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Review Article

Natural products as inhibitors against pancreatic cancer cell proliferation and invasion: possible mechanisms

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Abstract: Pancreatic cancer is one of the gastrointestinal tumors with the lowest survival rate and the worst prognosis. At the time of diagnosis, the majority of patients have missed the opportunity for radical surgical resection and opt for chemotherapy as their primary treatment choice. And drug resistance emerges during the application of the most widely used chemotherapeutic regimens such as modified FOLFIRINOX regimen, gemcitabine monotherapy or 5-Fluorouracil combination therapy, which further reduces the therapeutic efficacy. Therefore, it is urgent to explore better treatment strategies for pancreatic cancer. In recent years, more and more studies have found that natural products have significant anti-pancreatic cancer properties. In this paper, we reviewed the possible mechanisms by which natural products inhibit the proliferation and invasion of pancreatic cancer cells, including the possible mechanisms of targeting the inhibition of the growth and proliferation regulatory pathways of pancreatic cancer cells, inducing apoptosis and autophagy of pancreatic cancer cells, inhibiting the EMT process of pancreatic cancer cells, and inhibiting the angiogenesis of pancreatic cancer. Meanwhile, natural products have also hindered the progress of their basic and clinical research due to the complexity of their composition and the limitation of biological extraction technology. Further exploration of the specific molecular mechanisms of natural products to inhibit the proliferation and invasion of pancreatic cancer cells, optimization of purification and preparation techniques, and enrichment of basic and clinical trials to verify their efficacy and safety may be the future direction of natural products in the field of anti-pancreatic cancer research.

Keywords: Natural product, pancreatic cancer, apoptosis, autophagy, EMT, anti-angiogenesis

Introduction

Pancreatic cancer (PC) is a gastrointestinal tumor with extremely high malignancy, low survival rate and poor prognosis, and has ranked as the 7th leading cause of cancer-related fatalities globally [1, 2]. Recent statistics indicate that the incidence of PC is rising at a rate of 0.5% to 1.0% annually and is projected to become the second most common cause of cancer-related deaths in the U.S. by 2030 [3]. Its treatment mainly includes surgery, radiotherapy, chemotherapy and interventional therapy [4]. Currently, the only radical treatment for PC is surgical resection. However, most of the PC patients have already progressed to advanced stage and lost the condition of radical surgical resection when they are diagnosed [5]. Therefore, systemic chemotherapy is the main or even the only treatment option for advanced PC. Common chemotherapy regimens for PC include modified FOLFIRINOX regimen, gemcitabine monotherapy or 5-Fluorouracil combination therapy, etc. [6]. At the same time, the NALIRIFOX regimen composed of Irinotecan Hydrochloride Liposomes and Oxaliplatin has also entered the phase III clinical trial for the treatment of metastatic pancreatic cancer. The results showed a better survival rate compared to Nab-paclitaxel and Gemcitabine [7]. With the therapeutic advances in chemotherapeutic agents, PC cells have induced an increase in their resistance to chemotherapeutic agents through a variety of mechanisms, making the treatment of advanced PC tremendously impeded and challenging [8-10]. In recent years, many natural products have been found to have positive anti-tumor effects [11, 12]. The most repre-

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sentative is Paclitaxel, which has been used in the treatment of PC, inhibiting the development of PC by blocking the division and growth of tumor cells [13]. Several clinical trials have shown that paclitaxel can be used as a first-line chemotherapeutic agent for PC, either alone or in combination with other chemotherapeutic agents, to significantly prolong patient survival and improve quality of life [14, 15]. In addition, paclitaxel can be used as adjuvant chemotherapy in the perioperative period to help reduce tumor size and improve the success rate of surgical resection [16, 17]. Other substances such as Antroquinonol A have also entered clinical trials in PC treatment studies [18]. Natural products refer to natural substances extracted from plants, animals, and other natural sources possessing diverse biological activities and pharmacological properties. Studies have shown that certain natural products may have an inhibitory effect on the process of PC development [19]. For example, triptolide inhibits decoy receptor 3 (DcR3) expression in PC cells, and the promoted Fas ligands (FasL) binds to Fas receptors (FasR) to enhance pro-apoptotic signaling [20], and inhibited 5-lipoxygenase (5-LOX) and downstream leukotriene B4 (LTB4) signaling pathway in PC cells which in turn enhanced Bid and Mcl-1 protein expression and further induced apoptosis [21]. Chrysin inhibits PC progression by activating G Protein Coupled Estrogen Receptor (GPER) and thereby decreasing ROCK1, TAGLN2 and FCHO2 expression [22]. Meisoindigo inhibits Liver kinase B1 (LKB1) expression and activates AMPK to target PC stem cell killing [23]. A growing amount of experimental evidence suggests that natural products inhibit the proliferation of PC mainly by regulating the cell cycle, inhibiting tumor-related signaling pathways, or affecting the expression of genes related to cell proliferation [24]. Natural products can also induce apoptosis in PC cells by regulating the expression of apoptosis-related protein kinases, mitochondrial pathways, or apoptosis-related genes [25], and inhibit the angiogenic process, thus blocking the blood supply to the tumor and limiting the growth and spread of tumor cells [26]. At the same time, based on the high quality anti-tumor activity of natural products, they have also been widely investigated in combination with conventional chemotherapeutic agents such as gemcitabine to enhance the therapeutic efficacy by synergizing or improving drug resistance [11, 24, 25, 27]. However, natural products themselves also have certain limitations that hinder their research and future clinical application, and more clinical and experimental studies are still needed to verify the exact effect of natural products on PC. Nevertheless, it is undeniable that the finding that natural products hinder the progression of PC holds significant clinical importance for treating patients with advanced PC. This paper reviews the possible mechanisms by which natural products inhibit the growth and invasion of pancreatic cancer cells, and discusses the limitations of natural products in future studies and the direction of research development. We aim to provide new directions and ideas for the application of natural products in future anti-pancreatic cancer growth and invasion studies, as well as the application of natural products in pancreatic cancer treatment programs.

Possible mechanisms of action of natural products in the fight against PC

The mechanism by which natural products act in PC involves multiple complex biological processes. Natural products inhibit the progression of PC by inducing apoptosis or autophagy, a process mediated by multiple pathways and factors, including the STAT3/NF-κB and PI3K/Akt signaling pathway, etc. [28-30]. It can also inhibit the invasion and metastasis of PC by inhibiting EMT-related genes, proteins, and signaling pathways of PC cells [31, 32], as well as targeting angiogenesis-related cytokines and pathways, exerting its anti-angiogenic properties, and thus inhibiting the growth and invasion of PC [33]. In addition, natural products have been extensively studied in combination with chemotherapeutic agents such as gemcitabine to improve their resistance and enhance therapeutic efficacy [11, 34]. Therefore, exploring the specific molecules and mechanisms of autophagy and apoptosis, anti-metastasis and angiogenesis of PC cells induced by natural products, investigating the synergistic effect with chemotherapeutic agents and the mechanism related to the improvement of drug resistance are of great clinical significance for the future application of natural products in the formulation of targeted therapeutic regimens for PC.

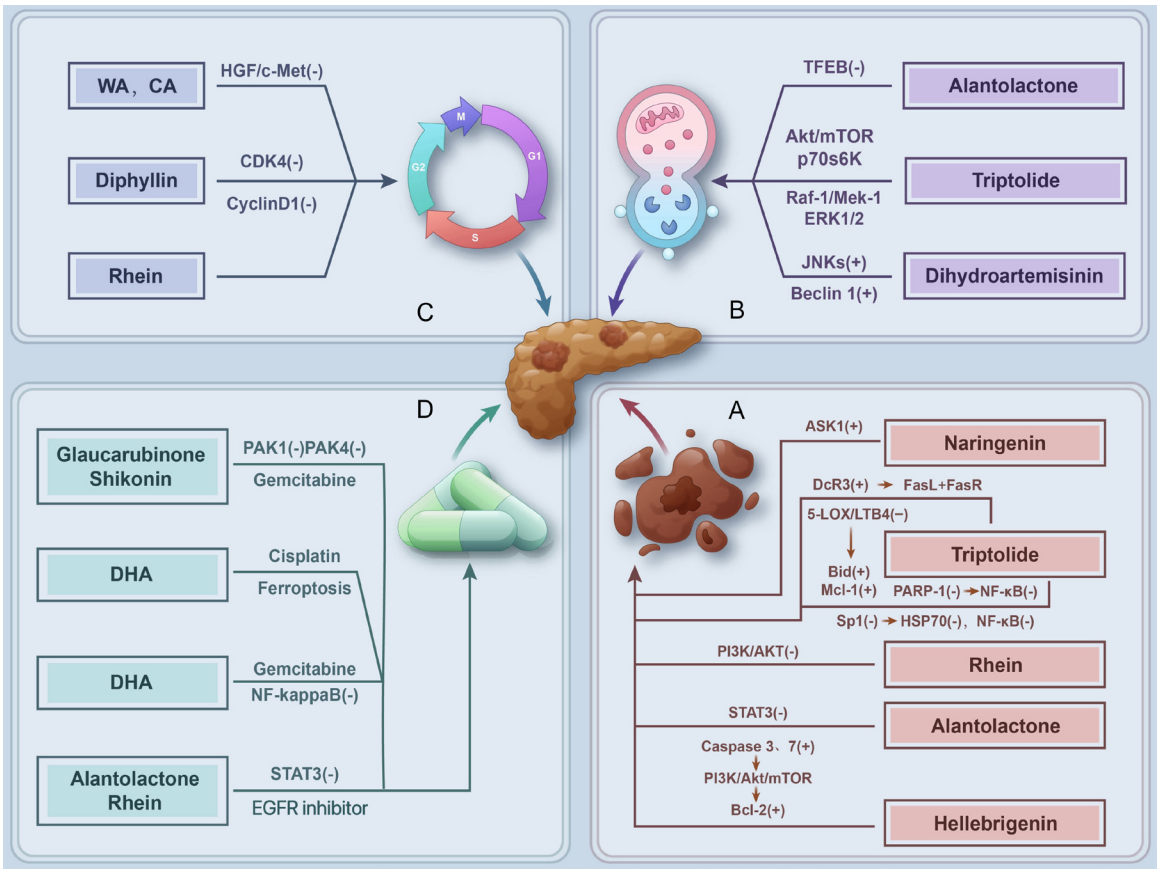

Figure 1. Possible mechanisms of natural product-induced apoptosis and autophagy, cell cycle arrest, and improved drug resistance in pancreatic cancer cells. The main mechanisms by which natural products inhibit PC progression include inducing apoptosis (A) and autophagy (B) in PC cells and inducing cell cycle arrest (C). They can also improve the resistance to conventional chemotherapeutic drugs such as gemcitabine (D). Part a describes that Naringenin induces PC cell apoptosis by promoting ASK1 expression and thereby inducing PC cell apoptosis. Triptolide induces PC cell apoptosis by promoting DcR3 expression leading to more binding of FasL to FasR, and induces PC cell apoptosis by inhibiting the level of 5-LOX/LTB4 leading to increased Bid and Mcl-1 expression, etc. Rhein induces PC cell apoptosis by inhibiting the PI3K/AKT pathway. Alantolactone induces PC cell apoptosis by inhibiting STAT3. Part b describes that Alantolactone induces PC autophagy by inhibiting TFEB expression and thereby inducing PC autophagy. Triptolide induces PC autophagy through the Akt/mTOR/p70s6K and raf-1/Mek-1/ERK1/2 pathways. DHA mediates PC autophagy by promoting JNKs and Beclin 1 expression. Part c describes that WA and CA cause PC cell cycle arrest by inhibiting the HGF/c-Met axis. Diphyllin induces PC cell cycle arrest by inhibiting CDK4 and cyclinD1 expression. Rhein is capable of inducing PC cell cycle arrest. Part d describes the ability of Glaucarubinone and Shikonin to ameliorate gemcitabine resistance through inhibition of PAK1 and PAK4 expression. DHC ameliorates cisplatin resistance through the iron death pathway. DHC ameliorates gemcitabine resistance through inhibition of NF-kappaB expression. Alantolactone and Rhein ameliorate PC Resistance to EGFR Inhibitors by Inhibiting STAT3.

Possible mechanism of inhibition of PC proliferation by natural products

The anti-proliferative effects of natural products on PC cells are mainly manifested in targeting the growth and invasion regulatory pathways of PC cells, as well as inducing apoptosis or autophagy, thereby inhibiting the growth and proliferation of PC cells [35]. Therefore, it is important to investigate the molecular mechanisms associated with the suppression of PC progression by natural products for the development of novel natural product-related targeted drugs as well as for the formulation of new therapeutic strategies in the future (**Figure 1**).

Induction of apoptosis and autophagy in PC cells: Natural product-induced apoptosis and autophagy in PC cells is one of the possible mechanisms by which it exerts anti-tumor growth and proliferation effects. Apoptosis is one of the forms of programmed cell death and

can inhibit the growth and proliferation of tumor [36]. Also in cancer cells, autophagy can reduce intracellular stress and maintain intracellular homeostasis by degrading damaged proteins and organelles. However, excessive autophagy may also lead to tumor cell death. Some studies have found that certain natural products can affect the survival and proliferation of PC cells by inducing autophagy in PC cells [37]. Apoptosis and autophagy may interact with each other to form a complex regulatory network, which then forms one of the regulatory mechanisms by natural products to inhibit the proliferation of PC.

Naringenin, a representative of flavonoid natural products, is the most abundant flavonoid in natural citrus fruits, and has been found to have the biological activity of inhibiting the growth and proliferation of cancerous tumors such as breast cancer [38], colorectal cancer [39]. In the study of inhibition of PC development, Hyun et al [40] found from in vitro cellular experiments using SNU-213 cell as the target that naringenin can increase ROS in PC cells and then upregulate the expression of apoptosis signal-regulated kinase 1 (ASK1) to achieve the therapeutic purpose of inhibiting PC cell invasion. In addition, based on the antitumor properties of naringenin, Lee et al [41] found that naringenin could inhibit FAK and p38 signaling pathways in both tumor xenograft nude mouse models and in vitro cellular assays, and to maximize the anticancer effect of naringenin on human PC cells after the combination of naringenin and another product, nerolidol, which was enzymatically digested by warm water pericarp (εCUP) and extracted by fermentation of warm water pericarp (*f*CUP) in an optimal ratio for the treatment of naringenin. Thus, it is evident that flavonoid natural products represented by naringenin alone or in combination will produce inhibitory effects on PC cells through multiple pathways. The function of the Naringenin is shown in **Figure 1**.

Triptolide is a natural product which is mostly utilized as a new immunosuppressive and anti-inflammatory medication, especially for the treatment of rheumatoid arthritis [42]. In recent years, increasing studies have shown that triptolide has some anti-tumor activity against PC. Wang et al [20] established AsPC-1 xenografts for probing the inhibitory effect of triptolide on PC cells. They found that triptolide inhibited the expression of competitive DcR3 in PC cells, so that more FasL would be able to bind to FasR, and thus enhance the binding of PC cells to FasR, which in turn, enhanced the pro-apoptotic signaling in PC cells. In addition, triptolide was able to enhance the expression of Bcl-2 protein family, such as Bid protein [43] and Mcl-1 protein [44], which regulate the sensitivity of cancer cells to apoptosis, in PC cells by inhibiting the 5-LOX and the downstream LTB4 signaling pathway [21], which promotes the increase in the permeability of mitochondrial membranes, and consequently enhances apoptosis of PC cells. Meanwhile, Wang et al [43] also found that triptolide was able to reduce the accumulation of NF-κB in the nucleus by cleaving poly(ADP-ribose) polymerase 1(PARP-1) protein into an inactive form in PANC-1 cells [20], which in turn promotes apoptosis of PC cells. It was also able to cause a decrease in NF-κB expression in pancreatic cancer cells by inhibiting the expression of transcription factor-specific protein 1 (Sp1), a mechanism demonstrated in the SCID mouse xenograft model [45]. With the in-depth study of Sp1, Banerjee et al [45] also found that the inhibition of heat shock protein 70 (HSP70) expression by triptolide was caused by inactivation of Sp1, followed by an increase in lysosomal permeability and a further enhancement of mitochondrial membrane permeability, leading to enhanced apoptosis-inducing activity in PC cells. Interestingly, the combination of triptolide and artesunate (an anti-malarial natural derivative used in the treatment of cancer) inhibited the growth of PC and induced apoptosis in PC cells, a process that coincided with the upregulation of HSP20 and HSP27 from the heat shock protein family, suggesting important synergistic effects in in vitro studies [46]. In addition to its pro-apoptotic effects, triptolide is also able to exert its anti-tumor properties by inducing autophagy in PC. Mujumdar et al [47] found that triptolide was able to induce autophagy in MiaPaCa-2, Capan-1 and BxPC-3 cell lines through common mechanisms such as Akt/mTOR/p70s6K pathways, raf-1/Mek-1/ERK1/2 pathways. Taken together, all these mechanisms express the ability of triptolide to exert important anti-tumor activity in promoting apoptosis in PC cells. Thus, triptolide is an important natural product to inhibit the development of PC cells, and it is an important direction for future research on the treat-

ment of PC with natural products. The function of the Triptolide is shown in **Figure 1**.

Artemisinin, a pharmaceutical ingredient extracted from the Artemisia annua plant, which has been used in the treatment of malaria because it has been found to be able to act on the membrane structure of Plasmodium, disrupting the nuclear and mitochondrial membranes of Plasmodium, thereby killing the parasite [48]. Dihydroartemisinin (DHA), a semi-synthetic derivative of artemisinin, has been found to induce apoptosis in pancreatic cells and inhibit PC cell proliferation in a concentration-dependent manner [49]. DHA was able to activate the JNK pathway, inducing an increase in the expression and activity of c-Jun NH2-terminal kinases (JNKs), which in turn up-regulated the expression of its catalytic product, autophagy-associated protein Beclin 1, and caused an accumulation of ROS in PC cells, inducing autophagy in PC cells, which was demonstrated in vitro cellular experiments [50]. This finding expands a new direction for artemisinin in the field of PC therapy. The function of the Artemisinin is shown in **Figure 1**.

Natural sesquiterpene lactones are the major bioactive compounds present in many medicinal plants, and their representative substance, Alantolactone, can induce apoptosis by targeting a variety of cell signaling pathways [51]. In recent years, the JAK-STAT3 signaling pathway has been extensively studied, and it has been shown to mediate the development of PC and drug resistance [52]. Zheng et al [53] found that Alantolactone could inhibited STAT3 expression in PC cells in both in vivo and in vitro experiments. In addition, the combination of Alantolactone and the EGFR inhibitors (Erlotinib or Afatinib) demonstrated a synergistic therapeutic effect on PC cells. The mechanism is that propiolactone can sensitize PC cells to EGFR inhibitors by inhibiting the STAT3 signaling pathway. Fortunately, Bao et al [54] designed and validated a nanoparticle piggybacked with Alantolactone and erlotinib (ERL, an EGFR inhibitor), which induced significant PC cell apoptosis after application for the treatment of a wild-type BALB/c mouse xenograft model, showing desirable anticancer effects. This suggests that the combination of Alantolactone with other EGFR-targeting drugs may be a new direction for PC treatment in the future. Meanwhile, He et al [55] also found that the expression of transcription factor EB (TFEB), a transcription factor that regulates lysosomal biogenesis and function, was decreased in PC cells from BALB/c mice after the application of Alantolactone, which led to lysosomal dysfunction and the subsequent occurrence of autophagy. At the same time, experiments also revealed the ability of Alantolactone to enhance the therapeutic sensitivity of PC cells to oxaliplatin. This once again opens up new research hotspots for Alantolactone in PC treatment. The function of the Alantolactone is shown in **Figure 1**.

Rhein, the main component of the Chinese herb rhubarb, has been shown to induce apoptosis in a variety of cancer types, such as hepatocellular carcinoma [56], colon cancer [57], etc. Liu et al [30] found that Rhein was able to inhibit Panc-1 and MIAPaca-2 cells from growing and proliferating by causing them to stagnate in the G1 phase. In addition, in vivo and in vitro studies have found was found that the combination of Rhein and the platinum-based chemotherapeutic agent oxaliplatin resulted in an increase in the generation of ROS in PC cells and the inactivation of the PI3K/AKT pathway, which led to the eventual apoptosis of PC cells. This suggests that Rhein has some anti-PC bioactivity and may be able to increase the sensitivity of PC cells to platinum-based chemotherapeutic agents. In addition to this, Rhein also exhibited both in vivo and in vitro inhibition of STAT3 bioactivity, sensitizing pancreatic cancer cells to EGFR inhibitors [58]. This is similar to the combination therapy with Alantolactone above and may lead to additional treatment options for PC patients. Meanwhile, natural products targeting STAT3 have been widely discovered in recent years. For example, Trienomycin A (TA), a polycyclic antibiotic. It can directly bind to STAT3 and inhibit STAT3 phosphorylation, thus inhibiting the STAT3 pathway to exhibit inhibitory effects on the growth and invasion of PC cells [59]. And Hellebrigenin is also a natural product found in the skin secretions of toads and plants of Urgelae. Wei et al [60] found that Hellebrigenin could cause SW1990 and BxPC-3 cells to block in the G0/G1 phase leading to apoptosis, and promote cellular autophagy by activating autophagy marker proteins in the autophagy family and most of the related proteins. High-resolution

transmission electron microscopy observation during the experiment showed that the SW1990 and BxPC-3 cells treated with Hellebrigenin showed typical apoptosis and autophagy patterns. This phenomenon was induced by activating the expression of caspase 3 and 7 in caspase family proteins, which in turn activated the PI3K/Akt/mTOR signaling pathway to increase the Bax/Bcl-2 ratio and induced the onset of apoptosis. Fraxetin, a natural product derived from the bark of Fraxinus bungeana A. DC., exhibits anti-inflammatory, analgesic, and anti-dysenteric properties. Guo et al [61] found that Fraxetin was able to reverse the onset of EMT in PC cells in an in vivo xenograft model in male BALB/c mice, which in turn inhibited the proliferation, invasion and metastasis of PC. It also inhibited the growth and proliferation of PC cells by suppressing STAT3 activation triggered by oncogenic KRAS in PC cells, thereby inhibiting the downstream signaling pathway STAT3-Ref1 axis and thus mediating apoptosis in PC cells (**Figure 1**).

In summary, natural products mediate their anti-tumor growth and proliferation effects by inducing apoptosis in PC cells, which provides important references and insights for the development of novel anti-tumor drugs. In the future, researchers will continue to explore the anti-tumor mechanism of natural products in depth and search for more natural products with potential anti-tumor effects to provide more options for clinical treatment.

Induction of cell cycle arrest in PC: The cell cycle is an important process of cell growth and division, and its dysregulation is intricately linked to the initiation and progression of tumors, so inhibiting the growth of pancreatic tumors by interfering with the cell cycle has become an important anti-tumor strategy [62]. Some natural products are able to inhibit pancreatic tumor growth by stalling the cell cycle.

Withaferin A (WA) and carvacrol (CA) are two natural products with inhibitory properties against the c-Met kinase structural domain [63]. C-Met is a hepatocyte growth factor (HGF) receptor and belongs to the receptor tyrosine kinase (RTK) family of proto-oncogenes. The disruption of the HGF/c-Met pathway and the consequent activation of downstream signaling pathways such as ERK/MAPK, STAT PI3K/Akt, FAK, among others, play a role in promoting angiogenesis, proliferation, invasion, and the modulation of cancer stem cells (CSCs) in the process of tumorigenesis [64]. Aliebrahimi et al [65] found that the use of 1 μM WA in various established c-Met$^+$ cancer cell lines was able to lead to G2/M cell cycle arrest, whereas CA was able to increase the proportion of S-phase PC cells and decrease the proportion of G0/G1-phase cells, and this behavior was achieved by its inhibition of the HGF/c-Met axis in PC cells. Diphyllin, a natural lignan extracted from various traditional Chinese medicinal plants, has been demonstrated to inhibit V-ATPase activity by suppressing the phosphorylation of Recombinant Low Density Lipoprotein Receptor Related Protein 6 (LRP6) in the Wnt/β-catenin signaling pathway, which in turn inhibits the development of gastric cancer [66, 67]. The diphyllin derivative PHY34 was found to inhibit late autophagy by inhibiting V-ATPase activities, thereby reducing the invasive ability of ovarian cancer cells [68]. However, the low water solubility and poor metabolic stability of luteolin have hindered its further development as an antitumor drug. Yang Li et al [69] designed and synthesized two types of nitrogen-containing derivatives of the natural product luteolin (triazole-linked L-rhamnose derivatives and 4-amino substituted derivatives) to enhance their antitumor effects and metabolic stability. They used it to treat male C57BL/6 mice xenografted with PANC02 tumor cells and found that the two nitrogen-containing derivatives not only significantly induced the proliferation arrest of PC cells at the G0/G1 phase, but also down-regulated CDK4 and cyclinD1 in a dose-dependent manner, which resulted in stronger anti-tumor activity against PC cells. Thus, the induction of cell cycle arrest may be a new direction for exploring PC treatment in the future (**Figure 1**).

Other mechanisms: In addition to inducing apoptosis and autophagy and cell cycle arrest in PC cells. Targeting the proliferation regulatory pathway of PC stem cells and inducing ferroptosis of PC cells are also other possible mechanisms by which natural products inhibit the development of PC. These findings also provide new ideas for future targeted therapy of PC.

Glaucarubinone, a natural product isolated from the seeds of Simarouba glauca, has been found to be able to act as an antimalarial drug.

In recent years, some studies have confirmed its anticancer activity [70], but its mechanism of action is not yet fully understood. Dannel et al [71] conducted a study on KRas-mutated PC cells, targeting the Ras downstream effector PAKs proteins in PC cells. It was found that Glaucarubinone could reduce the proliferation and migration of PC by decreasing the amount of active p21-activated kinase 1(PAK1) and p21-activated kinase 4(PAK4) in human PC cells. Meanwhile, in vivo experiments also revealed that the combination of Glaucarubinone and gemcitabine may synergistically inhibit PC development in xenografts from SCID mice by inhibiting pathways including PAK1 and PAK4, which provides a new direction for the treatment of PC. Shikonin is the main component of Lithospermum erythrorhizon, which has been shown to have multiple mechanisms of anticancer action. As an illustration, shikonin triggers apoptosis and autophagy in colorectal cancer cells through its interaction with the galectin-1/JNK signaling pathway [72] and hinders proliferation while enhancing apoptosis in gastric cancer via modulation of the PI3K/Akt signaling pathway [73]. Ruan et al [74] found that shikonin was able to inhibit the NF-κB/STAT3 and NF-κB/CSN5 signalling pathways by inhibiting and arresting immune escape from PC, which in turn led to the degradation of PD-L1. Ji et al [75] found that shikonin markedly inhibited the PAK1 activity and its downstream signalling pathway, inhibited BxPC-3 and PANC-1 cells proliferation, and showed synergistic effects with the chemotherapeutic drug gemcitabine in the treatment of PC. This suggests that Shikonin may be able to show significant therapeutic value as an inhibitor of PAK1 kinase in PC treatment in the future.

In addition to the above-mentioned induction of autophagy in PC cells, ferroptosis is also another research direction of artemisinin in terms of its antitumor activity. Antoszczak et al [76] found that DHA was able to induce ferroptosis in drug-resistant PC cells in their experiments, implying that the induction of ferroptosis may be an antitumor mechanism of DHA against PC. This finding was also confirmed by wang et al [77] in their experiments of designing nanoparticles harboring DHA for the treatment of PC. These different mechanisms make DHA show the value of research in the field of PC treatment. DHA has also been investigated in adjuvant combination therapy. Du et al [78] found that DHA strongly enhances the cytotoxicity of cisplatin (DDP). The combination of DHA and DDP synergistically inhibits the proliferation of PC cells and induces DNA damage in both in vivo and in vitro experiments. This phenomenon is attributed to the ability of DHA to induce the onset of ferroptosis in PC cells due to lipid peroxidation resulting from the accumulation of free iron and lethal ROS in PC cells. This also demonstrates the synergistic effect of DHA and DDP in PC therapy, predisposing PC cells to ferroptosis, which may be a promising therapeutic strategy. Meanwhile, Wang et al [79] demonstrated for the first time in the male BALB/c nude mouse model that DHA greatly reduced the expression of its target gene products, such as c-myc, cyclinD1, Bcl-2, and Bcl-xL, by inhibiting gemcitabine-induced NF-kappaB activation, resulting in improved expression of PC cell resistance to gemcitabine when combined with gemcitabine and improved anti-tumour efficacy. Artesunate, another derivative of artemisinin, also showed good antitumor activity against PC cells. Du et al [80] applied artesunate treatment in an in vivo PC xenograft model and found that the tumor model produced tumor regression. Also upon addition of the ROS scavenger N-acetylcysteine (NAC), the previously induced cell death was inhibited. This suggests that artesunate may exhibit its antitumor properties by inducing a form of oxidative stress-induced cell death. Wang et al [81] demonstrated that artesunate induced ferroptosis in human PC cells with a mutation in KRAS, and found that artesunate was able to increase expression of glucose-regulated protein 78 (GRP78) in PC cells. GRP78 has been suggested to be a therapeutic target for PC which can mediate metabolic reprogramming and therapeutic resistance in PC [82]. Wang et al [81] showed that PC cells with down-regulated GRP78 exhibited greater responsiveness to artesunate-induced ferroptosis when artesunate was combined with a GRP78 inhibitor. Thus, the combination of artesunate with GRP78 inhibitors may be a new direction for effective killing of KRAS-mutant PC cells.

In the process of studying natural product therapeutic targets, some new therapeutic targets have also been explored. Two enzymes, phosphodiesterase 3B (PDE3B) and Rap guanine nucleotide exchange factor 3 (RAPGEF3), are

two important enzymes in the metabolism of cyclic adenosine monophosphate (cAMP) [83, 84]. Li et al [85] extracted a natural product from the leaves of Cinnamomum pauciflorum Nees and named it as KOLR. The experimental results demonstrated that KOLR was able to promote the establishment of the RAPGEF3/PDE3B protein complex, which in turn inhibited the expression of Rap-1 protein and the activation of PI3K/AKT pathway, thus promoting apoptosis of BxCP-3 cells. This finding also suggests that the PDE3B/RAPGEF3 complex may be a potential target for future PC therapy. The natural product BE-43547A2 was found to inhibit the growth and proliferation of PC stem cells [86]. However, the specific molecular mechanisms by which it exerts anticancer activity need to be further explored. Based on the special biological activity and chemical structure of BE-43547A2, Liu et al [87] explored its anticancer targets by synthesizing a specific probe. The experimental results showed that BE-43547A2 inhibited the growth of PC stem cells in a xenograft mouse model by linking covalently to the cysteine 234 (C234) residue of eukaryotic translation elongation factor 1 alpha 1 (eEF1A1). This also suggests that eEF1A1 may be a new covalent target for future PC therapeutic research. Thus, the study of natural product-targeted therapy is of great significance for the discovery of new therapeutic targets and the development of new drugs or therapeutic strategies.

PC often shows resistance to conventional chemotherapeutic drugs, which is an important problem in the treatment of PC. The emergence of drug resistance leads to a decrease in the anticancer effect of chemotherapeutic drugs on tumor cells, thus making it difficult to achieve the desired effect of treatment [88]. In addition to some of the aforementioned natural products that have been found to have improved resistance or synergistic therapeutic effects when used in combination with conventional chemotherapeutic agents while exploring their anti-tumor mechanisms, there are also some natural products that have shown improved resistance and enhanced anti-tumor effects when used in combination with chemotherapeutic agents, which has been a great boon to the therapy of advanced PC. Curcumin, a component of Curcuma longa, is a drug that has been shown to inhibit the transcription factor nuclear factor-kappaB (NF-kappaB). Kunnumakkara et al [89] found that curcumin inhibited the proliferation of PC cell and inhibit NF-kappaB activation in PC cells thereby enhancing gemcitabine-induced apoptosis. The experimental results showed that the expression of NF-kappaB-regulated gene products such as c-myc, Bcl-2, Bcl-xL, cyclooxygenase-2, matrix metalloproteinase and vascular endothelial growth factor was suppressed in pancreatic tumors of nude mice treated with curcumin and gemcitabine. In addition to this, some natural products have been found to have properties that improve drug resistance. Michele et al [90] found in the mutant Kras and p53-expressing LSL-$Kras^{G12D/+}$; LSL-$Trp53^{R172H}$; Pdx-1-Cre mouse model of PC that the natural product Dimethylaminoparthenolide (DMAPT) may improve the resistance of PC cells to gemcitabine and enhance the effect of gemcitabine on PC by inhibiting NF-κB. Orthosiphon stamineus is a natural product from the natural product from Malaysian herbs and has been found to have some combined therapeutic effects with the chemotherapeutic agent gemcitabine [91]. Yehya et al [92] found that a standardized ethanolic extract of Orthosiphon stamineus enhanced the therapeutic effects of gemcitabine on PC cells by reducing the multidrug resistance protein family (MDR) (MDR-1, MRP-4, and MRP-5) and the epithelial-mesenchymal transition-associated molecules (ZEB-1), as well as induced expression of the human equilibrium nucleoside transporter-1 (hENT-1) gene, a gemcitabine transporter, resulted in an improvement in the resistance of PC cells to gemcitabine. Guo et al [61] found that fraxetin enhances the antitumor activity of gemcitabine and inhibits the progression of PC by antagonizing the activation of STAT3. All these findings suggest that the increased sensitivity of PC cells to chemotherapeutic drugs demonstrated by the combination of natural products with chemotherapeutic agents such as gemcitabine is a new direction for future PC treatment.

In conclusion, natural products have shown certain potential in the treatment of PC, and many natural products have demonstrated high quality anti-tumor activity in experiments. At the same time, natural products combined with traditional chemotherapeutic drugs show better therapeutic effects for PC patients, which is of great significance, and also has sig-

nificant clinical value for the future neoadjuvant therapy for PC, chemotherapy and other traditional therapies. However, more research is still needed to improve its target and specific molecular mechanism, in order to explore the optimization of therapeutic strategies, evaluate its safety, efficacy and optimal use, and bring better treatment for PC patients.

Possible mechanism of natural products inhibiting metastasis of PC

PC metastasis is closely related to epithelial-mesenchymal transition (EMT) [93]. Through EMT, PC cells can detach from the original tumor focus, invade the surrounding tissues, and eventually enter the vascular or lymphatic system for distant metastasis [94, 95]. In addition, EMT can make tumor cells resistant to treatment, leading to tumor recurrence and metastasis [96]. Studies have demonstrated that certain natural products have the biological activity to inhibit the EMT process in PC cells, which can effectively inhibit the metastasis and invasion of PC and provide new ideas for treatment [11]. Therefore, understanding the mechanism of inhibiting the development of EMT in PC by natural products is important for research and development of new therapeutic strategies.

Robinin, a flavonoid enriched in cowpea leaves [97], inhibits the up-regulated expression of TLR2 and TLR4, thereby attenuating inflammation and immune responses [98]. Zhang et al [99] found that after Robinin treatment, the TLR2 protein, a member of the toll-like receptor family, which is closely related to its invasive ability in PC cells, and its downstream PI3k/ATK signaling pathway were significantly inhibited, causing an arrest of the EMT process in MiaPACA2 and PANC-1 cells, which in turn mediated a decrease in tumor metastasis. Meanwhile, Tosendanin (TSN) is a triterpenoid compound that possesses a variety of antitumor effects, such as in vitro against breast [100] and ovarian cancers [101]. The in vivo and in vitro findings of Pei et al [32] demonstrated that the phosphorylation index of the AktS473 and PRAS40T246 sites in PANC-1 and AsPC-1 cells was significantly reduced in the presence of neem. This suggests that TSN inhibits EMT in PC cells by suppressing the Akt/mTOR signaling pathway, which leads to its excellent anti-tumor metastatic activity. In addition, naringenin also has a certain anti-metastatic ability, Lou et al [102] found that the expression of EMT-related proteins, such as N-cadherin, MMP2 and MMP9, decreased in human PC cell lines exposed to naringenin treatment, and further studies showed that naringenin was able to suppress the EMT process by inhibiting the TGF-β1/Smad3 signaling pathway in PC cells. Of course, Chinese propolis (CP), as a hive product rich in flavonoids, also has some anticancer effects. Tao et al [103] applied CP to the human PC cell line Panc-1 and found that CP inhibited the migration of Panc-1 cells by regulating EMT. Meanwhile, Hippo-YAP Pathway was found to be activated in PC cells, which may be one of the mechanisms by which CP exerts its anti-metastatic effects. Hydroxychavicol (HC) was also found to inhibit migration and invasion of PC cells by extensively suppressing genes involved in EMT [104]. These discoveries indicate that certain natural products may serve as a novel strategy for treating metastatic PC (**Figure 2**).

Anti-angiogenic mechanisms of natural products against PC

Angiogenesis refers to the process by which tumor cells can obtain more nutrient and oxygen supply by promoting the formation of new blood vessels, which also facilitates the metastasis of tumor cells to other sites through blood circulation. Therefore, interventions targeting the angiogenic process of tumors have become one of the important strategies in tumor therapy [105].

The anti-angiogenic effect of natural products on PC is a hot topic in recent years. Natural products exert their anti-angiogenic properties mainly by inhibiting the expression of VEGF and NF-κB, as well as inhibiting the growth of vascular endothelial cells, etc. Naringenin, a flavonoid natural product mentioned above, has a certain anti-angiogenic effect while inhibiting the development of PC cells. Li et al [26] showed that naringenin has anti-angiogenic activity both in vivo and in vitro. There are four possible mechanisms for naringenin to inhibit angiogenesis. Firstly, angiogenesis is inhibited by inducing cell cycle arrest in the G0/G1 phase of vascular endothelial cells, leading to apoptosis; By inhibiting the secretion of inflammatory cytokines, such as IL-6 and MCP-1, which

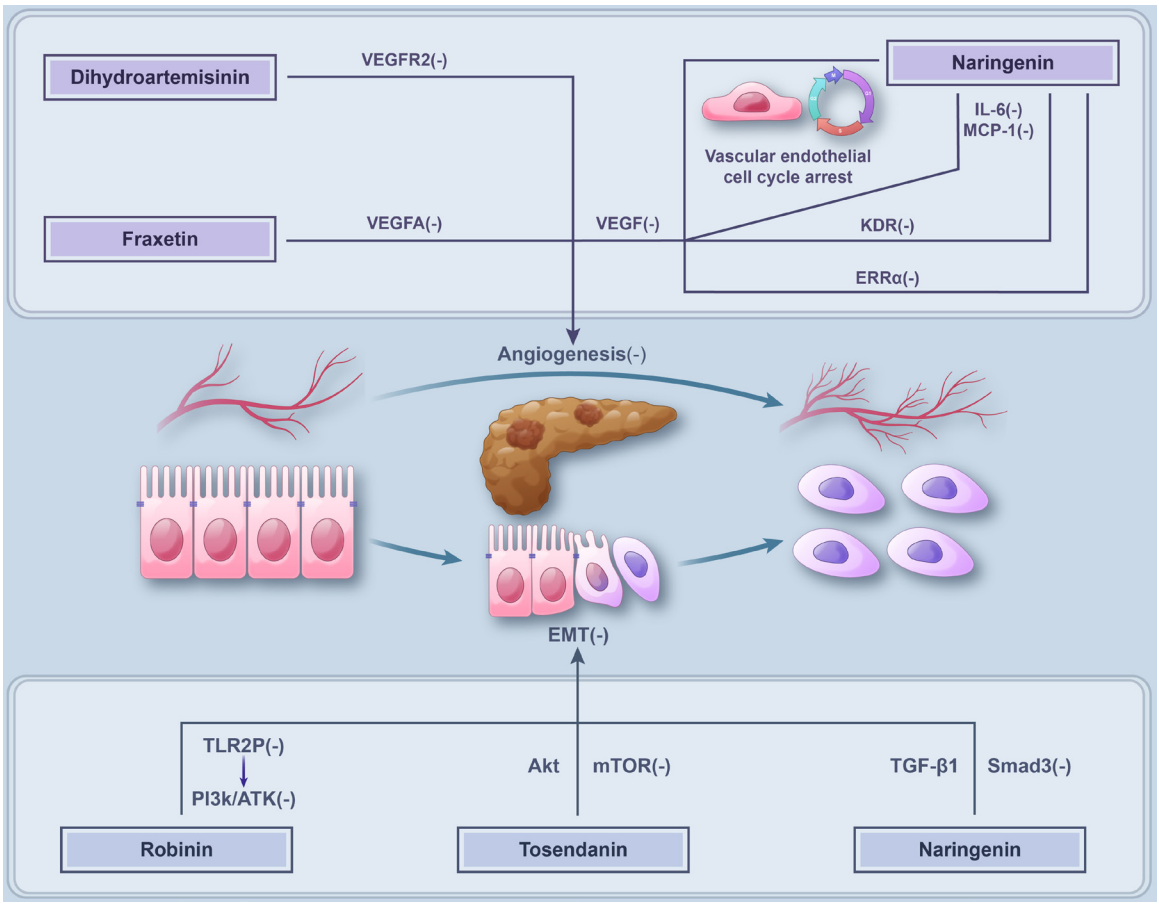

Figure 2. Possible mechanism of natural products inhibiting metastasis and Anti-angiogenic of PC. Natural products inhibit metastasis by inhibiting the EMT process of PC. Robinin inhibits the expression of TLR2P and then inhibits the PI3k/ATK pathway, resulting in the inhibition of EMT in PC. Tosendanin inhibits PC EMT by inhibiting Akt/mTOR pathway. Naringenin inhibits PC EMT by inhibiting TGF-β1/Smad3 pathway. Natural products inhibit tumour angiogenesis by inhibiting the expression of VEGF and its receptors. Naringenin inhibits VEGF production and mediates its anti-angiogenic effects by inducing cell cycle arrest in vascular endothelial cells at the G0/G1 phase; by inhibiting the secretion of inflammatory cytokines (e.g., IL-6 and MCP-1); by inhibiting KDR; and by down-regulating ERRα. Triptolide inhibits VEGF expression while DHA inhibits VEGFR2 expression to suppress angiogenesis.

reduces the interactions between angiogenic factors (HIF-1α and VEGF) and inflammatory mediators; And by directly inhibiting the tyrosine kinase activity of the vascular endothelial growth factor receptor (KDR) and inhibiting the phosphorylation of related cytokines in the downstream signaling cascade pathway, such as FAK and Akt; And also inhibit the production of VEGF through the down-regulation of estrogen receptor α (ERRα) to mediate its anti-angiogenic effect. Therefore, the anti-angiogenic effect of naringenin may be a future therapeutic approach against PC. Meanwhile, triptolide also has a certain anti-angiogenic effect on PC cells. Some studies have shown that triptolide can inhibit angiogenesis by suppressing the expression of VEGF in PC cells [106, 107]. And Ma et al [108] also found a substantial reduction in the expression of VEGF and COX-2 in PC cells treated with triptolide, which inhibited angiogenesis while enhancing the intensity of autophagy signaling in PC tissues. In addition, Feng et al [109] found DHA also has strong anti-angiogenic activity. They established a model of hypoxia-induced retinal neovascularization in mice and found that DHA could specifically down-regulate the expression of VEGFR2 in endothelial cells by preventing the nuclear translocation of NF-κB p65, thus exhibiting certain anti-vascular properties. Thus, DHA may be used as an ideal candidate as an angiogenesis inhibitor for cancer treatment. Guo et al [61]

found that the natural product fraxetin impeded hypoxia-induced angiogenesis in PC tissues by reducing the expression of HIF-1α and VEGFA to show its special anti-angiogenic effect. This shows that the anti-angiogenic property of natural products is one of the important manifestations of their anti-tumor activity, which is an important issue for future research in the field of PC treatment (**Figure 2**).

Limitations and future directions of natural products in PDAC treatment research

Challenges and opportunities exist in the research of natural products in PC treatment. While natural products show their high-quality anti-tumor properties, some of their own limitations should not be ignored. Thus, more detailed research of natural products in the future will clarify their anti-tumor molecular mechanisms, improve their own limitations, and achieve better therapeutic effects through the combination of multiple therapeutic means.

Limitations of natural products in clinical applications

Natural products have some limitations in clinical applications. Many natural products are complex mixtures containing multiple active ingredients. This increases the difficulty of controlling and standardizing their content and quality. These complexities make it more difficult for natural products to be manufactured and used [110]. Secondly, certain natural products may face difficulties and high costs in collection and extraction. Some plants may be available only in specific geographical areas or during specific seasons, which limits their continued availability [111]. At the same time, the active ingredients of natural products may vary significantly between different plants, animals or microorganisms. This variability makes it more challenging to standardize and promote the use of their active ingredients [112]. In addition, some natural products may have unstable pharmacokinetic properties in the body, such as the timing and rate of absorption, distribution, metabolism and excretion. These properties may give inconsistent or unpredictable effects in clinical applications [113]. Finally, although natural products are generally considered to be relatively safe, some may have potential toxicity or side effects. This includes potential risks to specific populations, such as pregnant women, children, or patients with long-term chronic diseases. Therefore, their safety and potential risks need to be carefully assessed in clinical applications [114]. Despite these limitations, natural products have the potential for a wide range of clinical applications. Through further research and development, these limitations can be overcome and the effectiveness and safety of natural products in clinical applications can be improved.

Future directions for natural products in PDAC research

The huge treasure trove of natural products has received extensive attention from researchers in recent years, and the excellent antitumor activities they exhibit have been widely studied in the field of PC therapy. With the advancement of science and technology, high-throughput screening and advanced natural product extraction techniques enable more rapid discovery and extraction of new natural products, which can be used to search for new compounds with anti-PC activity by screening and analyzing natural product libraries [115, 116]. Combining natural products with modern medical technology to develop new therapeutic strategies. For example, the use of nano drug carriers to deliver natural products to PC cells to improve drug efficacy and reduce side effects [117, 118]. Meanwhile, for natural products known to have anti-PC activity, further study of their mechanisms of action to understand how they affect PC progression will provide a basis for the optimization and improvement of natural products. The exploration of specific molecular mechanisms is of great clinical value for targeted therapy of PC and avoidance of side effects. The combination of natural products and other therapeutic means to explore the personalized treatment system for patients may be the future research direction of PC treatment. This kind of comprehensive treatment can utilize the advantages of different treatments and improve the therapeutic effect. For example, natural products can be used in combination with traditional drugs to enhance the therapeutic effect or reduce drug side effects [119]. Based on the well-established mechanism of natural products against PC, and the research evidence that the antitumor effects of many natural products are fur-

ther enhanced by combination therapy with chemotherapeutic agents, a variety of natural products with anti-PC activity can be combined and further applied in combination with conventional chemotherapeutic agents to achieve better therapeutic effects such as enhanced efficacy, reduced drug resistance, and fewer side effects. Natural products can also be used to enhance immunity, reduce side effects of PC treatment and improve quality of life [120]. In conclusion, the development and application of natural products will be of great value in PC research in the future. Through more detailed scientific research and further clinical trials, it has been proved that natural products may is emerging as a new strategy with great promise for the therapy of PC. Their combined application with other therapeutic means may also be able to provide patients with more comprehensive and personalized treatment plans and achieve better therapeutic effects.

Conclusions and prospects

In recent years, the exploration of natural products in the therapy of PC has become one of the focuses of research. PC is a challenging malignancy to treat and is associated with a grim prognosis. As one of the sources of drugs, natural products have diverse chemical structures and biological activities, and have been widely studied for use in PC treatment. For example, paclitaxel is a natural product derived from the Pacific yew tree. In PC treatment, paclitaxel can inhibit tumor development by blocking the division and growth of tumor cells. A few clinical trials have shown that paclitaxel has shown good therapeutic effects in the treatment of PC [15, 121, 122]. It has also been used in combination with gemcitabine or 5-Fluorouracil in chemotherapy regimens for advanced PC [123].

Natural products have shown great potential in PC therapy. The results of many studies listed in this paper show that some natural products can mediate their antiproliferative activity by targeting the proliferation-regulating signaling pathway of PC stem cells, inducing PC cell cycle arrest, and promoting apoptosis and autophagy of PC cells, etc.; they can also mediate their antiangiogenic effect by targeting the angiogenesis-related pathway; and they can mediate their anti-metastatic effect by regulating the EMT process of PC cells through the signaling pathway related to the tumors. It can also inhibit the EMT process of PC cells by regulating tumor-related signaling pathways to mediate its anti-metastatic effects, and its diverse antitumor activities have brought great benefits to patients with advanced PC. However, the specific molecular mechanisms behind the excellent anti-PC activities exhibited by natural products have yet to be further explored, and their enormous regulatory networks against inhibiting PC development may be the future hotspots of natural products in the field of PC therapeutic research. Only by further exploring the specific mechanism of inhibiting the growth and proliferation of PC by natural products can we prepare clinical drugs with stronger targeting, more stable biological activity and better therapeutic effect. In addition, these natural products can not only be used as single drug regimens for PC treatment, but also as adjuvants to chemotherapeutic drugs to enhance their antitumor efficacy and reduce side effects. The mechanism behind the stronger anti-tumor efficacy of natural products in combination with traditional chemotherapeutic drugs needs to be further investigated, whether it is due to the superimposed anti-tumor effects of both, the synergistic effect of signaling pathway regulation in the specific molecular mechanism of anti-tumor, or whether the natural products may improve the resistance of PC cells to the traditional chemotherapeutic drugs and thus show a better therapeutic effect. The mechanism of action of multiple therapeutic means in combination will be of great clinical significance for the development of future therapeutic strategies and programs for PC patients.

Of course, the limitations of natural products in the therapeutic application of PC should not be ignored, and more basic and clinical experiments targeting their antitumor mechanisms and exploring the optimization of Biological extraction technology may be important means to improve their limitations. Meanwhile, even though natural products have demonstrated high-quality antitumor activities in basic experiments and animal models, the clinical effects of many natural products in human PC treatment still need more validation. The lack of large-scale clinical trial data limits our understanding of their safety and efficacy. In the future, the development of natural products in

PC research and clinical applications is promising. With in-depth research on the anti-tumor mechanisms of natural products, we are expected to discover more natural products with potential anti-tumor activity and to better understand their mechanisms of action. At the same time, with the continuous progress of technology, we can use biotechnological means to modify and optimize natural products to improve their anti-tumor activity and bioavailability. In addition, with the development of clinical trials, we are expected to verify the safety and efficacy of natural products in the treatment of human PC, providing a more reliable basis for their clinical application. In conclusion, natural products show great potential in PC treatment and have great research exploration space as well as future development prospects. Further exploration of the specific anti-tumor molecular mechanism of PC, optimization of purification and preparation techniques, and enrichment of clinical trials will bring us new hopes and opportunities.

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Disclosure of conflict of interest

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