulate ECM levels through regulating the CAFs, and enhance penetration of GEM, which greatly enhanced the therapeutic efficacy on pancreatic cancer. Recently, Zhang et al.[24] also modulated CAFs to promote the accumulation of docetaxel in tumor with dexamethasone, which gave insights in overcoming the physiological abnormalities in desmoplastic tumor and provided a rational strategy to increase antitumor efficacy. Therefore, CAFs have emerged as the key target of drug delivery in anti-desmoplastic tumor therapies.

In recent years, natural products have been widely studied and showed promising ability to improve treatment on desmoplastic tumors. They have been reported to regulate tumor stroma especially CAFs through multiple mechanisms (Fig. 2), thus normalizing the microenvironment of desmoplastic tumors to improve

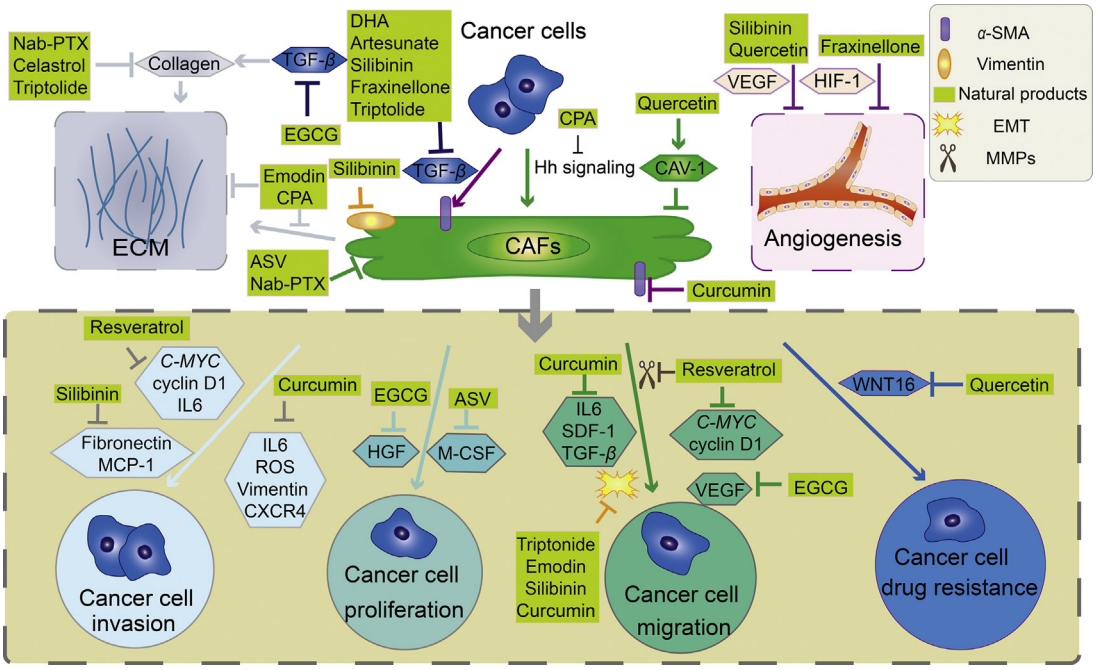

Figure 2 Schematic diagram illustrates the CAF-remodeling effects of natural products in the desmoplastic tumor microenvironment. There are three general aspects that natural products target or modulate CAFs in the desmoplastic tumor microenvironment. First, natural products inhibit the expression of mediators which could initiate cell crosstalk between CAFs and tumor cells and result in cancer invasion, proliferation and migration. Second, natural products induce the ECM remodeling process and indirectly inhibit cancer cell invasion. Third, natural products can inhibit angiogenesis which is promoted by CAFs. CAV-1, caveolin 1; CXCR4, CXC chemokine receptor 4; M-CSF, macrophage colony-stimulating factor; MCP-1, monocyte chemotactic protein-1; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor 1.

the delivery of chemotherapeutics and nanomedicines[26]. Besides, natural products can inhibit the interaction between tumor-associated stroma and cancer cells, thus inhibiting cancer cell proliferation, invasion, migration and drug-resistance. The delivery of chemotherapeutics could be improved and the efficacy of chemical drugs could be enhanced through remodeling CAFs by natural products. In this review, we summarize recent studies on natural products which can inhibit desmoplastic tumor progression by remodeling CAFs.

2. Natural products affect the CAF–cancer cell crosstalk

CAFs produce a wide range of mediators, which are receptor ligands overexpressed by other cell types in the tumor microenvironment, initiating cell crosstalk, resulting in cancer invasion, proliferation and migration. Natural products can modulate the signal transduction involved in the interaction of CAFs with cancer cells, thereby inhibiting the invasion, proliferation and migration of desmoplastic tumors.

2.1. *Curcumin*

Curcumin, commonly known as turmeric, is a natural yellow polyphenolic compound derived from the rhizomes of the plant *Curcuma longa Linnaeus* and is considered as an effective drug to cure various diseases, including allergy, asthma, anorexia, bronchial hyperactivity, cough and sinusitis[27]. Curcumin has a variety of biological functions, such as anti-oxidant, anti-bacterial, anti-inflammatory, anti-microbial, and anti-cancer effects[28].

Curcumin is capable of abrogating the invasion-promoting capacity of CAFs by increasing E-cadherin levels and decreasing vimentin levels. Moreover, through inhibiting monoamine oxidase A/mammalian target of rapamycin/HIF-1α signaling pathway, curcumin inhibits the production of reactive oxygen species and the expression of CXC chemokine receptor 4 (CXCR4) and IL-6 receptor in PC cells, which supports the therapeutic effects of curcumin in PC[29].

Curcumin is able to inhibit CAF-induced migration of desmoplastic tumors through reducing the mesenchymal characteristic of CAFs[30] or up-regulating tumor suppressor proteins (P16, P21, and P53). Curcumin can up-regulate tumor suppressor proteins in CAFs while inactivate the JAK2/STAT3 pathway, leading to the decrease of α-SMA. Moreover, curcumin also inhibits the migration of tumor cells which is induced by CAFs *via* reducing the secretion of SDF-1, IL-6, MMP-2, MMP-9, and TGF-β[31]. In addition, curcumin can repress CAF-induced migration and invasion of desmoplastic tumors through increasing the level of the P16 coding *CDKN2A* mRNA and miR-146b-5p which is an important tumor suppressor miRNA, leading to IL-6 production[32].

Since curcumin can improve the sensitivity of tumor cells to chemotherapeutic drugs and radiotherapy through regulating CAFs, scientists studied the inhibitory abilities of curcumin and 5-fluorouracil (5-FU) on the survival of cancer stem cell (CSC) in a 3D co-culture model (Table 1)[33]. Through NF-κB pathways, curcumin can sensitize CSCs to 5-FU treatment *via* blocking the CAF-induced invasion of CSCs, emphasizing that curcumin is a promising modulator to coordinate the crosstalk in the tumor microenvironment[33].

Table 1 Natural products that potentially target CAFs and their mechanisms.

Remodeling effect	Drug	Cancer model	Cell line	Animal model	Mechanism	Combination with	Ref.
The CAF-cancer cell crosstalk	Curcumin	PC	PC3; Human prostate CAFs	–	E-cadherin elevation; Vimentin inhibition	–	29
		Breast cancer	MDA-MB-231; MCF-10; human breast CAFs	MDA-MB-231 xenograft model;	Tumor suppressor proteins elevation; JAK2/STAT3 pathway inhibition; tumor suppressor miRNA elevation	–	31
		Colon tumor	HCT116; MRC-5	–	NF-κB pathways inhibition	5-FU	33
The CAF-cancer cell crosstalk	Silibinin	PC	PC3; DU-145; LNCaP; 22Rv1	PC3 xenograft model	TGF-β pathways inhibition; E-cadherin elevation; MCP-1inhition; fibronectin inhibition	–	34–36
Angiogenesis			LNCaP; 22Rv1	22Rv1 xenograft model	HIF-1 signaling pathways inhibition	–	37
Angiogenesis	Fraxinellone	Human non-small cell lung cancer	A549; HeLa; Hep3B; HUVEC; HLF-a; HCT110	A549 xenograft model	HIF-1 and STAT3 signaling pathways inhibition	–	38
The CAF-cancer cell crosstalk		Melanoma	BPD6	BPD6 transplantable tumor model	TGF-β pathways inhibition	Peptide vaccine	39
		Pancreatic tumor	Panc-1; NIH3T3	Orthotropic Panc-1 xenograft model		siRNA	40
The CAF-cancer cell crosstalk	Triptolide	Pancreatic tumor	KPC001; Panc-02	Patient-derived xenograft model; KPC transgenic mouse model	TGF-β pathways inhibition	Doxorubicin	41,42
The CAF-cancer cell crosstalk	Triptonide	Gastric cancer	BGC-823; human GCAFs	–	Regulate microRNA expression	–	43
The CAF-cancer cell crosstalk	ASV	Gastric cancer	BGC-823; Human GCAFs	–	Regulate microRNA expression	–	44
The CAF-cancer cell crosstalk	Resveratrol	Cholangiocarcinoma	KKU-213; KKU-100; MMNK-1; Cholangiocarcinoma CAFs	–	Inhibiting IL-6 expression	–	45
		Breast cancer	MCF-7; MDA-MB-231; human breast CAFs	–	Inhibiting the mRNA t ranscription	–	46
		PDAC	Capan1; AsPC1; PanO2; MP1070	Orthotropic xenograft model	–	5-FU	47
The CAF-cancer cell crosstalk	EGCG	PC	–	–	Inhibiting HGF and VEGF production	–	48
ECM			WPMY-1; HPS-19I	–	TGF-β pathways inhibition	Luteolin	49
The CAF-cancer cell crosstalk	Emodin	Breast cancer	BT20; human breast CAFs	–	EMT programming inhibition	–	50
The CAF-cancer cell crosstalk	Artesunate and dihydroartemisin	Breast cancer	4T1; L-929	Orthotropic xenograft model	TGF-β pathways inhibition	–	51
ECM and The CAF-cancer cell crosstalk	CPA	Non-small cell lung cancer	A549; NCI-H520; CCL-206; primary human lung squamous CAFs	–	Hh pathway inhibition	–	52
		Cholangiocarcinoma	SNU-1196; SNU-246; SNU-308; SNU-1079; HuCCT-1; Lx-2	HuCCT-1 xenograft model; co-implant xenograft with HuCCT-1 and Lx-2		–	53

(*continued on next page*)

Table 1 (*continued*)

Remodeling effect	Drug	Cancer model	Cell line	Animal model	Mechanism	Combination with	Ref.
		Pancreatic tumor	Capan-2; Human umbilical vein endothelial cell line	Capan-2 xenograft model		–	54
		PDAC	Miapaca-2; L3.6pl; PANC-1; human pancreatic stellate cell line	–		Cs-137 radiation	55
			MiaPaca-2-luc; human pancreatic stellate cell line	Orthotopic MiaPaca-2- luc pancreatic tumor xenografts; Patient-derived orthotopic model; KPC-Luc transgenic mouse model		PTX	56
ECM	Celastrol	Melanoma	BPD6; D4M; NIH-3T3	BPD6 transplantable tumor model	Reducing the production of collagen	Mitoxantrone	57
ECM and the CAF-cancer cell crosstalk	Quercetin	Bladder cancer	NIH3T3; UMUC3	Co-implant xenograft with NIH3T3 and UMUC3	WNT16 expression inhibition	Cisplatin	58
The CAF-cancer cell crosstalk		Breast cancer	MCF7; MDA-MB 231; human skin fibroblasts	–	CAV-1 expression elevation	–	59

–Not applicable.

2.2. *Silibinin*

Silibinin is the main bio-active component of silymarin which is isolated from the seeds of *Silybum marianum* (L.) Gaertn (Family Asteraceae). It is widely used as a hepatoprotective agent and has been marketed as a dietary supplement[60]. Silibinin has shown broad-spectrum anticancer activities, and is currently being studied clinically[61]. It has been reported that silibinin disrupts important signaling pathways which are necessary for PC cell proliferation, invasion, migration and metastasis, induces PC cell apoptosis and inhibits angiogenesis and EMT process[62].

It was also reported that silibinin could inhibit PC cells' ability to activate CAFs, which highlighted the potential use of silibinin in PC prevention. Silibinin could suppress the TGF-β2-induced CAF-like phenotype of naïve fibroblasts. Ting et al.[34] found that control conditioned medium (CCM) from human PC cells could induce a CAF-like phenotype in human prostate stromal cells, leading to increased α-SMA and vimentin expression. And silibinin could strongly inhibit the TGF-β2-dependent increase in α-SMA and CAF-like phenotype (Table 1)[34].

Silibinin is also able to inhibit CAF-induced invasion of desmoplastic tumors through enhancing E-cadherin expression. Ting et al.[35] explored the function of CAFs to promote PC invasion, and the targeting efficacy of silibinin on this response. They treated CAFs with silibinin or vehicle, and collected the conditioned media from CAFs, labeling as silibinin-treatment conditioned media (SBCM) or CCM, respectively. Their results illustrated that SBCM could significantly increase E-cadherin expression and inhibit invasiveness of PCA cells compared with CCM. Further studies found that silibinin was able to suppress CAF-induced invasion of tumors through reducing the expression of monocyte chemotactic protein-1 (MCP-1) which was a key component of CCM. Silibinin strongly reduced the expression of MCP-1 by inhibiting the DNA-binding activity of MCP-1 transcriptional regulators—AP-1 and NF-κB. Besides, silibinin can inhibit the CAF-induced desmoplastic tumor invasiveness and proliferation by inhibiting the CAFs' ability to secret fibronectin[36].

2.3. *Fraxinellone*

As a member of limonoids, fraxinellone is a natural product isolated from the root bark of the Rutaceae plant, *Dictamnus dasycarpus*, exhibiting neuroprotective, anti-inflammatory, anti-fibrosis and anti-cancer activities[38]. It has been reported that fraxinellone could suppress proliferation and angiogenesis of cancer cells *in vivo* through inhibiting programmed cell death-ligand 1 expression *via* reducing HIF-1 and STAT3 signaling pathways[38]. Besides, fraxinellone can cure liver fibrosis through decreasing the expression of CUG-binding protein 1 (CUGBP1) and then regulating TGF-β and interferon γ signaling[63].

Fraxinellone is reported to inhibit tumor cells' ability to activate CAFs through regulating the TGF-β signaling pathway. Hou et al.[39] designed a nanoemulsion (NE) formulation to deliver fraxinellone to CAFs in desmoplastic melanoma. To improve the anti-melanoma effect, they combined fraxinellone NEs with a tumor-specific peptide vaccine. They found that fraxinellone NEs could down-regulate the protein expression of α-SMA and CUGBP1 in the NIH-3T3 cell line (which was activated with TGF-β to mimic CAFs *in vitro*), and after treated with fraxinellone NEs in melanoma-bearing mice, the mRNA expressions of TGF-β were reduced, accompanying with a decreased expression of α-SMA and CUGBP1. Moreover, combining the tumor-specific

peptide vaccine with fraxinellone NEs could improve the tumor-specific T-cell infiltration, activate death receptors on the tumor cell surface, and induce the death of apoptotic tumor cells (Table 1)[39]. Pei et al.[40] designed a fraxinellone-loaded CGKRK peptide-modified nanoparticle (Frax-NP-CGKRK) to regulate the stromal TME of pancreatic cancer, and found that Frax-NP-CGKRK could also reverse the CAFs to the quiescent state by suppressing TGF-β signaling pathway, decrease the collagen accumulation and increase tumor blood perfusion (Fig. 3). Furthermore, they applied Frax-NP-CGKRK to enhance the intratumor drug penetration of siRNA-loaded lipid-coated calcium phosphate (LCP) biomimetic high-density lipoprotein nanoparticles (siKras-LCP-ApoE3), which could damage pancreatic cancer cells, and evaluated the antitumor activity of the combination therapy. They found that Frax-NP-CGKRK can make ways for the delivery of siKras-LCP-ApoE3, and this combination therapy remarkably suppressed the tumor growth and prolonged the survival time of animals bearing pancreatic cancer.

2.4. *Triptolide and triptonide*

Triptolide (TPL) is a diterpenoid epoxy compound extracted from the *Tripterygium wilfordii* Hook F, which has dual effects of anti-inflammatory and anti-tumor[64]. TPL is used to treat bleomycin-induced pulmonary fibrosis[65], liver fibrosis[66] and renal fibrosis[67] in mice. Besides the effect on fibrosis, TPL has also been tested in researches as an anticancer compound since the 1990's. It has been reported to have great efficacy on moderating pancreatic tumor[68]. However, the poor solubility of TPL in aqueous medium restricts its use in clinical and preclinical studies. Therefore, a water-soluble prodrug of TPL, minnelide, has been evaluated in a phase I clinical trial against gastrointestinal cancer. Besides weakening the primary tumor burden, minnelide also decreases metastasis in pancreatic, liver and ovarian cancers.

Recent publications demonstrated that both of minnelide and TPL are able to inhibit tumor epithelial cells' ability to activate CAFs, and normalize CAFs through inhibiting the TGF-β signaling pathway[41]. Besides, minnelide can deplete the stroma by preventing the hyaluronan synthesis and collagen stabilization in pancreatic tumor. Treatment with minnelide reduces the viability of CAFs isolated from the pancreatic tumor[42], leading to suppression of tumor invasion.

Triptonide is also a major active compound of *Tripterygium wilfordii* Hook F[64], which can also inhibit the pathological functions of CAFs, resulting in the inhibition of cancer cell migration. Wang et al.[43] found that triptonide treatment strongly suppressed the colony formation, migration and invasion-promoting abilities of gastric CAFs (GCAFs) by down-regulating miRNA-301a expression and up-regulating miRNA-149 expression in GCAFs. Furthermore, treatment with triptonide could inhibit EMT in gastric cancer cells induced by GCAFs (Table 1)[43]. Their research results showed that triptonide inhibited the cancer-promoting ability of GCAFs. Therefore, triptonide is a promising therapeutic agent to affect the CAF-cancer cell crosstalk and to treat gastric cancer.

2.5. *Astragaloside IV*

Astragaloside IV (ASV) is the main active component of Astragali Radix which is a crucial Chinese herb prescribed to strengthen the body of patients and eliminate toxins from their bodies[69]. ASV has multiple pharmacologic effects for its potent immunoregulatory, anti-asthma, anti-inflammatory and anti-fibrotic activities[70]. It has been demonstrated that ASV protects against the progression of liver fibrosis[71], renal fibrosis[72], myocardial fibrosis[73], as well as systemic sclerosis[74], all without evident toxicity or side effects. And the antifibrotic effect of ASV is mediated by the MAPK pathway and TGF-β/Smad signaling pathway[75]. Che et al.[76] examined the effect of ASV on the procedures associated with renal fibrosis in cultured TGF-β1-activated mouse renal fibroblasts. Their results illustrated that ASV inhibited TGF-β1-induced fibroblast proliferation, transdifferentiation, and ECM production in a dose-dependent manner. Moreover, the inhibition effect of ASV on fibroblast differentiation and ECM formation was achieved by regulating the activity of MAPK and NF-κB signaling pathways.

Besides the prominent antifibrotic effects, ASV is able to inhibit the proliferation- migration- and invasion-promoting abilities of GCAFs. Wang et al.[44] treated GCAFs with ASV, and then observed the effect of ASV on the malignancy-promoting capacity of GCAFs to explore the mechanism. They found that ASV could significantly inhibit the proliferation, migration and invasion-promoting effects of GCAFs through enhancing miRNA-214 and reducing miRNA-301a expression. By reestablishing the miRNA expression balance, ASV could effectively suppress macrophage colony-stimulating factor expression in CAFs which is an important role in promoting tumor proliferation, and elevate the tissue inhibitor of metalloproteinase 2 expression in CAFs which is a tumor suppressive factor. Thus, ASV can suppress the pathological functions of GCAFs, thereby inhibiting the gastric cancer cell progression, suggesting that ASV is a potent therapeutic agent for cancer by regulating CAFs.

2.6. *Resveratrol*

As a member of stilbenoids, resveratrol (*trans*-3,5,4′-trihydroxystilbene) was first isolated from the roots of white hellebore (*Veratrum grandiflorum O.* Loes) in 1940. It is also a component of grapes and a main constituent in red wine, the consumption of which has been closely related to the lower incidence of cardiac infarction in France than in other comparable countries[77]. Resveratrol is a phytoalexin which has broad-spectrum effects including anti-infective, anti-oxidant, and cardioprotective functions[78].

Since Jang et al.[79] published the first article about the anti-cancer potential of resveratrol in 1997, a great interest from cancer scientists has focused on this molecule from then on. Resveratrol is able to inhibit the NF-κB signaling pathway effectively and has been found to inhibit the growth of a wide variety of transplanted tumors in rodents including neuroblastoma, hepatoma, breast carcinoma, gastric carcinoma, colon carcinoma, and leukemia[80]. Additionally, studies demonstrate that resveratrol modulates the interaction between desmoplastic tumor cells and the CAFs in desmoplastic tumor microenvironment, thereby inhibiting cancer cell migration and invasion.

Resveratrol is able to inhibit CAF-induced invasion of desmoplastic tumors by inhibiting the expression of IL-6. Thongchot et al.[45] found that resveratrol blocked the pro-invasive communication between CAFs and cholangiocarcinoma cells through abrogating the secretion of IL-6 by CAFs. In their study, the CCM could strongly induce IL-6-mediated motility of cholangiocarcinoma cells, while the medium of CAFs pretreated with resveratrol could completely inhibit the movement of cancer cells and strongly induce autophagy of cholangiocarcinoma cells.

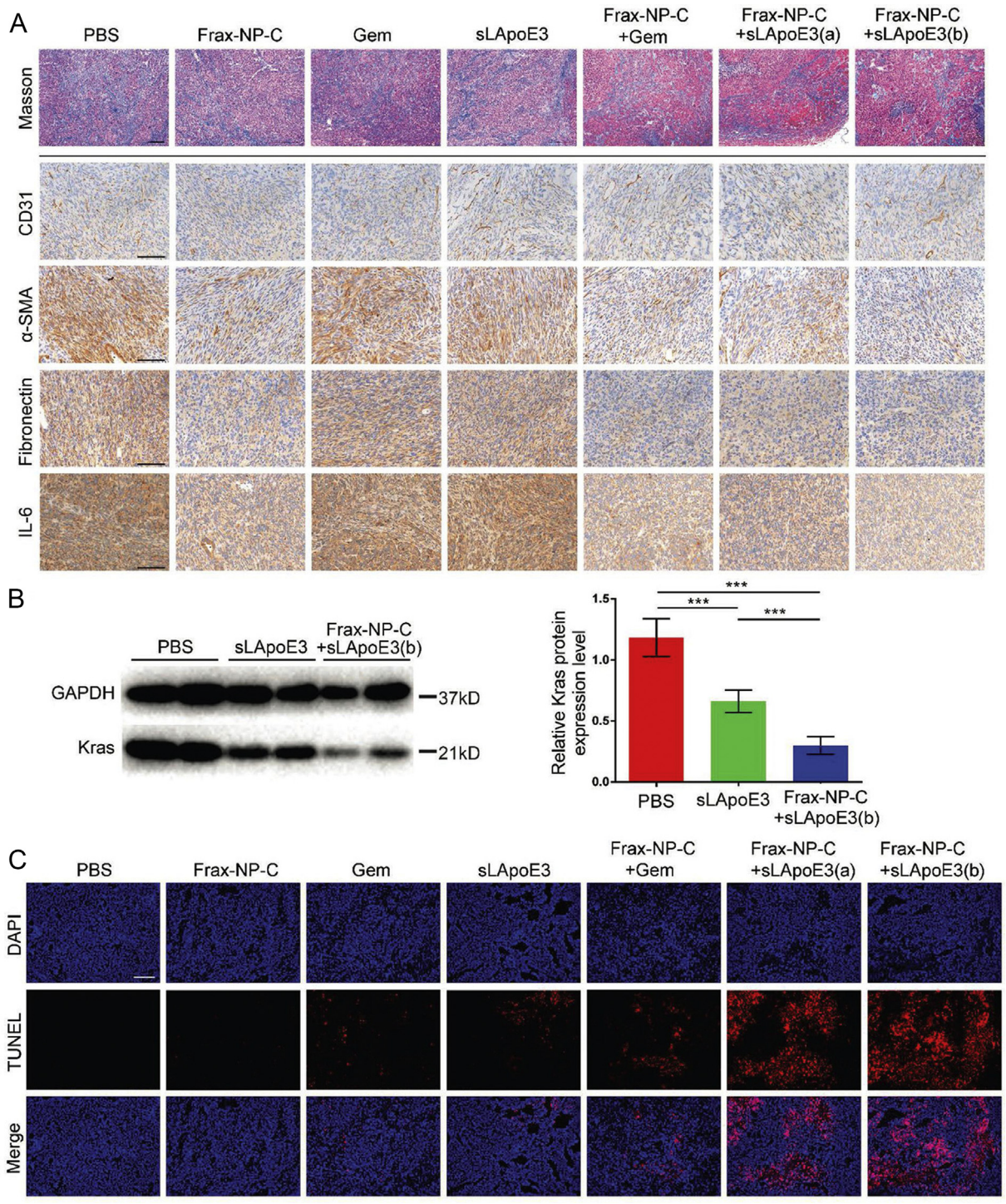

Figure 3 Combination therapy modulated the tumor microenvironment, silenced the KRAS mutation and induced apoptosis at the orthotropic pancreatic tumor sites. (A) Masson staining figures and immunohistochemistry images of indicators CD31, α-SMA, fibronectin, and IL-6 in all experimental groups. Scale bars, 200 μm. (B) KRAS protein expression levels in tumor tissues of siKras-LCPApoE3 and Frax-NP-C + sLApoE3 (b) groups. Data represent mea ±SD ($n = 6$). The significance of the differences (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$) was evaluated by two-tailed Student's *t*-test. (C) TUNEL analyses of *in vivo* apoptosis in pancreatic orthotropic tumor cells (red) on the day after the last administration. Nuclei (blue) were stained with Hoechst 33,258. Scale bar, 200 μm. (Used with permission from Ref. 40. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.)

What is more, resveratrol is also able to inhibit CAF-induced invasion and migration of tumor cells through influencing the mRNA transcription of various mediators. In MDA-MB-231 cells, Suh et al.[46] found that through suppressing CCM induced transcription of *C-MYC,* cyclin D1, MMP-2 and MMP-9 mRNA (Table 1)[46], resveratrol could decrease the expression of cyclin D1

and *C-MYC*, as well as regulate MMP-2 and MMP-9, so as to inhibit the migration and invasion of breast cancer cells induced by CCM.

Since resveratrol has a superior effect on remodeling the malignancy-promoting functions of CAFs, resveratrol is regarded as a promising chemo-protector which can be combined with chemotherapeutic agents for cancer treatment. Endostatin, as an angiogenesis inhibitor, can target proliferating endothelial cells. Cytosine deaminase (CD) linked to uracil phosphoribosyltransferase, converts the prodrug 5-fluocytosine (5-FC) to the chemotherapeutic drug 5-FU and has a greater effect to kill cancer cells than CD alone. 5-FC and the anti-angiogenic protein consisting of endostatin and CD (EndoCD) can both inhibit angiogenesis and chemo-therapeutically target tumors, and the targeting induce a bystander-killing effect on endothelial cells and tumor cells surrounding the vessels[81]. Chen et al.[47] investigated the efficacy of the EndoCD/5-FC/resveratrol combination on stroma in stroma-enriched PDAC models. They found that the EndoCD/5-FC/resveratrol combination reduced the amount of collagen, the number of CAFs, the density of tumor vessels, and the number of leukocytes, indicating that EndoCD/5-FC/resveratrol not only killed tumor cells, but also induced apoptosis of stroma cells, including CAFs, endothelial cells and immune cells. By using a noninvasive high-frequency ultrasound imaging technique, they found that resveratrol also increased the protein stability of EndoCD through suppressing chymotrypsin-like proteinase activity so that enhanced EndoCD-mediated 5-FC-induced cell killing. As a result, EndoCD/5-FC/resveratrol regimen suppressed the formation of pancreatic stroma in PDAC, leading to reduced tumor growth and extended survival. Their findings intimated that EndoCD/5-FC/resveratrol may be an ideal treatment strategy for PDAC and should be tested in clinical trials.

2.7. *Epigallocatechin-3-gallate*

Green tea polyphenols, showing potential in cancer therapy, have been attracting the attention of scientists for a long time[82]. Epigallocatechin-3-gallate (EGCG) isolated from green tea leaves, is reported with anti-oxidant, anti-fibrotic, anti-cancer and anti-inflammatory activities. As a prominent antioxidant agent, EGCG is able to be used as an electron trap to scavenge free radicals, suppress the formation of ROS and reduce oxidative stress[83]. The highly potent antioxidant capability makes EGCG to be a good candidate for reducing both oxidative stress and fibrogenesis in patients with scleroderma (SSc)[84], decreasing the production of ECM (collagen type I, fibronectin) and the markers of fibrosis (connective tissue growth factor) in scleroderma fibroblasts. Furthermore, it has been reported that the reduction of both oxidant stress and the fibrotic effects on SSc induced by EGCG is associated with the intracellular ROS, ERK1/2 kinase signalling and NF-κB activity[85].

In addition to the prominent antifibrotic effects, EGCG can inhibit the proliferation and invasion of tumors through reducing the HGF in CAFs, and suppress the metastasis of tumors through reducing VEGF as well[48], which indicated a potential role for EGCG in the treatment of desmoplastic tumors. Furthermore, it was reported that EGCG combined with luteolin could inhibit the TGF-β-induced CAFs. Gray et al.[49] found that both of EGCG and luteolin inhibited fibronectin expression which was induced by TGF-β, and decreased RhoA activation which was found to be necessary for fibronectin expression induced by TGF-β. Besides, they found EGCG and luteolin could inhibit TGF-β-induced ECM contraction, thereby suppressing tumor cell invasion. Their study results imply that combining EGCG with luteolin in clinic can prevent cancer progression by targeting CAFs, besides the tumor cell itself.

2.8. *Emodin*

Emodin (1,3,8-trihydroxy-6-methylanthraquinone), an predominant active component extracted from the rhizomes of rhubarb, aloes and other plants, has diverse biological activities, including laxative, immunosuppressive, anti-fibrosis, anti-inflammatory and anti-cancer effects. The anti-fibrosis effect of emodin is found in pulmonary[86], pancreatic[87] and liver fibrosis[88]. Emodin is able to downregulate the activity of myeloperoxidase which is a marker for neutrophil influx into tissue, inhibit the expression of TGF-β1 and collagen I, as well as suppress the cell proliferation in lung fibroblasts to weaken pulmonary fibrosis induced by bleomycin[86]. Guan et al.[89] demonstrated that emodin was capacity of blocking pro-fibrotic signalings which were activated by TGF-β1 in pulmonary fibroblasts, therefore inhibiting myofibroblast differentiation and ECM deposition. Their results also provide *in vivo* evidence for emodin to significantly inhibit bleomycin-induced lung inflammation and fibrosis.

Emodin has also been reported to possess the anti-cancer activity, such as inducing apoptosis in human lung adenocarcinoma cells[90]. Studies have demonstrated that emodin inhibits migration and invasion of human breast cancer cells through downregulating MMP-2 and MMP-9[91]. In addition, emodin represses cell migration and invasion by regulating EMT-related genes in head and neck squamous cell carcinoma[92], colorectal cancer[93] and ovarian cancer[94]. What is more, emodin is also able to inhibit the migration-promoting capacity of CAFs in tumors through blocking the EMT programming. Hsu et al.[50] tested the effects of emodin on EMT programming induced by CCM or the medium of interface zone fibroblasts (INFs-CM) in triple negative breast cancer. They analyzed the mesenchymal-marker expression, such as vimentin, β-catenin and MMP-2, and found that the increase of these mesenchymal markers stimulated by CCM or INFs-CM was reversed by emodin. The results showed that emodin inhibited INFs-CM or CCM-induced EMT programming in BT20 breast cancer cells, illustrating that emodin is a promising candidate for triple negative breast cancer prevention.

2.9. *Derivatives of artemisinin*

Artemisinin is a chemical isolated from the leaves of *Artemisia annua* Linn., a member of the Artemisia family which has a history of more than 2000 years in traditional Chinese medicine[95]. Belonging to the family of sesquiterpene trioxane lactone, artemisinin has been used as a leading antimalarial drug since the end of 1990s. Besides, artemisinin possesses the highest efficacy among all the antimalarial drugs at present[96]. Currently, a series of artemisinin derivatives, such as artemether (ARM), artesunate (ARS) and dihydroartemisinin (DHA), have been synthesized and shown improved bioactivity or solubility. Besides their antimalarial effects, it has been reported that artemisinin and its derivatives are efficacious in the treatment of infection and inflammatory diseases[97]. Over the past two decades, studies have showed the anti-cancer effect of artemisinin and its derivatives, disclosing that artemisinin and its derivatives might also be effective therapeutic drugs to treat cancer[51].

Researches have been also performed to study the ability of artemisinin and its derivatives to inactivate CAFs. ARS and DHA are found to be able to suppress the activation of CAFs through inhibiting the TGF-β pathway, and moreover, suppress the breast cancer growth and metastasis induced by CAFs *in vivo*. Yao et al.[98] explored the effects of artemisinin derivatives to inactivate breast cancer CAFs. They found that both ARS and DHA were capable of inhibiting TGF-β signaling, reverting CAFs from activated state to inactivated state, and suppressing the growth and metastasis of breast cancer induced by CAFs in the orthotopic model. Their study illustrated that artemisinin derivatives could be potential therapeutic drugs for breast cancer treatment.

3. Natural products normalize ECM

Besides the effects on the CAF–cancer cell crosstalk, natural products can also directly affect the ECM. By mechanical remodeling the ECM, CAFs contribute to invasion of desmoplastic tumor[21]. Natural products can effectively degrade the ECM and improve tumor perfusion[99] while maintaining the tumor-restraining function of ECM with minimal toxicity.

3.1. Cyclopamine

Cyclopamine (CPA) is an isosteroid alkaloid isolated from natural plants including *Veratrum californicum,* cornlily*, V. grandiflorum* and *Fritillaria pallidiflora* Schrenk. CPA is an inhibitor of smoothened, a G protein-coupled receptor presenting on CAFs that activates hedgehog (Hh) signaling[100]. Thus, CPA is a potential treatment for patients with Hh-overexpressing tumors, such as cholangiocarcinoma, uveal melanoma, osteosarcoma, pancreatic, breast, and colon cancers. The paracrine Hh signaling between cancer cells and CAFs is a key regulator in promoting CAF growth and maintenance in desmoplastic cancers. Blocking the Hh pathway not only suppresses the proliferation of tumor cells but also disrupts tumor ECM and facilitates the delivery of other chemotherapy drugs to the tumor nest[101]. In non-small cell lung cancer, the increase of Hh expression by cancer cells improved CAF survival and proliferation, while CPA decreased it[52]. Kim et al.[53] focused on the interaction of cholangiocarcinoma cells with stromal cells to investigate the role of Hh signaling on the growth of cholangiocarcinoma cells. In animal experiments, they found that CPA scarcely suppresses cholangiocarcinoma cell proliferation at the concentration of lower than 10 μmol/L, while, in contrast, CPA could inhibit the growth of Lx-2 cells (stromal cells) at the same concentration. And they found CPA attenuated tumor growth in the co-implant xenograft group, but not in the single implant xenograft group (Table 1)[53]. Their results indicated that stromal cells render cholangiocarcinoma cells susceptible to necrosis by CPA. As a result, CPA is a promising candidate to pharmacologically inhibit the interaction between tumor-associated stroma and cancer cells, thus inhibiting cancer cell proliferation, invasion, migration and drug resistance.

Because CPA is insoluble in water and has high systemic toxicity, it cannot be administrated directly to humans. To reduce toxicity of CPA and to enhance blood circulation, bioavailability and effects on tumor-microenvironment modulation of CPA, researchers developed various methods to deliver CPA to the tumor site. Jiang et al.[54] developed CPA-loaded membrane-camouflaged PLGA nanoparticles to effectively deliver CPA to the pancreatic tumor site, disrupt tumor ECM, increase functional vessels, and improve tumor perfusion. To enhance the response of PDAC to ionizing radiation (IR), Zhao et al.[55] combined CPA-loaded core-crosslinked polymeric micelles (M-CPA) with Cs-137 radiation to enhance the radiation cytotoxicity of Cs-137. In their results, M-CPA treatment can decrease the number of CAFs, intimating that M-CPA may disrupt the tumor-associated stroma *in vivo*, thus relieving the hypoxia condition within the tumor microenvironment. Later, in order to further enhance the effects on PDAC, Zhao et al.[56] co-delivered CPA, and paclitaxel (PTX) with a polymeric micelle formulation (M-CPA/PTX) to simultaneously regulate PDAC stroma and suppress tumor growth. The M-CPA could effectively modulate tumor stroma by increasing blood perfusion, improving tissue hypoxia, reducing matrix stiffness while sustaining the ECM tumor-compression function. The results that M-CPA/PTX apparently extended rodent survival suggested that it was a promising strategy for PDAC therapy to use multifunctional nanoparticles to target stromal and tumor cells concurrently.

3.2. Celastrol

Celastrol, also known as a tripterine, is a member of triterpenoids purified from traditional Chinese medicine named *Trypterygium wilfordii* Hook F. and has been used to treat autoimmune and neurodegenerative diseases, such as lupus erythematosus[102]. Celastrol possesses the activities of immunosuppressive, anti-inflammatory, antioxidant and anti-fibrosis. It has been reported that celastrol could attenuate liver fibrosis through inhibiting inflammation by activating AMPK-SIRT3 signaling[103], and alleviate renal fibrosis through upregulating the expression of cannabinoid receptor 2 which is an anti-fibrotic factor through inhibiting the activation of *Smad3* signaling pathway[104].

Besides, celastrol has attracted great attention for its potent anticancer effects in breast cancer[105], PC[106], and osteosarcoma[107], etc. It has been reported that celastrol can promote tumor cells apoptosis through regulating mitochondria signal pathways[108]. Recently, scientists found that celastrol could increase the sensitivity of CAFs to mitoxantrone. Liu et al.[57] combined celastrol with mitoxantrone to treat desmoplastic melanoma, and found that celastrol could decrease the IC_{50} of mitoxantrone in CAF cell lines. Besides, co-delivery of mitoxantrone and celastrol in aminoethylanisamide-polymerdisulfide bond nanoparticles could reduce the amount of collagen in the tumor microenvironment and increase drug delivery to the tumor cells (Fig. 4).

3.3. Quercetin

Quercetin (3,3′,4′,5,7-penta-hydroxyflavone) is a natural flavonoid commonly found in fruits and vegetables. It is also the most abundant dietary flavonoid, which is widely used to prevent and treat cardiovascular diseases and cancers[109]. Quercetin regulates multiple biological signaling pathways, inducing apoptosis of cancer cells as well as inhibiting proliferation of cancer cells[110]. Quercetin has also been proved to have anticancer effects on different cell lines in numerous *in vitro* studies[111]. The anticancer effects of quercetin are primarily attributed to its anti-oxidant activity[112].

Quercetin is able to down-regulate the CAF-induced cancer drug resistance of desmoplastic tumors through suppressing the WNT16 expression, which is a key factor that can contribute to chemotherapy resistance in malignant tumors. However, quercetin is difficult to dissolve in water and its bioavailability is low, which limit its application as a pharmaceutical. Therefore,

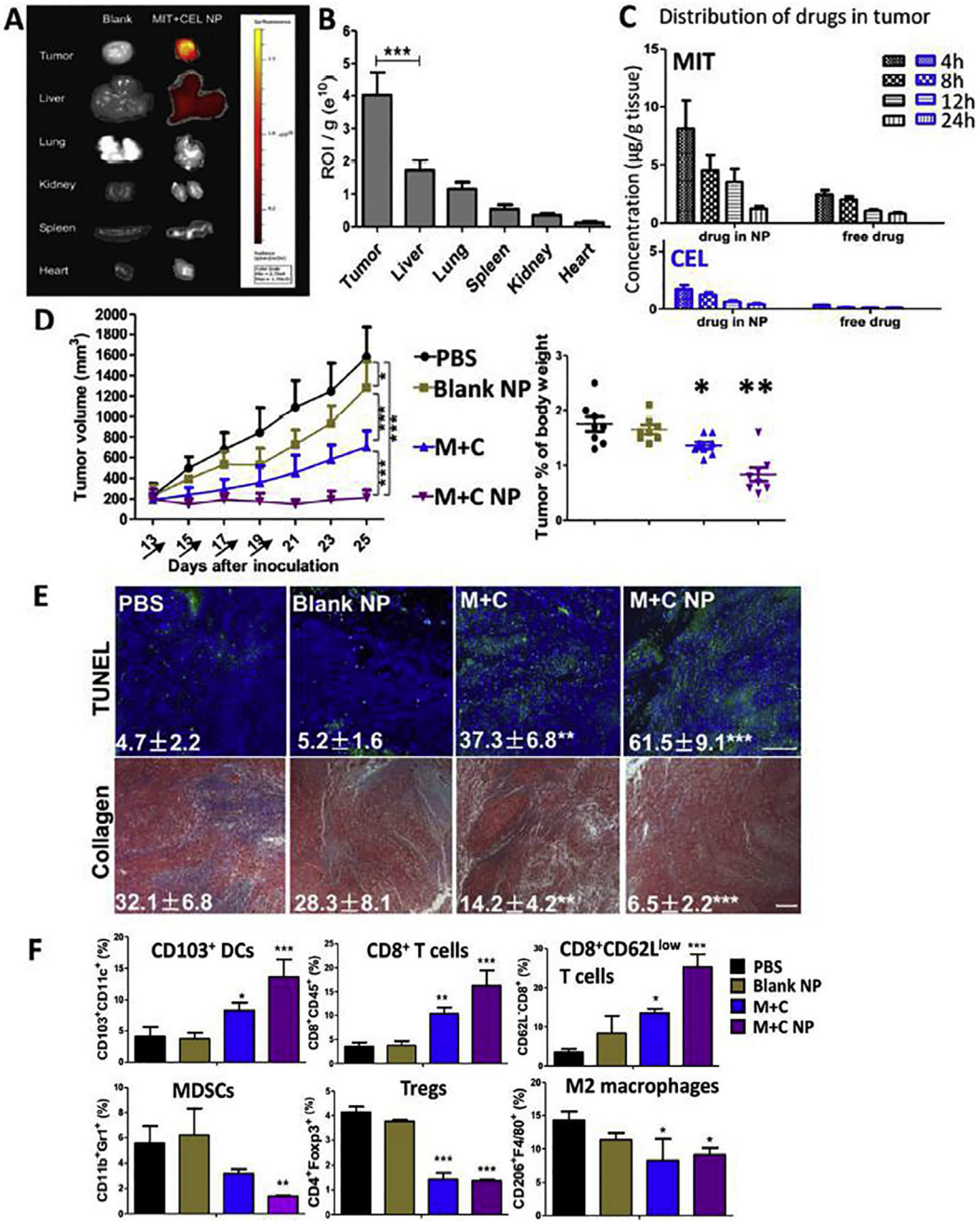

Figure 4 Effective therapy significantly improved anti-tumor response and remodeled suppressive tumor microenvironment. (A) NP distribution in tumor-bearing mice. Mice were i.v. injected with Cy5-loaded (3 μg/kg) NPs and measured by IVIS imaging 24 h post-injection, $n = 3$; (B) Region-of-interest intensities of fluorescence signals among tumor and organs, $n = 3$; (C) Pharmaco-distribution of mitoxantrone and celastrol within tumor were measured by LC–MS, $n = 5$; (D) Tumor inhibition study and tumor weight comparison. Arrows indicate days of drug injection. Dosage: for M + C group: ~2 mg/kg of celastrol per dose; for M + C NP group: ~160 μg/kg of celastrol per dose. Tumors were surgically removed from the hosts at endpoint of study, weighted and compared between groups, $n = 10–12$; (E) Cell apoptosis were measured by TUNEL staining and collagen morphology changes were measured by Masson's trichrome staining, scale bar indicates 300 μm, $n = 3$. (F) Flow cytometry analysis of immune functioning cells within tumor microenvironment, $n = 3$. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Used with permission from Ref. 57. Copyright © 2018 American Chemical Society).

Hu et al.[58] developed a quercetin prodrug by phosphorylating quercetin hydroxyl groups. In order to promote drug delivery, they prepared a targeted lipid/calcium/phosphate nanoparticle preparation composed of the quercetin phosphate. They found that quercetin could significantly remodel the CAFs and collagen content within the bladder cancer through a significant down-regulation of WNT16 expression. They also investigated the combination efficacy of the quercetin phosphate nanoparticles with cisplatin nanoparticles in a UMUC3 bladder cancer xenograft model, and found the antitumor efficacy of cisplatin

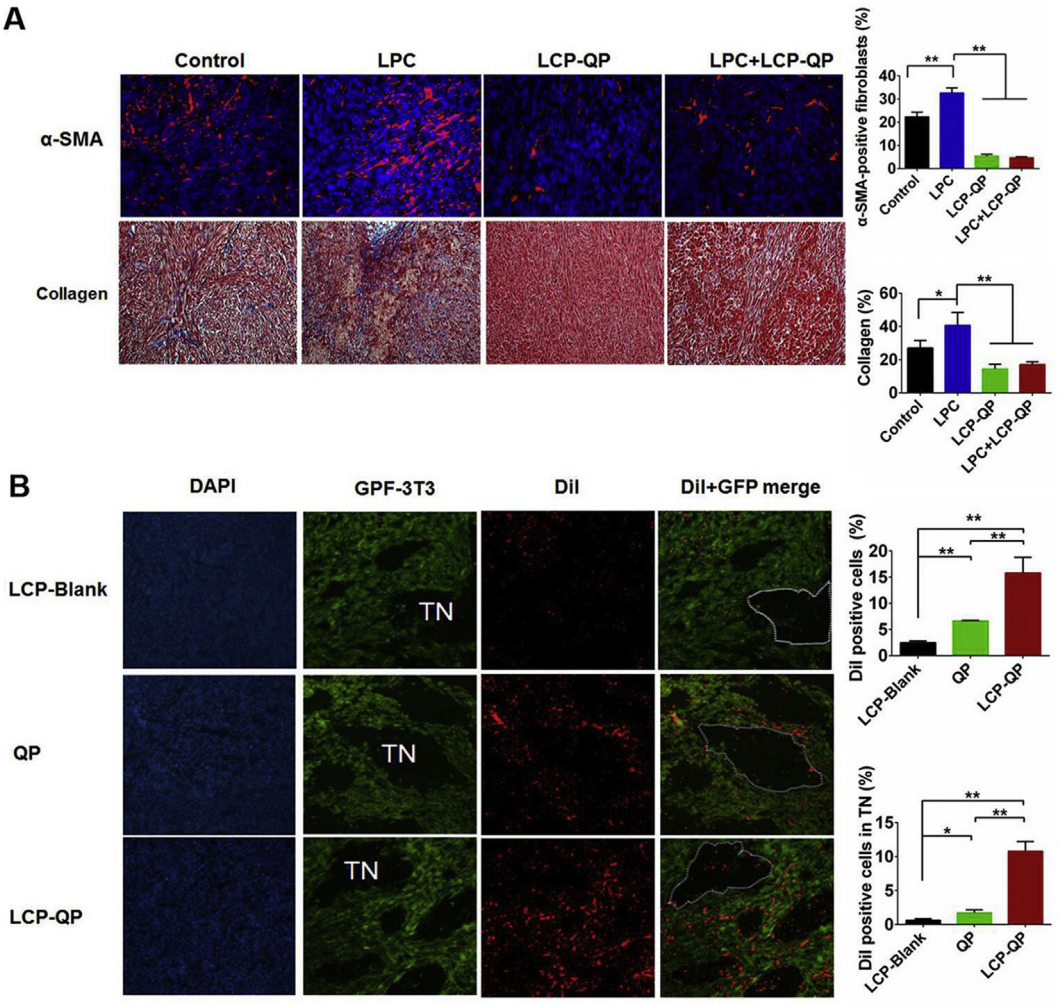

Figure 5 Nanoparticle distribution and tumor microenvironment remodeling *via* LCP-QP. (A) Effects of different treatments on the inhibition of fibroblast growth and Masson's trichrome stain for collagen and quantification results expressed as the percentage of total cell number. (B) Effect of LCP-QP on the penetration of DiI NPs and quantification of fluorescence signal (DiI labeled red) expressed as the percentage of cell number (DAPI signal) detected on frozen tumor sections. GFP positive fibroblasts (green), DAPI labeled nuclei (blue), and DiI labeled LCP-QP particles (red). $^{**}P < 0.01$, $^{*}P < 0.05$, $n = 5$. LCP, lipid calcium phosphate; QP, quercetin phosphate. (Used with permission from Ref. 58. Copyright © 2017 American Chemical Society.).

nanoparticles was improved by the quercetin phosphate nanoparticles (Fig. 5). Besides, in fibroblast-MCF7 co-cultures, studies found that treatment with quercetin can rescue Caveolin-1 expression which is related to early tumor recurrence, thus reversing the CAFs phenotypes[59].

3.4. *Nab-PTX*

Paclitaxel (PTX) is a taxane diterpenoid which was first isolated in 1971 from the Pacific yew and approved for medical usage in 1993. PTX has high anti-tumor activity and is widely used to treat ovarian cancer, breast cancer, non-small cell lung cancer, cervical cancer and brain cancer[113].

Secreted protein acidic and rich in cysteine (SPARC) is an albumin-binding 42-kDa matricellular glycoprotein, overexpressed by CAFs in different types of tumor such as breast tumor, lung tumor, PDAC and melanoma[114]. SPARC has been shown to involve in proliferation, migration, and escape mechanisms of PDAC cells, and inversely correlate with survival in PDAC. Therefore, SPARC is gaining significant clinical interest as a potential biomarker. SPARC is expressed both in PDAC stroma and tumor cells, leading to the hypothesis that it may assist the delivery to the tumor of albumin-bound therapeutics. A drug formulation of PTX bound to the albumin (nab-PTX, Abraxane) is effective in depleting desmoplastic tumor stroma such as CAFs and ECM through binding albumins of nab-PTX to SPARC[115]. Study found that the combination of nab-PTX and GEM decreased CAF content and remodeled the ECM content, and further experiment confirmed that the stromal remodeling effects, such as alteration of collagen architecture and elimination of CAFs, are due to nab-PTX but not GEM[116]. In addition, the combination effect of GEM plus nab-PTX to remodel CAFs was greater than the combination of GEM plus tegafur[117]. These findings propose a potential role for nab-PTX in suppressing chemoresistance and metastasis by altering the tumor microenvironment.

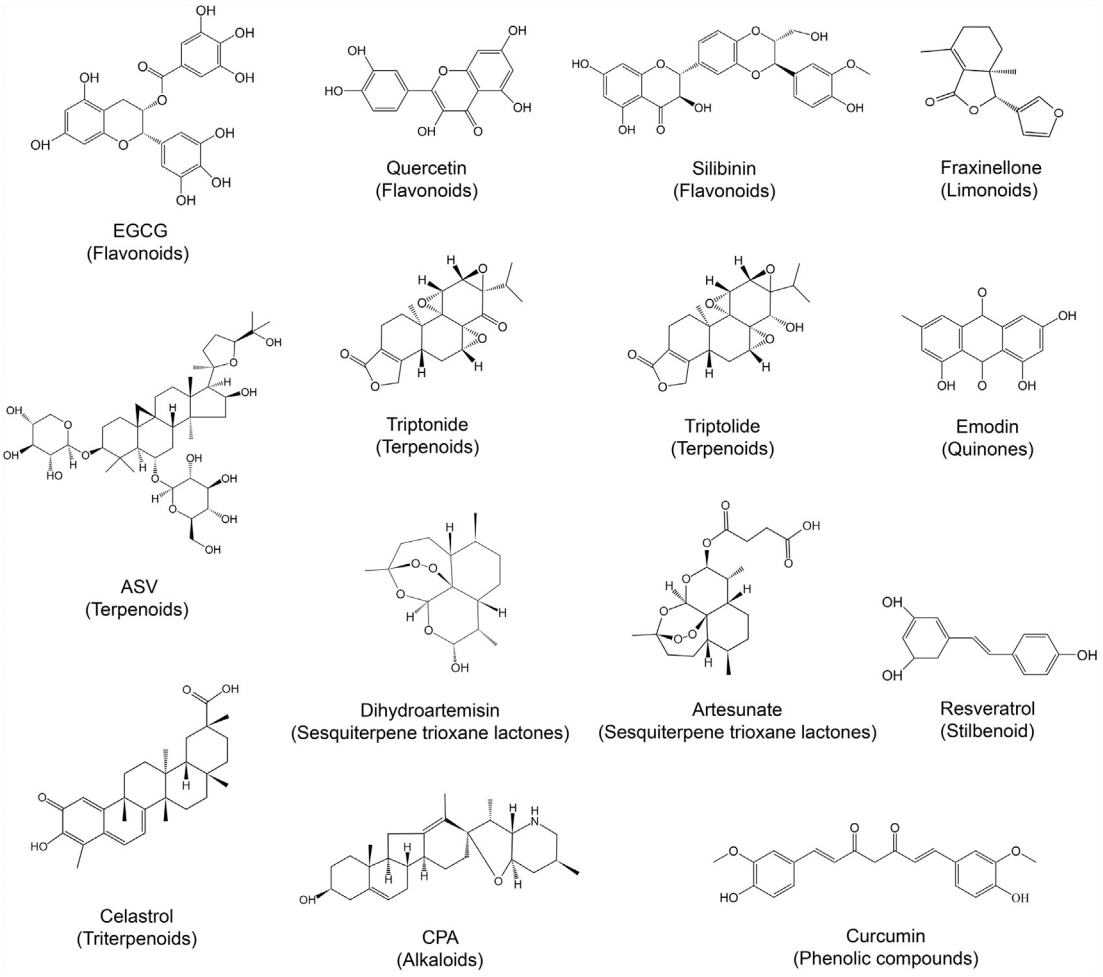

Figure 6 Chemical structures of natural products mentioned in this review.

3.5. Epigallocatechin-3-gallate

Besides the effects of EGCG on HGF and VEGF and on CAF-cancer crosstalk, Gray et al.[49] found that both of EGCG and luteolin inhibited fibronectin expression, and decreased RhoA activation which was disclosed to be essential for the expression of fibronectin induced by TGF-β. Furthermore, they found EGCG and luteolin could inhibit TGF-β-induced ECM contraction, thereby suppressing tumor cell invasion. Their study results imply that combining EGCG with luteolin in clinic can prevent or even reverse cancer progression by normalizing ECM through targeting CAFs.

4. Natural products inhibit the angiogenesis

Angiogenesis is a prerequisite for the growth and metastasis of tumors since tumors cannot maintain expansion without neovascularization to supply oxygen and nutrients. CAFs play a critical role in the construction of microenvironment to favor tumor angiogenesis through producing multiple regulatory molecules and ECM proteins, therefore promoting angiogenesis to meet the growth requirements of tumors.

Anti-angiogenesis therapy reduces blood supply and starves tumor cells of oxygen and nutrients. In clinic, VEGF-mediated signaling is one of the most promising anti-angiogenic therapeutic targets. While, anti-VEGF agents that are currently in use are mainly monoclonal antibodies, which have many serious adverse effects, such as bevacizumab. On the contrary, compared with the currently used synthetic medicines, natural products can suppress angiogenesis through multiple signal pathways in tumors with low systemic side effects. It has been reported that fraxinellone could suppress angiogenesis of tumors *in vivo* by inhibiting programmed cell death-ligand 1 expression *via* reducing HIF-1 and STAT3 signaling pathways[38]. Silibinin and quercetin have been reported to inhibit the angiogenesis and proliferation of cancer cells in desmoplastic tumors through inhibiting VEGF expression[37,118].

Collectively, as an important complement to therapies targeted against cancer cells in desmoplastic tumors, various natural products that affect the CAF signals and effectors in the stroma have attracted scientists' attentions.

The pharmacological effects of natural products on desmoplastic tumors mainly reflect in three aspects: regulating ECM, inhibiting tumor angiogenesis, and influencing the interaction between tumor cells and CAFs. The current studies show that, through influencing the communication between CAFs and tumor cells, the proliferation, migration, invasion and drug resistance of tumor cells induced by CAFs can be significantly inhibited. On the one hand, CAFs can be depleted; on the other hand, CAFs can be reverted from the activated state into a quiescent state. However, direct CAF depletion could enhance hypoxia in the tumors and

thus induce EMT in the desmoplastic tumor cells, which ultimately led to aggressive cancer progression[119]. Therefore, attempts to normalize CAFs could be a better way to provide new opportunities for the development of novel anti-desmoplastic cancer therapies. Natural products such as silibinin, DHA, artesunate, fraxinellone, and triptolide can effectively suppress the activation of CAFs induced by TGF-β, impel the normalization of CAFs, and then inhibit the development of desmoplastic tumors without the negative effects caused by the direct depletion of CAFs.

In addition, the current researches indicate that the effects of natural products are usually on multi-channels and multi-targets. They can affect the interaction between tumor cells and CAFs, while regulating the ECM or inhibiting tumor neovascularization, thus enhance the therapeutic effects for the desmoplastic tumor. For example, fraxinellone and silibinin can not only inhibit the activation of CAFs, but also inhibit tumor angiogenesis by inhibiting HIF-1 and VEGF, respectively; EGCG can suppress the CAF-induced proliferation and migration of tumor cells by down-regulating the expressions of HGF and VEGF, and it can also remodel ECM through inhibiting the secretion of collagen induced by TGF-β; triptolide can inhibit the activation of CAFs, while regulating ECM through inhibiting the secretion of collagen; quercetin can inhibit the activation of CAFs by promoting the expression of CAV-1, hinder tumor neovascularization by suppressing the secretion of VEGF, and inhibit CAF-induced drug resistance of tumor cells by down-regulating the expression of WNT16 (Fig. 2). From these natural products, we should be clearly aware that the pharmacological research of natural products should not be limited to a certain pathway or a target. Researchers should conduct extensive researches on the pharmacological mechanism of a natural product in multiple ways and directions.

A brief summary of the above mentioned natural products that potentially target CAFs is given in Fig. 6 and Table 1. Natural compounds that modify CAF signaling are waiting for further mechanistic and functional investigation.

5. Concluding remarks

The proliferation, migration and invasion characteristics of tumor cells must rely on their microenvironment. In the tumor microenvironment, fibroblasts as one important component of the dense desmoplastic stroma[120], contribute to the aggressiveness and chemotherapeutic resistance of desmoplastic tumor. As a consequence, it has been recognized that CAFs are attractive targets to reduce chemotherapy resistance for anticancer therapy and tumor recurrence over the past few years[12]. Besides inhibiting the proliferation of tumor cells, many natural products also have the ability to target different types of stromal cells, by which exhibiting an indirect inhibitory effect on the invasion, proliferation and migration of desmoplastic tumors. These natural products usually modulate tumor microenvironment through various signal pathways, playing a comprehensive coordinating role in tumor treatment.

However, most of the natural products whose stability are poor are difficult to dissolve in water or general organic solvents, resulting in low bioavailability *in vivo*, which limits their pharmacological studies by researchers and their clinical application. Therefore, it is of great significance to develop rational drug delivery systems[121] to enhance the bioavailability of natural products for their preclinical studies. In the study of anti-desmoplastic tumors, how to target natural products to tumor tissues to regulate CAFs should also be the focus of the researchers. Although there were a few studies which could deliver natural compounds to the tumor sites through using targeted drug delivery systems to load the natural product components, most studies of these formulations stayed at the pharmacodynamics level and the mechanisms were not widely explored. In addition, in the aspect of exploring the pharmacological mechanism of natural products for remodeling CAFs to inhibit tumor progression, the current researches mainly focused on TGF-β pathway. Therefore, the effect of natural products on other pathways such as WNT and Hh for CAF regulation should have potential values to be explored. Besides, there are still some important questions that should be further elucidated, such as when is the best time to deplete or remodel the CAFs by natural products in the tumor microenvironment? Are there other aspects of CAFs related to cancer progression which can be affected by chemicals from natural products? Are there any relations among the different remodeling aspects of natural products? And how can we better utilize natural products to assist current clinical treatments for desmoplastic tumors?

Furthermore, a combination of anti-cancer chemicals and natural product compounds is able to provide promising advantages in sensitizing monotherapy efficacy and overcoming drug-induced resistance in desmoplastic tumor patients. The combination effects seen in these preclinical observations highlight the future application of such combinations for effective desmoplastic cancers treatments and reveal their clinical potential.

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Author contributions

Rujing Chen wrote the manuscript and made the figures; Kaili Hu and Leaf Huang supervised and edited the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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