Review

The Importance of Bioactive Compounds and Plant Extracts in the Treatment of Pancreatic Cancer

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The Importance of Bioactive Compounds and Plant Extracts in the Treatment of Pancreatic Cancer

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Abstract: Pancreatic cancer is a serious and aggressive type of cancer that affects the digestive system and has a low chance of survival. Although traditional treatment methods have achieved some efficacy, the survival rate of patients remains low. Therefore, exploring novel treatment strategies is important. This article looks at the research done on bioactive compounds and plant extracts for treating pancreatic cancer. Bioactive compounds, such as naringenin and ziyuglycoside II, have significant anticancer activity and exert anti-pancreatic-cancer effects by inducing cell apoptosis, inhibiting the cell cycle, and blocking signaling pathways. Plant extracts, such as epigallocatechin-3-gallate and resveratrol, also demonstrate good anti-pancreatic cancer activity and inhibit tumor growth and metastasis. Additionally, the combined application of bioactive compounds and plant extracts may result in improved therapeutic effects. This article aims to provide a theoretical basis for the application of bioactive compounds and plant extracts in the treatment of pancreatic cancer and to help guide future medical research and practice.

Keywords: pancreatic cancer; bioactive compounds; plant extracts; molecular pathways; antitumor activity; treatment

1. Introduction

Pancreatic cancer is a very aggressive and harmful tumor. that often presents significant challenges during clinical treatment [1]. Common treatments like chemotherapy, radiation therapy, and surgery, do not yield satisfactory results for the care for pancreatic cancer. The chance of surviving for 5 years after being diagnosed with pancreatic cancer is just 10%. This shows that we really need to find new ways to treat this disease. [2,3]. Bioactive compounds and plant extracts have received a lot of attention because of their natural sources, fewer toxic side effects, and diverse biological activities, and thus, they show great potential to become a new choice for treating pancreatic cancer [4,5].

Recently, researchers have made a series of major advances in pancreatic cancer treatment. Bioactive compounds and plant extracts have attracted considerable attention [6]. These natural products are rich in various cytokines, enzymes, antioxidants, and anti-tumor active ingredients, and show multiple biological activities, such as inhibiting tumor growth, promoting apoptosis, and regulating immune responses [7–11]. Some substances like caffeine, resveratrol, and baicalein have been found to be effective in slowing down pancreatic cancer cells. This gives new ideas for treating pancreatic cancer [12–14].

Overall, the importance of bioactive compounds and plant extracts for pancreatic cancer treatment cannot be underestimated [15]. Their unique mechanisms and diverse biological activities provide new strategies and ideas for treating pancreatic cancer, making them potentially significant components of the future treatment regimes. Therefore, further research on how bioactive compounds and plant extracts work in pancreatic cancer may bring new vitality to conventional treatment methods, offering patients more hope and opportunities [16–19].

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2. Bioactive Compounds and Plant Extracts

2.1. Definition and Classification of Bioactive Compounds and Plant Extracts

Biologically active compounds and plant extracts are collective terms for various Natural substances that can be sorted by their chemical makeup and where they come from in nature. The most common types of compounds studied in tumors include polyphenols (among which flavonoids, phenolic acids, and lignans are the most common subclasses), saponins, alkaloids, quinones, terpenes, and polysaccharides [20–22]. These compounds have different effects on the body, like reducing inflammation, fighting damage from free radicals, and helping to prevent cancer, playing various physiological and pharmacological roles in organisms [23,24]. They can be taken from plants, animals, and tiny living things, and are used in medicine, food, and beauty products [25,26].

Polyphenols are a class of polymers with multiple hydroxyl groups. They are mostly found in the fruits, leaves, and seeds of plants and have benefits like fighting against oxidation, reducing inflammation, and killing bacteria [27]. Flavonoids are a type of chemical found in many fruits, vegetables, and Chinese herbal medicines. They have several hydroxyl (OH) groups and are known for their health benefits, such as reducing inflammation, fighting free radicals, and helping to prevent cancer[28,29]. Phenolic acid compounds are widely present in the leaves, fruits, and seeds of plants, especially citrus fruits, tea leaves, olive oil, and certain herbs. Phenolic acids help reduce inflammation, fight germs, and protect against cancer. They can be used to help prevent and treat heart diseases, cancer, and diabetes [30,31]. Lignan compounds mainly exist in the woody tissues of plants, especially in conifers, such as pine and spruce. Lignans have anti-inflammatory, antibacterial, antiviral, and anticancer effects and can be used to treat different illnesses, like heart diseases, cancers, and viral infections [32–34]. Saponins mainly exist in the roots, stems, and fruits of plants, especially in Chinese medicinal herbs, such as ginseng, licorice, and astragalus. Saponins have anti-inflammatory, antibacterial, anticancer, immunomodulatory, and liver-protective effects and can be used to treat various diseases, such as cardiovascular diseases, cancers, and hepatitis [35–37]. Alkaloids are organic compounds with nitrogen atom skeletons, mainly found in the roots, stems, and flowers of plants. They have antibacterial, anti-inflammatory, and anticancer activities [38–40]. Quinone compounds are mainly present in the leaves, roots, and fruits of plants, particularly tea leaves, Chinese herbal medicines, and other natural plant products. In medicine, quinone compounds have antioxidant, anti-inflammatory, antibacterial, and antiviral effects and can help treat different illnesses like heart problems, cancers, and diabetes [41–43]. Terpene compounds are a class of heterocyclic compounds with multiple isoprene units that are mostly found in the roots, stems, and leaves of plants. They show biological activities, like reducing inflammation, easing pain, and fighting cancer[44–46]. Polysaccharides are big molecules made up of many smaller sugar units linked together by special bonds. Natural polysaccharides are commonly found in plants, animals, and microorganisms, and have activities such as antiviral, anticancer, antioxidant, immunomodulatory, blood-glucose-lowering activities [47–49].

Biologically active compounds and plant extracts play various physiological and pharmacological roles in the human body. For example, they can alleviate inflammation by inhibiting the release of inflammatory factors, prevent oxidative stress by scavenging free radicals, and help fight cancer by stopping tumor cells from growing and spreading [50–52]. Therefore, research and utilization of these compounds are of great significance for human health and disease treatment.

2.2. Mechanisms of Action of Bioactive Compounds and Plant Extracts in the Treatment of Pancreatic Cancer

This article explains how these natural compounds and plant extracts work to help treat pancreatic cancer, including slowing down tumor growth, encouraging cell death in tumors, preventing the formation of new blood vessels in tumors, and controlling the immune system's reactions. In addition, we analyze the specific effects and research progress of various compounds in pancreatic cancer treatment.

2.2.1. Polyphenols

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Polyphenolic bioactive compounds and plant extracts have been very effective in fighting pancreatic cancer, and they work in several ways. First, polyphenolic compounds can help fight tumors by stopping tumor cells from growing through their natural actions [53]. They can regulate the behavior of the tumor microenvironment, indirectly slow down the growth and spread of tumor cells, and lower the multiplication rate of cancer cells, thereby slowing the growth and spread of tumors [54].

Second, polyphenolic compounds also have an important part in promoting apoptosis [55,56]. By regulating multiple apoptosis-related genes or pathways, these compounds can cause the apoptosis of cancer cells, leading to the self-destruction of cancer cells, thereby stopping tumors from growing and spreading [57–59]. This mechanism of promoting apoptosis helps eliminate abnormal cells and maintain the balance of normal cell ecology [60–63].

Furthermore, polyphenolic compounds also have the ability to inhibit tumor angiogenesis [64]. They can interfere with the process of tumor angiogenesis, limit blood supply to tumors, and block the source of nutrients for tumors, thereby inhibiting tumor development [65]. Inhibiting tumor angiogenesis is an important therapeutic strategy that helps control tumor growth and spread [66–68].

Polyphenolic compounds also affect tumor development by regulating immune responses [69,70]. Activating immune cells against tumor cells enhances the body's immune surveillance of tumors, inhibiting their growth and spread [71]. This mechanism of regulating immune responses is crucial for enhancing the ability of the body to fight tumors. They can also enhance the immune response [72–74].

2.2.1.1. Polyphenolic compounds and pancreatic cancer

Researchers are quickly looking for polyphenolic compounds to help treat pancreatic cancer. Some compounds, like catechins and resveratrol, can help prevent pancreatic cancer cells from growing and are considered important in cancer research [75–78]. Future research will further explore how polyphenols work to help treat pancreatic cancer, seek more potential anti-tumor candidates, and give better treatment choices for people with pancreatic cancer [79–81]. Some specific examples of recent research on polyphenolic compounds and pancreatic cancer are as follows.

PGG (a natural compound made from sugar and found in plants) works against a protein called UBE2T. When used together with a drug called gemcitabine, it greatly slows down the growth of humanized pancreatic cancer organoids and xenograft model tumors and prolongs the long-term survival of mice spontaneous pancreatic cancer. A recent study targeted UBE2T to counteract gemcitabine resistance in pancreatic cancer, providing a promising treatment strategy [82].

Resveratrol is a special compound that can help slow down the growth of pancreatic cancer stem cells. It does this by blocking certain proteins (Bcl-2 and XIAP) and activating others (caspase-3 and caspase-7). This process leads to a decrease in important genes that help keep cancer cells alive, which triggers cell death (apoptosis). Resveratrol treatment stops cancer stem cells (CSCs) from moving and spreading. It also lowers the levels of certain proteins involved in a process called epithelial-mesenchymal transition (EMT), specifically Zeb-1, Slug, and Snail. Additionally, it greatly reduces the expression of a gene called ATP-binding cassette subfamily G member 2 in human pancreatic CSCs. Tests done on live mice have shown that resveratrol can reduce the size and weight of pancreatic tumors [83].

Epigallocatechin-3-gallate (EGCG) is the main healthy part of green tea. EGCG stops Akt from being activated in different ways, such as preventing the making of its instructions, stopping the creation of the protein, and stopping the breakdown of the protein. EGCG, by itself or with gemcitabine, stops the "cadherin switch" and lowers the levels of TCF8/ZEB1, vimentin, and β-catenin. This helps reduce the features of mesenchymal cells. When used together with gemcitabine, it helps slow down the movement and spread of pancreatic cancer cells by blocking a certain pathway in the cells [76].

2.2.1.2. Flavonoid compounds and pancreatic cancer

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Considerable research is being done on how flavonoid compounds can help treat pancreatic cancer. Some flavonoids, like soy isoflavones and anthocyanins, can help block pancreatic cancer cells [84–86]. Additionally, some flavonoid compounds, when used in combination with CBD and GEM, greatly extend the life of mice with pancreatic cancer [87]. Genistein, used on its own or with other cancer-fighting medications (such as cisplatin and gemcitabine), has been shown in various experiments to slow down the spread of pancreatic cancer cells and stop tumors from growing [88,89]. Flavonoid compounds are being studied a lot for their potential to fight tumors. Future studies should further look into how flavonoid compounds work to help treat pancreatic cancer, search for more potential anti-tumor candidates, and give better treatment choices for people with pancreatic cancer. Below are specific examples of recent studies on flavonoid compounds in pancreatic cancer.

A study from Dalian University of Technology and Conde Biotech in 2022 found that a flavonoid drug called wogonin can make pancreatic cancer cells more responsive to the treatment gemcitabine. A study discovered that wogonin helps to kill PANC-1 cells by blocking the AKt pathway. Using wogonin along with gemcitabine works better to stop pancreatic cancer cells than using gemcitabine by itself [90].

Recent studies using a system that analyzes cells in real-time have shown that a natural compound called fisetin can stop the growth of PANC-1 cells. The cancer-fighting effects of fisetin were tested and confirmed in a special type of mouse with pancreatic cancer. After treatment with fisetin, the AMPK/mTOR signaling pathway was stronger. However, when compound C was added, autophagy did not go down, which means there is likely another way that regulates autophagy. RNA sequencing showed an increase in the unfolded protein response pathway, which is triggered by stress in the endoplasmic reticulum (ER). Researchers discovered that after treating PANC-1 cells with fisetin, the amount of a protein called p8 went up. They also found that shutting down p8 stopped the process of autophagy that was started by fisetin. Researchers discovered that p8-dependent autophagy does not rely on AMPK. Instead, p8 controls ATF6, ATF4, and PERK using a signaling pathway that involves p53 and PKC-α when there is stress in the endoplasmic reticulum (ER). Also, problems with mitochondria are linked to Parkin and PINK1. Interestingly, the levels of ATF4 and ATF6 went up in cells that were treated with fisetin and compound C. [91].

Naringenin slows down tumor growth in several ways. It helps to trigger cell death, stops cells from growing and dividing, disrupts the formation of new blood vessels, and changes some important signaling pathways in the body, like Wnt/β-catenin, PI3K/Akt, NF-kB, and TGF-β [92].

In a study conducted in 2024, tiliroside (TIL), a glycosidic flavonoid, was discovered to successfully attach to and block the activity in CAPN2. TIL also significantly stops the production of p-AKT in PANC-1 cells, thereby impeding AKT activation and the build-up of reactive oxygen species (ROS), a process called autophagy, and a type of cell death known as ferroptosis. Therefore, the abundant presence of TIL in plant sources provides effective inhibition of CAPN2 [93].

2.2.1.3. Phenolic acid compounds and pancreatic cancer

Certain compounds called phenolic acids, like caffeic acid(CFA) and chlorogenic acid(CA), have been found to help fight pancreatic cancer. Different phenolic acid compounds may exhibit unique effects via different mechanisms [94–96]. Phenolic acid bioactive compounds and plant extracts play important roles in treating pancreatic cancer, and their different ways of working give us new ideas and approaches, offering hope for treating pancreatic cancer. More detailed studies are needed to help use these compounds for treating pancreatic cancer, understand how phenolic acid compounds work in this treatment, and make it easier to use them in medical practice. Here are some recent studies about phenolic acid compounds and pancreatic cancer.

CFA is a natural phenolic acid found in green tea, new olives, coffee, olive oil, vegetables, white wine and fruits. The cytotoxic effects of the CFA on Cells from pancreatic ductal adenocarcinoma(PDAC) have been evaluated in vitro. Additionally, CFA has been utilized as a pre-sensitizer of PDAC cells, rendering PDAC cell lines sensitive to doxorubicin treatment. Therefore,

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CFA can be used as a treatment for PDAC on its own or before chemotherapy, but not together with other treatments[97].

CA is a natural acid found in plants. CA slows down the growth of PANC-28 and PANC-1 cells, and the effect depends on how much CA is used and how long it's applied. It also prevents the growth, movement, and spreading of PANC-28 and PANC-1 cells, and it causes the cells to die. More studies have found that CA reduces the levels of AKT, p-AKT(Thr308), p-GSK-3β (Ser9), β-catenin, N-cadherin, and vimentin in PANC-28 and PANC-1 cells. At the same time, it increases the levels of cleaved caspase-3 and cleaved caspase-7 [96].

Coumaric acid has been found to decrease the amount of 3H-glutamine that Aspc-1 cells take in.. Different phenolic acids have different effects on how Aspc-1 cells take in glucose and glutamine. Gallic acid significantly inhibits the absorption of glucose in Aspc-1 pancreatic cancer cells by affecting a protein called GLUT1, providing a theoretical basis for developing novel research strategies targeting pancreatic cancer and potentially bringing about new breakthroughs in pancreatic cancer treatment [98].

2.2.1.4. Lignan compounds and pancreatic cancer

Although studies of lignan compounds in pancreatic cancer treatment are relatively limited, some research has found that compounds such as Arctigenin might help fight pancreatic cancer by stopping the growth of cancer cells [99]. Future research should explore how lignan compounds work for treating pancreatic cancer, investigate how they specifically act, and create better treatment methods. Specific examples of recent studies on lignan compounds in pancreatic cancer are discussed in this section.

A dibenzylbutyrolactone lignan called Matairesinol is comes from Forsythia fruits and a type of sea grass called *Halophila stipulacea* [100,101]. It has been confirmed that Matairesinol helps cells grow and slows down the growth of certain human pancreatic cancer cells, such as the MIA, PaCa-2, and PANC-1 types. Matairesinol also leads to cell death and harms the mitochondria, which are the energy centers of the cell. This is shown by changes in the mitochondrial membrane, problems with calcium levels, stopping cell movement, and affecting important signaling processes inside the cell. In the end, metairesinol works well with 5-fluorouracil (5-FU), which is a common cancer treatment for pancreatic ductal adenocarcinoma (PDAC). These results show that metairesinol could be useful for treating PDAC [102].

Honokalin (HNK) is a low-molecular-weight biphenolic lignan isolated from *Magnolia* plants [103]. In previous studies, we observed that HNK showed it can fight pancreatic cancer by stopping the cancer cells from growing and causing them to die [104]. A recent study found that NF-κB is a target of HNK, showing that NF-κB plays a part in how HNK helps reduce the levels of CXCR4 and SHH in pancreatic cancer cells. NF-κB is also believed to mediate the enhanced chemosensitization effect of HNK. The importance of targeting NF-κB by HNK has been confirmed, and it has been shown to lead to the downregulation of molecular mediators involved in tumor-stroma crosstalk, indicating the broader significance of the anti-tumor efficacy of HNK. HNK not as it were essentially hinders tumor development, but too smothers dangerous phenotypes, potentially being meaningful for both pancreatic cancer treatment and prevention. HNK reduces the growth of connective tissue by lowering the production of collagen type I, a protein found in the extracellular matrix, and by decreasing the presence of myofibroblasts, which are marked by a specific stain called α-SMA. CXCR4 is a receptor that interacts with a protein called CXCR12, which is also known as stromal-derived factor 1. HNK helps stop communication between tumor cells and surrounding stromal cells by controlling the CXCR4/CXCR12 system and reducing a protein called SHH. This, in turn, influences the relationship between the tumor and the surrounding tissue[105].

2.2.2. Saponins

Saponin-like compounds and plant extracts may play important roles in treating pancreatic cancer in several ways.

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Saponin-like compounds can interfere with the proliferation and division processes of pancreatic cancer cells, stopping tumor cells from growing and thus, inhibiting their spread and development [106,107]. Some studies have found that saponin-like compounds stop tumor cells from multiplying by interfering with their growth cycle and regulating cell-proliferation-related signaling pathways [108].

Saponin-like compounds also play important roles in promoting apoptosis [106]. These compounds cause cancer cells in the pancreas to die, stop the process that clears out unhealthy cells, and slow down tumor growth. [109].

In addition, saponin-like compounds have shown the potential to inhibit tumor angiogenesis. They can lower the amounts of certain substances that help new blood vessels form, which can slow down the growth of pancreatic tumors by reducing the number of blood vessels [108].

Moreover, saponin-like compounds can modulate and boost the body's defense system to fight against cancer cells [110]. They can enhance the cytotoxicity of NK cells, strengthen the immune system, improve the clearance of tumors by the immune system, and help control tumor growth and spread [111,112].

Increasing research attention is being focused on the possible benefits of saponin-like substances in treating pancreatic cancer. Some saponin-like compounds, such as *Anemarrhena asphodeloides* and ginsenosides, have been shown to have anticancer effects against tumors [113,114]. Future research should explore how saponin-like compounds work in treating pancreatic cancer, find other possible treatment targets, and encourage the use of these compounds in hospitals.

In summary, saponin-like substances and plant extracts are important in treating pancreatic cancer. They help stop tumors from growing, encourage cancer cell death, prevent the formation of new blood vessels for the tumors, and help control the immune system's response. As research continues, these compounds are likely to become useful medicines for treating pancreatic cancer, offering more hope and options for patients. The following are specific examples of recent studies of saponin-like compounds in pancreatic cancer.

Saikosaponin d (SSd) is the main active part of triterpene saponins. SSd can help stop the death and spread of pancreatic cancer cells, improve the immune environment, and boost local immune responses. It does this mainly by reducing the levels of a protein called phosphorylated STAT6 and affecting a signaling pathway known as PI3K/AKT/mTOR, thereby reducing the transition of macrophages to M2 polarization [115].

Panax notoginseng saponins not only stops the growth, movement, and spread of Miapaca 2 and PANC-1 cells, but also causes pancreatic cancer cells to undergo programmed cell death (apoptosis) and makes these cancer cells more sensitive to Gem chemotherapy [109]. Importantly, *Panax notoginseng* saponins can promote apoptosis and chemical sensitivity to gemcitabine through a caspase-dependent pathway, and gold nanoparticles derived from the leaves of *Panax notoginseng* have been shown to have anti-pancreatic-cancer activity [98,116].

Paraphylaxis Rhizoma, a traditional chinese medicine that contains active components, such as steroidal saponins (e.g., polyphyllin I, II, VI, and VII), significantly inhibits the proliferation of PDAC cells and changes their morphology. It also helps to move lactate dehydrogenase from PANC-1 cells into the space outside the cells. PI staining showed that PPI/CCRIS/PSV made the membranes of PANC-1 cells more permeable and helped break down PANC-1 cells through the caspase-3/GSDME pathway. It greatly slows down the growth of skin tumors in mice with weak immune systems by triggering a type of cell death called GSDME-dependent pyroptosis[117].

Ziyuglycoside II (ZYG II) is an important active part of the Sanguisorba officinalis L plant extracts. It has a strong effect on PANC-1 pancreatic cancer cells by stopping their growth, causing stress in the cells, leading them to die in a certain way (mitochondrial apoptosis), and affecting a specific signaling pathway (EGFR). ZYG II works together with the cancer drug 5-FU to help stop cancer cells from growing [118].

Polyphyllin D, a monomer of polyphyllin, slows down the growth of PANC-1 cells depending on how much is used and how long it is applied; blocks cells in the S and G2/M phases in a concentration-dependent way; significantly reduces the activity of cellular matrix metalloproteinases;

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and induces apoptosis by upregulating Bax, Cyto C, cleaved caspase-3, and cleaved caspase-9 protein expression levels and downregulating Bcl-2 expression levels. This suggests that polyphyllin D effectively represses the multiplication of PANC-1 cells by blocking the cell development cycle and actuating apoptosis through the mitochondrial pathway [119]. Escin is a natural mix of certain compounds taken from horse chestnut. Escin boosts the ability of gemcitabine to stop the growth and kill cells in BxPC-3 and PANC-1 cell lines. It also greatly increases gemcitabine's ability to slow down tumor growth in mice without immune systems. It works by partly blocking the activity of NF-kB. It also reduces the levels of proteins like C-Myc, COX-2, cyclin D1, survivin, Bcl-2, and Bcl-xL, while activating caspase-3 [120].

Pulsatilla, a traditional herbal medicine, has yielded active compounds such as *Pulsatilla* saponins A and D. *Pulsatilla* saponin A significantly stops pancreatic cancer cells from growing, BXPC3 and SW1990 cell lines, and the treated cells exhibit DNA damage, G2 blockade, and apoptosis. The levels of P53 and cyclin B proteins are greater in cells given anemonin-A than in those given a control treatment. In contrast, there is less Bcl-2 protein in cells that were treated with Pulsatilla saponin A compared to the cells that were not treated[121]. *Pulsatilla* saponin D (SB365) greatly stops the growth and spread of five types of human pancreatic cancer cells (MIAPaCa-2, BXPC-3, PANC-1, AsPC-1, and HPAC). The effect of SB365 in causing cell death shows as higher levels of caspase-3, a loss of mitochondrial energy, lower levels of Bcl-2, and more cells that are dying (identified by TUNEL staining). SB365 helps stop the growth of new blood vessels by lowering the levels of important factors that promote this growth, specifically HIF-1α and VEGF. This effect is also shown by its ability to prevent the formation of pancreatic cancer tumor clusters. Studies in mice with xenografts have shown that SB365 inhibits tumor growth by inducing apoptosis and inhibiting angiogenesis, demonstrating strong anticancer activity. Therefore, SB365 is a hopeful natural treatment for pancreatic cancer [106].

2.2.3. Alkaloids

Alkaloid bioactive compounds and plant extracts works in special ways to treat pancreatic cancer. This includes stopping tumors from growing, helping cancer cells die, preventing new blood vessels from forming in tumors, and managing the immune system's response. The unique structures of these compounds make them potentially valuable for treating pancreatic cancer.

First, alkaloid compounds exert antitumor effects by inhibiting tumor growth [122]. These compounds stop cancer cells from growing and changing, and slows down how quickly they multiply., thereby slowing tumor growth and spread [123]. Moreover, alkaloid compounds can stop tumors from growing and spreading by causing pancreatic cancer cells to kill themselves [124].

Second, alkaloid compounds play an important role in inhibiting tumor angiogenesis [125]. They can stop the growth of blood vessels in tumors and lower the blood supply to tumors, which helps to slow down tumor growth [126].

In addition, alkaloid compounds can affect tumor development by regulating immune responses. They help immune cells live, change, activate, and move, which makes immunotherapy work better. This can help get past resistance to treatment and slow down tumor growth by managing the body's immune response to tumors. They can also show a synergistic anti-tumor immune response and can inhibit the anti-tumor immune response. [127]

Research on alkaloid compounds for pancreatic cancer is moving forward quickly. Some alkaloid compounds, such as vinca alkaloids and camptothecin, help to slow down pancreatic cancer cells [128,129]. The FDA has given FL118, which comes from camptothecin, a special status as an orphan drug to treat pancreatic cancer. Future studies will look more into how alkaloid compounds work to treat pancreatic cancer. They will look for new substances that could fight tumors and aim to find better treatment options for patients with pancreatic cancer[130]. With the continuous increase in research, these compounds are expected to become important drugs for pancreatic cancer. Recently, there have been some studies on alkaloid compounds and pancreatic cancer, which are explained below.

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The alkaloid component, dehydroevodiamine (DeHE), derived from the Chinese medicine Evodiae fructus, slows down the growth and spread of pancreatic cancer cells in lab tests and in living organisms.. In particular, it effectively prevents the growth of pancreatic cancer stem cells and stops tumor cells from acting like stem cells, revealing that its molecular mechanism acts by targeting intracellular DDIT3 (endoplasmic reticulum stress protein) and regulating the downstream DDIT3/TRIB3/AKT/mTOR signaling pathway [131].

Professor Suresh Awale from Japan, in collaboration with Professor Gerhard Bringmann from Germany, studied a substance called ancistrolikokine E3, which was extracted from the vine, *Ancistrocladus likoko*, from a rainforest in the Democratic Republic of the Congo. They found that ancistrolikokine E3 causes "significant changes" in cancer cell morphology, ultimately leading to massive death. This compound inhibits the AKT/mTOR and autophagy processes in cancer cells, which would otherwise enable cancer cells to survive in harsh tumor microenvironments. Furthermore, vine-derived compounds prevented the movement and growth of cancer cells in the pancreas. This suggests that at certain doses, this compound can prevent metastasis, as it also stops the production of important proteins needed for a process called autophagy, which includes Atg5, Atg12, Beclin-1, LC3-I, and LC3-II. These results show that ancistrolikokine E3 is important in the early stages of autophagy in PANC-1 human pancreatic cancer cells [132].

Tomatidine is a naturally steroidal alkaloid. Tomatidine treatment slows down tumor growth in pancreatic cancer cells both in the lab and in living organisms. Tomatidine inhibits the nuclear translocation of ATF4, reduces ATF4 binding to downstream promoters, and enhances chemical sensitivity to gemcitabine in three-dimensional extracellular matrix hydrogels and *in vivo*. Tomatidine treatment leads to a type of cell death that depends on iron. This is shown by higher levels of lipid damage, increased production of new mitochondria, and lower levels of a protein called GPX4 in pancreatic cancer cells [133].

2.2.4. Quinones

Quinone bioactive compounds and plant extracts have shown potential in the treatment of pancreatic cancer, with various mechanisms. Quinone compounds help fight tumors by stopping tumor cells from multiplying and growing [134]. These compounds can disrupt tumor cells's metabolic pathways, control the cell cycle, and inhibit the apoptosis and proliferation of tumor cells, thus inhibiting tumor growth and spread [135,136].

Quinone compounds can help kill cancer cells. These substances can cause cancer cells to die by changing the processes that control cell death and by affecting the genes involved in this process. This helps speed up the death of unhealthy cells and can slow down the growth of tumors [137,138].

In addition, quinone compounds have important roles in the inhibition of tumor angiogenesis. They can interfere with tumor angiogenesis and prevent tumor cells from receiving a supply of oxygen and nutrients, thereby limiting tumor growth. These compounds effectively block the development and metastasis of tumors by inhibiting angiogenesis [139].

Furthermore, quinone compounds can regulate immune responses and enhance the body's anti-tumor immune response [140].

Some quinone compounds, such as anthraquinones and anthraquinone alkaloids, have been shown to help fight pancreatic cancer [141,142]. Overall, quinone bioactive compounds and plant extracts have shown significant value in pancreatic cancer, and their different ways of working have provided new treatment strategies and choices. Future studies should keep looking into how quinone compounds can help treat pancreatic cancer to create better treatment options. Below are specific examples of recent studies of quinone compounds in pancreatic cancer.

Alizarin, a quinone compound derived from madder root [143], stops TNF-α from activating NF-κB by blocking the TAK1/TAB1 complex and preventing the IKKα/β-IκBα-NF-κB signaling pathway. This also reduces the levels of NF-κB target genes like Bcl-2, Bcl-xL, XIAP, TARF2, cyclin D, and c-Myc. In a study using mice with pancreatic cancer, a treatment that included alizarin and gemcitabine greatly slowed down the growth of cancer cells in the mice's pancreas by blocking NF-

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κB activation, without significant liver or kidney damage. This suggests that alizarin may make pancreatic cancer treatment work better, either by itself or along with chemotherapy [143].

Last year, it was discovered that the simple derivative of plumbagin, 3f, caused changes in the morphology of PANC-1 cells and cell death compared to the control group, 24 hours after administration at 1 μM, indicating that compound 3f caused changes in the shape of PANC-1 cells, which led to cell death. After giving compound 3f at doses of 0. 5, 1, 5, and 10 μM for 3 and 6 hours, we checked the levels of certain proteins: PI3K (p110α, p110β), Akt, p-Akt (ser 473), mTOR, and p-mTOR. We found that compound 3f stopped the activation of the PI3K/Akt/mTOR signaling pathway, and this effect depended on the time and the amount used. In a mouse model with MIA PaCa-2 cancer cells, compound 3f showed strong anti-tumor effects at both low and high amounts. In summary, compound 3f could be a promising treatment for pancreatic cancer and should be studied more [135].

Thymoquinone, plumbagin, and juglone are naturally occurring quinones that significantly stop PANC-1 cells from growing and cause ROS-mediated apoptosis, and exhibit anti-migratory effects in PANC-1 cells, potentially serving as effective anti-metastatic drugs [84].

Dihydrotanshinone I (DHT), a liposoluble compound belonging to the phenanthrene quinone family, inhibits the EMT, invasion, proliferation, and migration abilities of Patu8988 and PANC-1 cells through the hedgehog/Gli signaling pathway. Additionally, it induces apoptosis via the caspase/BCL2/BAX signaling pathway. Tumor transplantation experiments in mice demonstrated the anticancer effects of DHT in vivo [144].

2.2.5. Terpenes

Terpenoid bioactive compounds and plant extracts are important in the treatment of pancreatic cancer through mechanisms such as slowing down tumor growth, encouraging cell death, blocking the formation of new blood vessels for tumors, and managing immune system responses [145,146].

Terpenoid compounds help fight tumors by stopping them from growing. [147]. They can trigger autophagy, a process in cells that helps break down damaged proteins and parts; inhibit tumor growth; and reduce cancer cell proliferation rates, thereby slowing tumor growth and spread [148]. Terpenoid compounds like paclitaxel and docetaxel are commonly used to treat different types of cancer, including pancreatic cancer [149,150].

Terpenoids also play crucial roles in promoting apoptosis [148,151]. They can stop tumor cells from growing, help them die off, and control different signaling pathways, like EMT, PTEN/PI3K/Akt, NF-kB, and Wnt/beta-catenin pathways [152]. This mechanism of promoting apoptosis helps eliminate abnormal cells and maintain the balance of normal cell ecology.

Terpenoid compounds are involved in tumor angiogenesis [153]. They can interfere with the process of tumor angiogenesis, limit tumor blood supply, and block the tumor's source of nutrients, thereby inhibiting tumor development. Stopping tumors from forming new blood vessels is an important way to help keep tumors from growing and spreading [154].

Terpenoid compounds can also affect tumor development by regulating immune responses [155]. They can enhance the body's immune response, activate immune cells against tumor cells, strengthen the body's immunosurveillance of tumors, and help inhibit tumor growth and spread [156]. This mechanism of regulating immune responses is crucial for enhancing the ability of the body to resist tumors [157].

Currently, research progress on terpenoid compounds for pancreatic cancer is progressing quickly, with findings showing that terpenoid compounds act on various signaling pathways in pancreatic cancer [158]. Some terpenoid compounds, such as paclitaxel and elemene, have been shown to slow down pancreatic cancer cells, attracting interest in cancer research [159,160]. Future research should look more into how terpenoid compounds work in treating pancreatic cancer. The goal is to find more substances that could help fight tumors and offer better treatment choices for pancreatic cancer patients. Following are specific examples of recent studies of terpenoid compounds in pancreatic cancer.

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Xanthatin, a sesquiterpene lactone monomer, may stop the growth of pancreatic cancer cells and cause them to die using the ROS/RBL1 signaling pathway [161].

Umbelliprenin (UMB) is a type of natural compound found in the plant Artemisia absinthium L. UMB greatly slows down the growth of pancreatic cancer cells both in the lab and in living organisms. It can also cause cell death and protect cells by blocking a specific signaling pathway called Akt. UMB lowers the number of pancreatic cancer stem cells by blocking the Notch1 signaling pathway. This indicated that UMB combined with 3-MA has great potential as an adjuvant therapy for pancreatic cancer [162].

Five new sesquiterpenoid compounds and 15 already known analogs were found in the methanol extracts of the roots and underground stems of Nardostachys jatamansi. The separate compounds were toxic to human pancreatic cancer cells (CFPAC-1, PANC-1, CAPAN-2, and SW1990). Preliminary mechanistic studies of nardostachin suggested that It triggers cell death through a process that depends on the mitochondria and stops SW1900 cells from going past the G2/M phase[163].

2.2.6. Polysaccharides

Natural polysaccharides help treat pancreatic cancer in various ways, and we can understood from the following perspectives.

Polysaccharides are recognized as immunomodulators With the potential to reduce the activity or completely stop several kinds of cancer cells [164,165]. In the treatment of pancreatic cancer, the tumor creates an immunosuppressive microenvironment, leading to escape from the host anti-tumor immune responses [166]. Polysaccharides can help the immune system recognize and fight cancer cells. They can also directly kill cancer cells in lab tests. Most polysaccharides can help prevent tumors in living organisms by boosting the activity of immune cells like T and B lymphocytes, macrophages, and natural killer (NK) cells, activating the complement system; promoting cytokine production; and regulating the immune system [167].

Furthermore, certain polysaccharides may directly slow down the growth and spread of pancreatic cancer cells [168]. This can be done by activating the mitochondrial and death receptor pathways; mediating signal transduction pathways; influencing how cancer-causing genes and genes that help stop cancer work[169]; and influencing their growth, migration, and survival. Polysaccharides induce apoptosis and inhibit autophagy to suppress pancreatic cancer cell growth [170].

Moreover, these polysaccharides directly inhibit tumor angiogenesis [153]. The process might include controlling the signals pathways and factors involved in the formation of blood vessels [171,172].

Additionally, new discoveries and drug development potential have emerged from polysaccharide synthesis and structural studies. A research team at Peking University identified a 10-sugar compound with anti-pancreatic cancer activity during the successful synthesis of ginseng polysaccharides (10.1038/s44160-023-00428-x). This suggests that, through in-depth studies of structure-activity relationships, specific polysaccharide segments with anti-tumor activity can be identified. These lead compounds may exert anti-pancreatic cancer effects via the various mechanisms mentioned above. Compared to the main medicine used now for pancreatic cancer treatment, gemcitabine, the newly discovered 10-sugar compound has lower cytotoxicity, indicating that it may have a better therapeutic window and fewer side effects. These results are a hopeful step toward creating new medicines to fight pancreatic cancer.

It is noteworthy that current research outcomes, such as a study by the team at Fudan University Affiliated Cancer Hospital on CRIP1, indicate possible mechanisms for the poor efficacy of pancreatic cancer immunotherapy and explore corresponding treatment methods [173]. Based on the immunomodulatory and anti-tumor effects of polysaccharide compounds, Future studies should aim to combine these compounds with personalized medicine to create better treatment plans for people with pancreatic cancer. As glycobiology keeps improving, we hope to see more studies on similar

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sugar compounds, which might offer new ways to treat pancreatic cancer. Here are some recent studies that look at how polysaccharide compounds affect pancreatic cancer.

Crude polysaccharide S1 from corn silk shows low toxicity and works well against tumors in lab tests. In the BxPC-3 model, S1 showed strong effects against pancreatic cancer, similar to gemcitabine. Corn silk contains natural sugars that can slow down the growth of pancreatic cancer cells both in living organisms and in lab studies by blocking a specific signaling pathway (EGFR/PI3K/AKT/CREB). S1 stops the production of a protein called phosphorylated β-catenin and another protein called Snail that are involved in the process of cell change related to EMT. Reducing these EMT-related proteins makes it harder for pancreatic cancer cells to move and spread, which greatly impacts how the cancer spreads to other parts of the body. S1 reduces the addition of phosphate groups to a protein called CREB that helps control gene activity in pancreatic cancer cells. CREB plays a role in many cell activities and reacts to stress signals and growth signals. [174].

IOP-1, a new polysaccharide comes from a black crystal area of a fungus called Inonotus obliquus. It stops the growth of pancreatic cancer cells (AsPC-1 and SW 1990) in three ways: by affecting the mitochondria, triggering the death receptor, and altering the ERS pathways. This leads to a halt in the cell cycle. [175].

A pectin-like polysaccharide RP 02-1, taken out and cleaned from the roots of Polygala tenuifolia and showed strong effects in stopping the growth of AsPC-1 and BxPC-3 cells, without affecting human liver cells (L02) or normal human pancreatic cells (HPDE 6-C7). In that study, The authors looked at the amounts of certain molecules related to cell death, like cleaved caspase-3, Bcl-2, and Bax, after treating with RP 02-1 for 24 hours. RP 02-1 treatment significantly downregulated the levels of Bcl-2 at both the mRNA and protein levels, but it did not affect the levels of Bax. The levels of cleaved caspase-3 were significantly enhanced by increasing concentrations of RP 02-1. Therefore, RP 02-1 may cause the death of pancreatic cancer cells. RP 02-1 significantly inhibits AsPC-1 and BxPC-3 cell migration and the effect changes depending on how much is given.. After RP 02-1 treatment, the amounts of mRNA and protein for Id-1 and β-catenin go down, while the phosphorylation of SMAD 1/5/9 and FAK is impaired, indicating that RP 02-1 inhibits PDAC cell growth by causing cell death and preventing a process called autophagy [170].

A polysaccharide, RN 1, made from the flowers of Panax notoginseng and has been shown to greatly stop the growth of PDAC cells in lab tests, in living organisms, and in tests using cancer cells from patients. RN 1 attaches to the epidermal growth factor receptor (EGFR) and Gal-3. This stops them from working together and reduces the activity of a protein called ERK and lowers the levels of a factor called Runx1 that helps control Gal-3. By blocking Runx1 with RN 1, the amount of Gal-3 was reduced. This caused related signaling pathways, like EGFR/ERK/Runx1, BMP/smad/Id-3, and integrin/FAK/JNK, to stop working. Also, RN 1 attaches to bone morphogenetic protein receptors (BMPR1A and BMPR2) and prevents Gal-3 from interacting with these receptors. So, these results suggest that RN 1 might help treat human PDAC by affecting different targets and signaling pathways [176].

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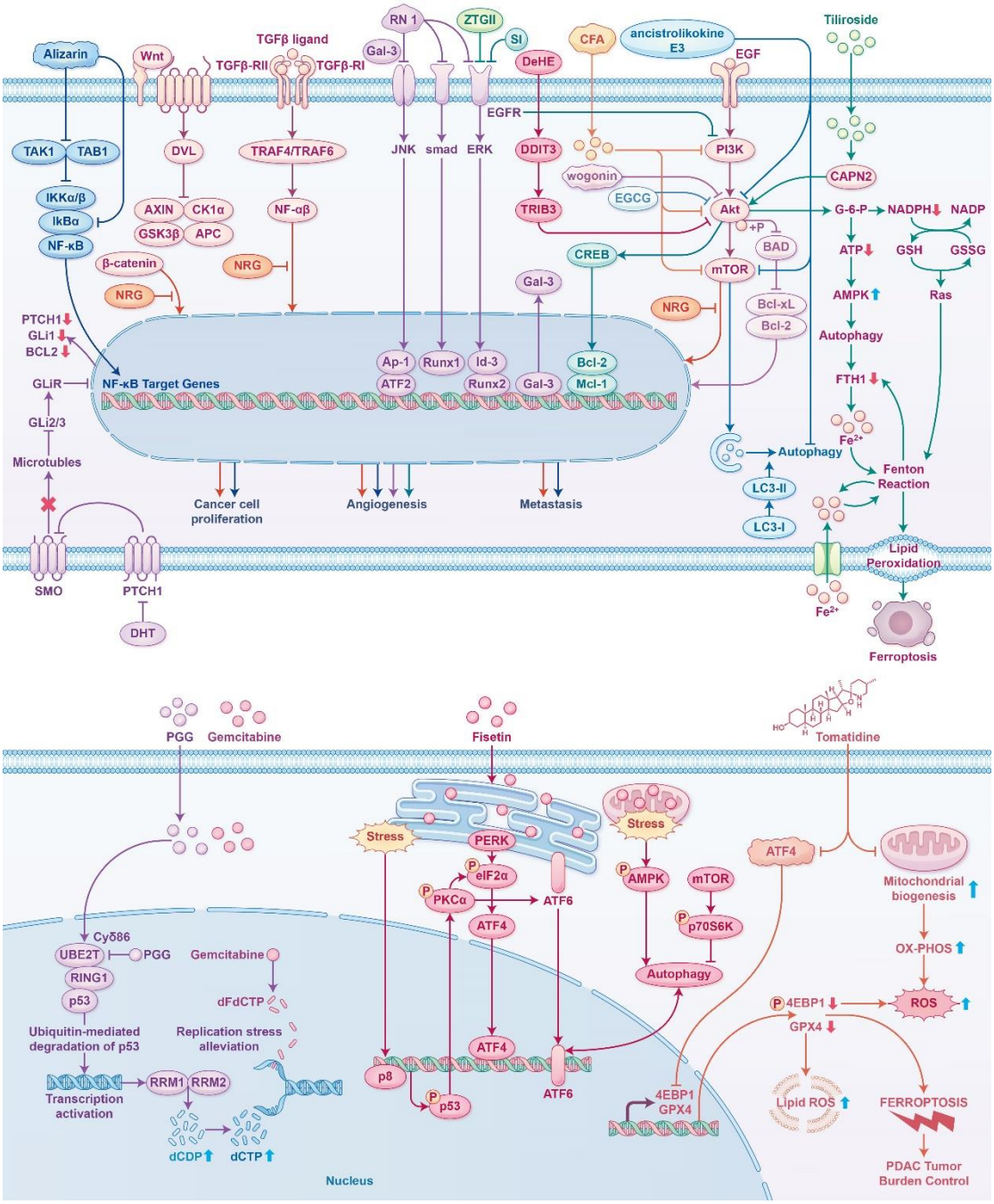

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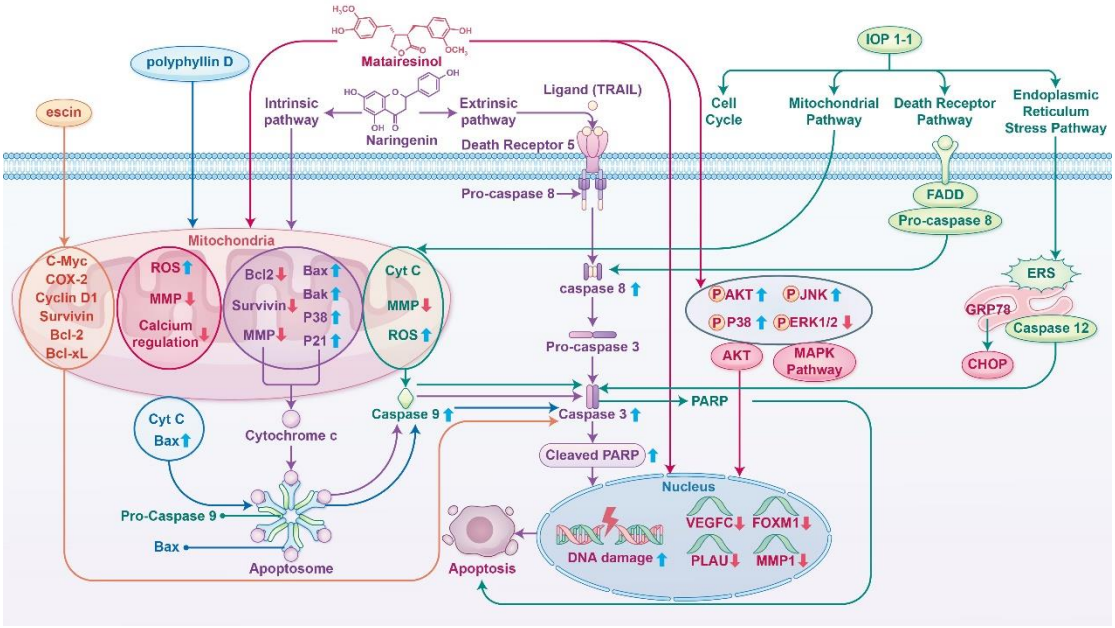

2.3. Clinical Applications and Safety of Bioactive Compounds and Plant Extracts.

Triptolide (TPL), a diterpenoid triepoxide found in thunder god vine, has exhibited good anti-tumor activity against various cancers, including pancreatic cancer, in preclinical studies [177–182]. This plant-derived compound is a water-soluble prodrug also known as minnelide. The mechanism of action of minnelide involves disrupting the super-enhancers required for maintaining the genetic stability of pancreatic cancer cells and aiding the formation of cancer-associated fibroblasts in the tumor microenvironment [183].

A meta-analysis conducted in 2022 on the use of traditional medicine preparations(TMPs) along with chemotherapy for advanced pancreatic cancer showed that combining TMP with chemotherapy significantly increased the chances of a good response to treatment (ORR; more than 1. 5 times better; very strong evidence), the rate of controlling the disease (DCR; about 29% better; very strong evidence), and the quality of life (based on different types of data) compared to just using chemotherapy. Additionally, the levels of pancreatic cancer markers CA19-9 and CEA were lower in the group that received combination therapy. Specifically, CA19-9 had a score of -0. 46 and CEA had a score of -0. 55, with both results being statistically significant. TMP helps lessen bad reactions during chemotherapy. It shows that using TMP with APC is both safe and effective, providing a possible way to improve treatment results and reduce side effects. [184].

In 2018, a cohort study in China looked into the advantages of using complementary and herbal medicine (CHM) for patients with pancreatic cancer. The study found that patients who used CHM for more than 90 days had a lower death rate compared to those who did not use CHM [185].

2.4. Research Trends and Challenges in the Development of Bioactive Compounds and Plant Extracts

In the area of treating pancreatic cancer, research on bioactive compounds and plant extracts is rapidly evolving, involving the screening of novel compounds, studying mechanisms of action, and optimizing drug formulations. However, these studies face challenges, such as target identification, issues with bioavailability, and individual differences.

Natural products could be excellent new options for treating cancer, which is why studying them is very important [186]. Cheminformatics, which utilizes computer-aided methods, high-throughput virtual screening, network-based approaches, and machine learning technologies, provides new avenues for identifying lead compounds and active components in natural products [186]. Researchers have utilized high-throughput screening techniques and computational biology methods to identify new compounds from natural products with anti-pancreatic cancer activities [187]. These new compounds may have different mechanisms of action than existing drugs, offering new therapeutic strategies for pancreatic cancer treatment [188,189].

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Research on how treatments work is very important for treating pancreatic cancer. A clear understanding of how cells work in the growth and spread of pancreatic cancer provides a theoretical basis for identifying new targets and developing novel therapeutic approaches, which is of significant importance [190]. Scientists are studying how bioactive compounds and plant extracts affect pancreatic cancer cells. They are using different lab techniques to understand how these substances slow down cancer cell growth, tumor growth, blood vessel formation, spread of cancer, inflammation, and cell death [133,191]. These studies help reveal the mechanisms underlying pancreatic cancer occurrence and development, setting the stage for creating better medicine.

Optimization of drug formulations is a crucial aspect of pancreatic cancer treatment. Researchers utilize nanotechnology and drug delivery systems to optimize the formulation of bioactive compounds and plant extracts, enhance their stability and bioavailability in the body, reduce side effects, and improve treatment efficacy [192–196].

However, research on pancreatic cancer treatment faces several challenges. First, the targeted identification is challenging. Pancreatic cancer is a complicated illness that affects many different processes and targets in the body, and we have a limited understanding of these mechanisms [197,198], necessitating further research to identify effective therapeutic targets. Second, the bioavailability of bioactive compounds poses a challenge. The effectiveness of many bioactive compounds and plant extracts may be affected by different body processes, like how the body takes in, spreads, breaks down, stores, and gets rid of substances. Other factors, like the presence of other antioxidants and minerals, can also influence their healing effects [199]. Finally, the impact of individual differences cannot be disregarded. Variations in patient genetic backgrounds and disease states may lead to different responses to the same medication, emphasizing the need for personalized treatment strategies [200–203].

In conclusion, bioactive compounds and plant extracts have immense potential for treating pancreatic cancer. However, the research and development processes have encountered numerous challenges. Future studies are needed to further optimize drug screening and mechanism of action research methods, address bioavailability and individual differences, and give pancreatic cancer patients better and safer treatment choices.

2.5. Summary and Outlook

This review summarizes the importance of bioactive compounds and plant extracts in pancreatic cancer treatment and discusses future research directions and potential applications. Research on bioactive compounds and plant extracts offers new hope for pancreatic cancer treatment but requires in-depth exploration of the mechanisms of action, clinical applications, and safety considerations.

The importance of bioactive compounds and plant extracts in treating pancreatic cancer shouldn't be ignored. Their natural origin, fewer adverse effects, and diverse biological activities provide new strategies and ideas for pancreatic cancer treatment. These compounds play crucial roles in inhibiting tumor growth, promoting apoptosis, inhibiting tumor angiogenesis, and regulating immune responses, and are potentially integral components of future pancreatic cancer treatments.

Future research directions should mainly focus on two aspects: continuing to explore the anti-pancreatic cancer activity and how new natural substances and plant extracts work in the body to identify more promising therapeutic targets and optimizing drug formulations to enhance the bioavailability of bioactive compounds and plant extracts, reduce side effects, and improve treatment efficacy. More research is needed to understand how personal differences affect tailored treatment.

In terms of clinical applications, with further research progress, these bioactive compounds and plant extracts could be turned into new medicines for pancreatic cancer that provide patients with more diverse and effective treatment options. Safety assessments, tolerability, and the evaluation of side effects are essential to make sure these drugs are safe and work well in medical use.

In summary, research on bioactive compounds and plant extracts will become more important in treating pancreatic cancer, offering patients more hope and opportunities. Future research should focus on multiple aspects to achieve widespread applications and potential prospects for treating pancreatic cancer.

 doi:10.20944/preprints202407.2469.v1

References

1. Kim, J., et al., Pancreatic Cancer Treatment Targeting the HGF/c-MET Pathway: The MEK Inhibitor Trametinib. Cancers (Basel), 2024. **16**(5).
2. Ramalhete, L., et al., Proteomics-Driven Biomarkers in Pancreatic Cancer. Proteomes, 2023. **11**(3).
3. Huang, X., et al., A Self-Sustained Nanoplatform Reverses TRAIL-Resistance of Pancreatic Cancer Through Coactivating of Exogenous and Endogenous Apoptotic Pathway. Biomaterials, 2021. **272**: p. 120795.
4. Cao, Y., et al., Targeting Survivin With Tanshinone IIA Inhibits Tumor Growth and Overcomes Chemoresistance in Colorectal Cancer. Cell Death Discov, 2023. **9**(1): p. 351.
5. Khwaza, V., et al., Pentacyclic Triterpenoids With Nitrogen-Containing Heterocyclic Moiety, Privileged Hybrids in Anticancer Drug Discovery. Molecules, 2021. **26**(9).
6. Bouyahya, A., et al., Chemical Compounds of Berry-Derived Polyphenols and Their Effects on Gut Microbiota, Inflammation, and Cancer. Molecules, 2022. **27**(10).
7. Banik, K., et al., Wogonin and its Analogs for the Prevention and Treatment of Cancer: A Systematic Review. Phytother Res, 2022. **36**(5): p. 1854-1883.
8. Akter, M., et al., Anti-Tumor and Antioxidant Activity of Kaempferol-3-O-Alpha-L-Rhamnoside (Afzelin) Isolated from Pithecellobium dulce Leaves. BMC Complement Med Ther, 2022. **22**(1): p. 169.
9. Ziemlewska, A., et al., Assessment of Cosmetic and Dermatological Properties and Safety of Use of Model Skin Tonics With Kombucha-Fermented Red Berry Extracts. Int J Mol Sci, 2022. **23**(23).
10. Peng, B.Y., et al., AGA Induces Sub-G1 Cell Cycle Arrest and Apoptosis in Human Colon Cancer Cells Through p53-Independent/p53-Dependent Pathway. BMC Cancer, 2023. **23**(1): p. 1.
11. Tiwary, B.K., et al., The In Vitro Cytotoxic Activity of Ethno-Pharmacological Important Plants of Darjeeling District of West Bengal Against Different Human Cancer Cell Lines. BMC Complement Altern Med, 2015. **15**: p. 22.
12. Gururajanna, B., et al., Molecular Effects of Taxol and Caffeine on Pancreatic Cancer Cells. Int J Mol Med, 1999. **4**(5): p. 501-507.
13. Qin, T., et al., NAF-1 Inhibition by Resveratrol Suppresses Cancer Stem Cell-Like Properties and the Invasion of Pancreatic Cancer. Front Oncol, 2020. **10**: p. 1038.
14. Ma, D., et al., Baicalein Induces Apoptosis of Pancreatic Cancer Cells by Regulating the Expression of miR-139-3p and miR-196b-5p. Front Oncol, 2021. **11**: p. 653061.
15. Kaur, A., et al., In-Vitro Antiproliferative Efficacy of Abrus precatorius Seed Extracts on Cervical Carcinoma. Sci Rep, 2022. **12**(1): p. 10226.
16. Duan, H., et al., Exploring the Therapeutic Mechanisms of Gleditsiae Spina Acting on Pancreatic Cancer via Network Pharmacology, Molecular Docking and Molecular Dynamics Simulation. RSC Adv, 2023. **13**(20): p. 13971-13984.
17. Shukla, S.K., et al., Molecular and Physiological Evaluation of Pancreatic Cancer-Induced Cachexia. Methods Mol Biol, 2019. **1882**: p. 321-333.
18. Goyal, S., M. Sharma, and R. Sharma, Bioactive Compound from Lagerstroemia speciosa: Activating Apoptotic Machinery in Pancreatic Cancer Cells. 3 Biotech, 2022. **12**(4): p. 96.
19. Mousa, D.S., et al., Nanoformulated Bioactive Compounds Derived from Different Natural Products Combat Pancreatic Cancer Cell Proliferation. Int J Nanomedicine, 2020. **15**: p. 2259-2268.
20. Ng, C.X., et al., The Potential of Plant-Derived Extracts and Compounds to Augment Anticancer Effects of Chemotherapeutic Drugs. Nutr Cancer, 2022. **74**(9): p. 3058-3076.
21. Guha, B., et al., Unveiling Pharmacological Studies Provide New Insights on Mangifera longipes and Quercus gomeziana. Saudi J Biol Sci, 2021. **28**(1): p. 183-190.
22. Khater, S.I., et al., Autophagy Characteristics of Phytoestrogens in Management and Prevention of Diseases: A Narrative Review of In-Vivo and In-Vitro Studies. J Adv Vet Anim Res, 2023. **10**(2): p. 308-320.
23. Munir, N., et al., Phytochemical Constituents and In vitro Pharmacological Response of Cnidium monnieri; A Natural Ancient Medicinal Herb. Dose Response, 2022. **20**(3): p. 15593258221115543.
24. Figueiredo, L.C., et al., Propolis, Aloe Vera, Green Tea, Cranberry, Calendula, Myrrha and Salvia Properties Against Periodontal Microorganisms. Microorganisms, 2022. **10**(11).
25. Ekiert, H.M. and A. Szopa, *Biological Activities of Natural Products.* Molecules, 2020. **25**(23).
26. Chamcheu, J.C., et al., Graviola (Annona muricata) Exerts Anti-Proliferative, Anti-Clonogenic and Pro-Apoptotic Effects in Human Non-Melanoma Skin Cancer UW-BCC1 and A431 Cells In Vitro: Involvement of Hedgehog Signaling. Int J Mol Sci, 2018. **19**(6).
27. Kubra Sasmaz, H., et al., Antioxidant Capacity, Sugar Content, and Tandem HPLC-DAD-ESI/MS Profiling of Phenolic Compounds from Aronia melanocarpa Fruits and Leaves (Nero and Viking Cultivars). ACS Omega, 2024. **9**(13): p. 14963-14976.
28. Mei, X., et al., Necroptosis in Pneumonia: Therapeutic Strategies and Future Perspectives. Viruses, 2024. **16**(1).
29. Liu, H., et al., Rutin is a Potent Senomorphic Agent to Target Senescent Cells and Can Improve Chemotherapeutic Efficacy. Aging Cell, 2024. **23**(1): p. e13921.

30. Rutkowska, M. and M.A. Olszewska, Anti-Diabetic Potential of Polyphenol-Rich Fruits from the Maleae Tribe-A Review of In Vitro and In Vivo Animal and Human Trials. Nutrients, 2023. **15**(17).
31. Rybak, M. and A. Wojdylo, Inhibition of Alpha-Amylase, Alpha-Glucosidase, Pancreatic Lipase, 15-Lipooxygenase and Acetylcholinesterase Modulated by Polyphenolic Compounds, Organic Acids, and Carbohydrates of Prunus domestica Fruit. Antioxidants (Basel), 2023. **12**(7).
32. Jang, W.Y., M.Y. Kim, and J.Y. Cho, Antioxidant, Anti-Inflammatory, Anti-Menopausal, and Anti-Cancer Effects of Lignans and Their Metabolites. Int J Mol Sci, 2022. **23**(24).
33. Mikhaevich, E.I., D.V. Sorokin, and A.M. Scherbakov, Honokiol Inhibits the Growth of Hormone-Resistant Breast Cancer Cells: Its Promising Effect in Combination With Metformin. Res Pharm Sci, 2023. **18**(5): p. 580-591.
34. Teodor, E.D., V. Moroeanu, and G.L. Radu, *Lignans From Medicinal Plants and Their Anticancer Effect.* Mini Rev Med Chem, 2020. **20**(12): p. 1083-1090.
35. Xu, X.H., et al., Saponins From Chinese Medicines as Anticancer Agents. Molecules, 2016. **21**(10).
36. Sun, L.R., et al., Modulation of Multiple Signaling Pathways of the Plant-Derived Natural Products in Cancer. Front Oncol, 2019. **9**: p. 1153.
37. Elizalde-Romero, C.A., et al., Solanum Fruits: Phytochemicals, Bioaccessibility and Bioavailability, and Their Relationship With Their Health-Promoting Effects. Front Nutr, 2021. **8**: p. 790582.
38. Van Chen, T., et al., Antioxidant Activity and Alpha-Glucosidase Inhibitability of Distichochlamys citrea M.F. Newman Rhizome Fractionated Extracts: In Vitro and In Silico Screenings. Chem Zvesti, 2022. **76**(9): p. 5655-5675.
39. Xu, Y., et al., Alkaloids From the Roots of Sophora flavescens and Their Anti-Tumor Activity. Fitoterapia, 2023. **171**: p. 105685.
40. Ma, W., et al., In-Vitro and In-Vivo Anti-Breast Cancer Activity of Synergistic Effect of Berberine and Exercise Through Promoting the Apoptosis and Immunomodulatory Effects. Int Immunopharmacol, 2020. **87**: p. 106787.
41. Kamath, A.J., et al., Embelin: A Multifaceted Anticancer Agent With Translational Potential in Targeting Tumor Progression and Metastasis. EXCLI J, 2023. **22**: p. 1311-1329.
42. Cowan, J., et al., A Novel Marine Natural Product Derived Pyrroloiminoquinone With Potent Activity Against Skin Cancer Cells. Mar Drugs, 2019. **17**(8).
43. Byrne, F.L., et al., Phenotypic Screen for Oxygen Consumption Rate Identifies an Anti-Cancer Naphthoquinone That Induces Mitochondrial Oxidative Stress. Redox Biol, 2020. **28**: p. 101374.
44. Rui, X., et al., Gut Microbiota Were Altered With Platelet Count and Red Blood Cell Count in Immune Thrombocytopenia Patients With Different Treatments. Front Cell Infect Microbiol, 2023. **13**: p. 1168756.
45. Huang, M., et al., *Terpenoids: Natural Products for Cancer Therapy.* Expert Opin Investig Drugs, 2012. **21**(12): p. 1801-1818.
46. Bai, B., et al., Molecular Basis of Prostate Cancer and Natural Products as Potential Chemotherapeutic and Chemopreventive Agents. Front Pharmacol, 2021. **12**: p. 738235.
47. Xue, J.C., et al., *Natural Products Modulate NLRP3 in Ulcerative Colitis.* Front Pharmacol, 2023. **14**: p. 1265825.
48. Yang, S., et al., Glycobiology in Osteoclast Differentiation and Function. Bone Res, 2023. **11**(1): p. 55.
49. Zhou, S. and G. Huang, Preparation, Structure and Activity of Polysaccharide Phosphate esters. Biomed Pharmacother, 2021. **144**: p. 112332.
50. Alves, N.M., et al., Antioxidant Mechanisms Underlying the Gastroprotective Effect of Menthofuran on Experimentally Induced Gastric Lesions in Rodents. Evid Based Complement Alternat Med, 2023. **2023**: p. 9192494.
51. Ebrahimi, B., et al., Combination of Marine Bioactive Compounds and Extracts for the Prevention and Treatment of Chronic Diseases. Front Nutr, 2022. **9**: p. 1047026.
52. Boy, F.R., et al., Antifungal Effect of Autochthonous Aromatic Plant Extracts on Two Mycotoxigenic Strains of Aspergillus flavus. Foods, 2023. **12**(9).
53. Ziolkiewicz, A., et al., The Effect of In Vitro Digestion on Polyphenolic Compounds and Antioxidant Properties of Sorghum (Sorghum bicolor (L.) Moench) and Sorghum-Enriched Pasta. Molecules, 2023. **28**(4).
54. Jia, W., et al., Nano-Based Drug Delivery of Polyphenolic Compounds for Cancer Treatment: Progress, Opportunities, and Challenges. Pharmaceuticals (Basel), 2023. **16**(1).
55. Singh, N. and S.S. Yadav, A Review on Health Benefits of Phenolics Derived From Dietary Spices. Curr Res Food Sci, 2022. **5**: p. 1508-1523.
56. Basri, D.F., Z.A. Alamin, and K.M. Chan, Assessment of Cytotoxicity and Genotoxicity of Stem Bark Extracts From Canarium odontophyllum Miq. (dabai) Against HCT 116 Human Colorectal Cancer Cell Line. BMC Complement Altern Med, 2016. **16**: p. 36.
57. Rezaei, P.F., et al., Induction of G1 Cell Cycle Arrest and Cyclin D1 Down-Regulation in Response to Pericarp Extract of Baneh in Human Breast Cancer T47D cells. Daru, 2012. **20**(1): p. 101.

 doi:10.20944/preprints202407.2469.v1

58. Afsar, T., et al., Growth Inhibition and Apoptosis in Cancer Cells Induced by Polyphenolic Compounds of Acacia hydaspica: Involvement of Multiple Signal Transduction Pathways. Sci Rep, 2016. **6**: p. 23077.
59. Fakhri, S., et al., Modulation of TLR/NF-kappaB/NLRP Signaling by Bioactive Phytocompounds: A Promising Strategy to Augment Cancer Chemotherapy and Immunotherapy. Front Oncol, 2022. **12**: p. 834072.
60. Siriwaseree, J., et al., Exploring the Apoptotic-Induced Biochemical Mechanism of Traditional Thai Herb (Kerra) Extract in HCT116 Cells Using a Label-Free Proteomics Approach. Medicina (Kaunas), 2023. **59**(8).
61. Xu, J., et al., Current Advances and Future Strategies for BCL-2 Inhibitors: Potent Weapons against Cancers. Cancers (Basel), 2023. **15**(20).
62. Eissa, I.H., et al., Computer-Assisted Drug Discovery of a Novel Theobromine Derivative as an EGFR Protein-Targeted Apoptosis Inducer. Evol Bioinform Online, 2023. **19**: p. 11769343231217916.
63. Abotaleb, M., et al., *Flavonoids in Cancer and Apoptosis.* Cancers (Basel), 2018. **11**(1).
64. Fernandez-Cruz, E., et al., Inhibition of VEGFR-2 Phosphorylation and Effects on Downstream Signaling Pathways in Cultivated Human Endothelial Cells by Stilbenes From Vitis Spp. J Agric Food Chem, 2019. **67**(14): p. 3909-3918.
65. Vengryte, M. and L. Raudone, Phytochemical Profiling and Biological Activities of Rhododendron Subsect. Ledum: Discovering the Medicinal Potential of Labrador Tea Species in the Northern Hemisphere. Plants (Basel), 2024. **13**(6).
66. Rizzo, A., et al., PSMA Radioligand Uptake as a Biomarker of Neoangiogenesis in Solid Tumours: Diagnostic or Theragnostic Factor? Cancers (Basel), 2022. **14**(16).
67. Zhou, Z.Y., et al., Antiangiogenesis Effect of Timosaponin AIII on HUVECs In Vitro and Zebrafish Embryos In Vivo. Acta Pharmacol Sin, 2020. **41**(2): p. 260-269.
68. Huang, T.T., et al., E7050 Suppresses the Growth of Multidrug-Resistant Human Uterine Sarcoma by Inhibiting Angiogenesis via Targeting of VEGFR2-Mediated Signaling Pathways. Int J Mol Sci, 2023. **24**(11).
69. Wang, Y., et al., Potential of Dietary HDAC2i in Breast Cancer Patients Receiving PD-1/PD-L1 Inhibitors. Nutrients, 2023. **15**(18).
70. Liu, Y., et al., Curcumin Elevates microRNA-183-5p via Cathepsin B-Mediated Phosphatidylinositol 3-Kinase/AKT Pathway to Strengthen Lipopolysaccharide-Stimulated Immune Function of Sepsis Mice. Contrast Media Mol Imaging, 2022. **2022**: p. 6217234.
71. Derakhshan, A., et al., Efficacy of Herbal Medicines on Lung Function in Asthma: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Pharmacopuncture, 2023. **26**(2): p. 124-138.
72. Saki, E., et al., Chemopreventive Effects of Germinated Rough Rice Crude Extract in Inhibiting Azoxymethane-Induced Aberrant Crypt Foci Formation in Sprague-Dawley Rats. Biomed Res Int, 2017. **2017**: p. 9517287.
73. Pop, O.L., et al., Polyphenols-Ensured Accessibility from Food to the Human Metabolism by Chemical and Biotechnological Treatments. Antioxidants (Basel), 2023. **12**(4).
74. Duan, J., et al., The Mechanisms of Wine Phenolic Compounds for Preclinical Anticancer Therapeutics. Food Nutr Res, 2021. **65**.
75. Bimonte, S., et al., An Overview of Pre-Clinical Studies on the Effects of (-)-Epigallocatechin-3-gallate, a Catechin Found in Green Tea, in Treatment of Pancreatic Cancer. Recenti Prog Med, 2017. **108**(6): p. 282-287.
76. Wei, R., et al., Epigallocatechin-3-Gallate (EGCG) Suppresses Pancreatic Cancer Cell Growth, Invasion, and Migration partly through the Inhibition of Akt Pathway and Epithelial-Mesenchymal Transition: Enhanced Efficacy when Combined with Gemcitabine. Nutrients, 2019. **11**(8).
77. Srivani, G., et al., Resveratrol Binds and Inhibits Transcription Factor HIF-1alpha in Pancreatic Cancer. Exp Cell Res, 2020. **394**(1): p. 112126.
78. Xu, Q., et al., *Resveratrol in the Treatment of Pancreatic Cancer.* Ann N Y Acad Sci, 2015. **1348**(1): p. 10-19.
79. Gao, Y., et al., Farnesyl Phenolic Enantiomers as Natural MTH1 Inhibitors From Ganoderma sinense. Oncotarget, 2017. **8**(56): p. 95865-95879.
80. Thyagarajan, A., et al., Dietary Polyphenols in Cancer Chemoprevention: Implications in Pancreatic Cancer. Antioxidants (Basel), 2020. **9**(8).
81. Sobolewska, D., et al., The Genus Cuphea P. Browne as a Source of Biologically Active Phytochemicals for Pharmaceutical Application and Beyond-A Review. Int J Mol Sci, 2023. **24**(7).
82. Jiang, X., et al., Targeting UBE2T Potentiates Gemcitabine Efficacy in Pancreatic Cancer by Regulating Pyrimidine Metabolism and Replication Stress. Gastroenterology, 2023. **164**(7): p. 1232-1247.
83. Shankar, S., et al., Resveratrol Inhibits Pancreatic Cancer Stem Cell Characteristics in Human and KrasG12D Transgenic Mice by Inhibiting Pluripotency Maintaining Factors and Epithelial-Mesenchymal Transition. PLoS One, 2011. **6**(1): p. e16530.
84. *Retraction.* Cancer, 2016. **122**(20): p. 3247.
85. Banerjee, S., et al., Molecular Evidence for Increased Antitumor Activity of Gemcitabine by Genistein In Vitro and In Vivo Using an Orthotopic Model of Pancreatic Cancer. Cancer Res, 2005. **65**(19): p. 9064-9072.

86. Farhan, M., et al., Pomegranate Juice Anthocyanidins Induce Cell Death in Human Cancer Cells by Mobilizing Intracellular Copper Ions and Producing Reactive Oxygen Species. Front Oncol, 2022. **12**: p. 998346.
87. Ferro, R., et al., GPR55 Signalling Promotes Proliferation of Pancreatic Cancer Cells and Tumour Growth in Mice, and its Inhibition Increases Effects of Gemcitabine. Oncogene, 2018. **37**(49): p. 6368-6382.
88. Li, Y., et al., Apoptosis-Inducing Effect of Chemotherapeutic Agents is Potentiated by Soy Isoflavone Genistein, a Natural Inhibitor of NF-kappaB in BxPC-3 Pancreatic Cancer Cell Line. Pancreas, 2004. **28**(4): p. e90-e95.
89. Bhaumik, S.K., et al., Pre-Existing Dengue Immunity Drives a DENV-Biased Plasmablast Response in ZIKV-Infected Patient. Viruses, 2018. **11**(1).
90. Zhang, T., et al., Wogonin Increases Gemcitabine Sensitivity in Pancreatic Cancer by Inhibiting Akt Pathway. Front Pharmacol, 2022. **13**: p. 1068855.
91. Jia, S., et al., Fisetin Induces Autophagy in Pancreatic Cancer Cells via Endoplasmic Reticulum Stress- and Mitochondrial Stress-Dependent Pathways. Cell Death Dis, 2019. **10**(2): p. 142.
92. Motallebi, M., et al., Naringenin: A Potential Flavonoid Phytochemical for Cancer Therapy. Life Sci, 2022. **305**: p. 120752.
93. Xu, M., et al., Tiliroside Disrupted Iron Homeostasis and Induced Ferroptosis via Directly Targeting Calpain-2 in Pancreatic Cancer Cells. Phytomedicine, 2024. **127**: p. 155392.
94. Zaremba-Czogalla, M., et al., Evaluation of the In Vitro Cytotoxic Activity of Caffeic Acid Derivatives and Liposomal Formulation against Pancreatic Cancer Cell Lines. Materials (Basel), 2020. **13**(24).
95. Duan, J., et al., Direct Interaction Between Caffeic Acid Phenethyl Ester and Human Neutrophil Elastase Inhibits the Growth and Migration of PANC-1 Cells. Oncol Rep, 2017. **37**(5): p. 3019-3025.
96. Chen, X., et al., Chlorogenic Acid Inhibits Proliferation, Migration and Invasion of Pancreatic Cancer Cells via AKT/GSK-3beta/beta-catenin Signaling Pathway. Recent Pat Anticancer Drug Discov, 2024. **19**(2): p. 146-153.
97. Gupta, S., et al., Caffeic Acid, a Dietary Polyphenol, Pre-Sensitizes Pancreatic Ductal Adenocarcinoma to Chemotherapeutic Drug. J Biomol Struct Dyn, 2024: p. 1-15.
98. Torres, S.M., et al., Gallic Acid Markedly Stimulates GLUT1-Mediated Glucose Uptake by the AsPC-1 Pancreatic Cancer Cell Line. Can J Physiol Pharmacol, 2023. **101**(2): p. 90-105.
99. Brecht, K., et al., Mechanistic Insights Into Selective Killing of OXPHOS-Dependent Cancer Cells by Arctigenin. Toxicol In Vitro, 2017. **40**: p. 55-65.
100. Sung, Y.Y., A.Y. Lee, and H.K. Kim, Forsythia suspensa Fruit Extracts and the Constituent Matairesinol Confer Anti-Allergic Effects in an Allergic Dermatitis Mouse Model. J Ethnopharmacol, 2016. **187**: p. 49-56.
101. Bel Mabrouk, S., et al., The Marine Seagrass Halophila stipulacea as a Source of Bioactive Metabolites against Obesity and Biofouling. Mar Drugs, 2020. **18**(2).
102. Lee, W., G. Song, and H. Bae, Matairesinol Induces Mitochondrial Dysfunction and Exerts Synergistic Anticancer Effects with 5-Fluorouracil in Pancreatic Cancer Cells. Mar Drugs, 2022. **20**(8).
103. Arora, S., et al., Honokiol: a Novel Natural Agent for Cancer Prevention and Therapy. Curr Mol Med, 2012. **12**(10): p. 1244-1252.
104. Arora, S., et al., Honokiol Arrests Cell Cycle, Induces Apoptosis, and Potentiates the Cytotoxic Effect of Gemcitabine in Human Pancreatic Cancer Cells. PLoS One, 2011. **6**(6): p. e21573.
105. Averett, C., et al., Honokiol Suppresses Pancreatic Tumor Growth, Metastasis and Desmoplasia by Interfering With Tumor-Stromal Cross-Talk. Carcinogenesis, 2016. **37**(11): p. 1052-1061.
106. Son, M.K., et al., SB365, Pulsatilla saponin D Suppresses Proliferation and Induces Apoptosis of Pancreatic Cancer Cells. Oncol Rep, 2013. **30**(2): p. 801-808.
107. Ma, Y., et al., Advancements and Challenges in Pharmacokinetic and Pharmacodynamic Research on the Traditional Chinese Medicine Saponins: A Comprehensive Review. Front Pharmacol, 2024. **15**: p. 1393409.
108. Liu, C., et al., A Natural Food Sweetener With Anti-Pancreatic Cancer Properties. Oncogenesis, 2016. **5**(4): p. e217.
109. Yao, L.C., et al., Panax notoginseng Saponins Promote Cell Death and Chemosensitivity in Pancreatic Cancer Through the Apoptosis and Autophagy Pathways. Anticancer Agents Med Chem, 2021. **21**(13): p. 1680-1688.
110. Tezuka, H. and S. Imai, Fine-Tuning of Mononuclear Phagocytes for Improved Inflammatory Responses: Role of Soybean-Derived Immunomodulatory Compounds. Front Nutr, 2024. **11**: p. 1399687.
111. Shen, L., et al., Potential Immunoregulatory Mechanism of Plant Saponins: A Review. Molecules, 2023. **29**(1).
112. Timilsena, Y.P., A. Phosanam, and R. Stockmann, *Perspectives on Saponins: Food Functionality and Applications.* Int J Mol Sci, 2023. **24**(17).
113. MarElia, C.B., et al., Anemarrhena asphodeloides Bunge and its Constituent Timosaponin-AIII Induce Cell Cycle Arrest and Apoptosis in Pancreatic Cancer Cells. FEBS Open Bio, 2018. **8**(7): p. 1155-1166.

114. Zou, J., et al., Ginsenoside Rg3 Suppresses the Growth of Gemcitabine-Resistant Pancreatic Cancer Cells by Upregulating lncRNA-CASC2 and Activating PTEN Signaling. J Biochem Mol Toxicol, 2020. **34**(6): p. e22480.
115. Xu, X., et al., Saikosaponin d Modulates the Polarization of Tumor-Associated Macrophages by Deactivating the PI3K/AKT/mTOR Pathway in Murine Models of Pancreatic Cancer. Int Immunopharmacol, 2023. **122**: p. 110579.
116. He, X., et al., The Therapeutic Potential of Natural Products for Treating Pancreatic Cancer. Front Pharmacol, 2022. **13**: p. 1051952.
117. Liu, Y., et al., Steroidal Saponins PPI/CCRIS/PSV Induce Cell Death in Pancreatic Cancer Cell Through GSDME-Dependent Pyroptosis. Biochem Biophys Res Commun, 2023. **673**: p. 51-58.
118. Zhong, Y., et al., Ziyuglycoside II Inhibits the Growth of Digestive System Cancer Cells Through Multiple Mechanisms. Chin J Nat Med, 2021. **19**(5): p. 351-363.
119. Xiao, M.F., [Effect of Polyphyllin D on Proliferation and Apoptosis of Human Pancreatic Cancer Cells]. Zhongguo Zhong Yao Za Zhi, 2020. **45**(6): p. 1418-1422.
120. Wang, Y.W., et al., Escin Augments the Efficacy of Gemcitabine Through Down-Regulation of Nuclear Factor-kappaB and Nuclear Factor-kappaB-Regulated Gene Products in Pancreatic Cancer Both In Vitro and In Vivo. J Cancer Res Clin Oncol, 2012. **138**(5): p. 785-797.
121. Liu, Q., et al., Pulsatilla saponin A, an Active Molecule From Pulsatilla chinensis, Induces Cancer Cell Death and Inhibits Tumor Growth in Mouse Xenograft Models. J Surg Res, 2014. **188**(2): p. 387-395.
122. Zhou, Z.G., et al., Phenolic Alkaloids From Menispermum dauricum Inhibits BxPC-3 Pancreatic Cancer Cells by Blocking of Hedgehog Signaling Pathway. Pharmacogn Mag, 2015. **11**(44): p. 690-697.
123. Prabhu, K.S., et al., Sanguinarine Mediated Apoptosis in Non-Small Cell Lung Cancer via Generation of Reactive Oxygen Species and Suppression of JAK/STAT Pathway. Biomed Pharmacother, 2021. **144**: p. 112358.
124. Jang, H.J., et al., Chelidonine Induces Apoptosis via GADD45a-p53 Regulation in Human Pancreatic Cancer Cells. Integr Cancer Ther, 2021. **20**: p. 15347354211006191.
125. Zhao, J., et al., Total Alkaloids of Rubus alceifolius Poir Inhibit Tumor Angiogenesis Through Suppression of the Notch Signaling Pathway in a Mouse Model of Hepatocellular Carcinoma. Mol Med Rep, 2015. **11**(1): p. 357-361.
126. Wang, H., et al., Effects of Compound Kushen Injection on Pathology and Angiogenesis of Tumor Tissues. Oncol Lett, 2019. **17**(2): p. 2278-2282.
127. Qin, R., et al., Naturally Derived Indole Alkaloids Targeting Regulated Cell Death (RCD) for Cancer Therapy: From Molecular Mechanisms to Potential Therapeutic Targets. J Hematol Oncol, 2022. **15**(1): p. 133.
128. Ishii, N., et al., Conophylline Suppresses Pancreatic Cancer Desmoplasia and Cancer-Promoting Cytokines Produced by Cancer-Associated Fibroblasts. Cancer Sci, 2019. **110**(1): p. 334-344.
129. Wang, X., et al., The Recent Developments of Camptothecin and its Derivatives as Potential Anti-Tumor Agents. Eur J Med Chem, 2023. **260**: p. 115710.
130. Wang, W., et al., Structure-Activity Relationship of FL118 Platform Position 7 Versus Position 9-Derived Compounds and Their Mechanism of Action and Antitumor Activity. J Med Chem, 2023. **66**(24): p. 16888-16916.
131. Zhu, S.L., et al., A Novel DDIT3 Activator Dehydroevodiamine Effectively Inhibits Tumor Growth and Tumor Cell Stemness in Pancreatic Cancer. Phytomedicine, 2024. **128**: p. 155377.
132. Awale, S., et al., Ancistrolikokine E(3), a 5,8'-Coupled Naphthylisoquinoline Alkaloid, Eliminates the Tolerance of Cancer Cells to Nutrition Starvation by Inhibition of the Akt/mTOR/Autophagy Signaling Pathway. J Nat Prod, 2018. **81**(10): p. 2282-2291.
133. Mukherjee, D., et al., Tomatidine Targets ATF4-Dependent Signaling and Induces Ferroptosis to Limit Pancreatic Cancer Progression. iScience, 2023. **26**(8): p. 107408.
134. Liu, A., et al., Antiproliferative and Antimetastatic Effects of Emodin on Human Pancreatic Cancer. Oncol Rep, 2011. **26**(1): p. 81-89.
135. Awale, S., et al., Targeting Pancreatic Cancer with Novel Plumbagin Derivatives: Design, Synthesis, Molecular Mechanism, In Vitro and In Vivo Evaluation. J Med Chem, 2023. **66**(12): p. 8054-8065.
136. Colucci, M.A., C.J. Moody, and G.D. Couch, Natural and Synthetic Quinones and Their Reduction by the Quinone Reductase Enzyme NQO1: From Synthetic Organic Chemistry to Compounds With Anticancer Potential. Org Biomol Chem, 2008. **6**(4): p. 637-656.
137. Zhou, H., et al., Research Progress on the Synergistic Anti-Tumor Effect of Natural Anti-Tumor Components of Chinese Herbal Medicine Combined with Chemotherapy Drugs. Pharmaceuticals (Basel), 2023. **16**(12).
138. Zhao, Z., et al., Advances in Research on the Relationship Between Thymoquinone and Pancreatic Cancer. Front Oncol, 2022. **12**: p. 1092020.

139. Lin, S.Z., et al., Emodin Inhibits Angiogenesis in Pancreatic Cancer by Regulating the Transforming Growth Factor-Beta/Drosophila Mothers Against Decapentaplegic Pathway and Angiogenesis-Associated microRNAs. Mol Med Rep, 2015. **12**(4): p. 5865-5871.
140. Yamamoto, K., et al., Autophagy Promotes Immune Evasion of Pancreatic Cancer by Degrading MHC-I. Nature, 2020. **581**(7806): p. 100-105.
141. Wei, W.T., et al., Antitumor and Apoptosis-Promoting Properties of Emodin, an Anthraquinone Derivative From Rheum officinale Baill, Against Pancreatic Cancer in Mice via Inhibition of Akt Activation. Int J Oncol, 2011. **39**(6): p. 1381-1390.
142. Yagublu, V., et al., Treatment of Experimental Pancreatic Cancer by Doxorubicin-, Mitoxantrone-, and Irinotecan-Drug Eluting Beads. Pancreatology, 2013. **13**(1): p. 79-87.
143. Virtanen, P. and K. Isotupa, *Staining Properties of Alizarin Red S for Growing Bone In Vitro.* Acta Anat (Basel), 1980. **108**(2): p. 202-207.
144. Huang, W., et al., Dihydrotanshinone I Inhibits Pancreatic Cancer Progression via Hedgehog/Gli Signal Pathway. Curr Cancer Drug Targets, 2023. **23**(9): p. 731-741.
145. Enchev, P., et al., Terpenes From Cecropia Species and Their Pharmacological Potential. Pharmaceuticals (Basel), 2024. **17**(3).
146. Wang, Y., et al., The Multifaceted Mechanisms of Pristimerin in the Treatment of Tumors State-of-the-Art. Biomed Pharmacother, 2022. **154**: p. 113575.
147. Li, D., et al., Analysis of Anti-Cancer and Anti-Inflammatory Properties of 25 High-THC Cannabis Extracts. Molecules, 2022. **27**(18).
148. Wroblewska-Luczka, P., et al., *Anticancer Effect of Terpenes: Focus on Malignant Melanoma.* Pharmacol Rep, 2023. **75**(5): p. 1115-1125.
149. Amrutkar, M. and I.P. Gladhaug, *Pancreatic Cancer Chemoresistance to Gemcitabine.* Cancers (Basel), 2017. **9**(11).
150. Markowski, A., et al., Design and Development of a New Type of Hybrid PLGA/Lipid Nanoparticle as an Ursolic Acid Delivery System against Pancreatic Ductal Adenocarcinoma Cells. Int J Mol Sci, 2022. **23**(10).
151. Asgharian, P., et al., Potential Mechanisms of Quercetin in Cancer Prevention: Focus on Cellular and Molecular Targets. Cancer Cell Int, 2022. **22**(1): p. 257.
152. Kui, L., et al., High-Throughput In Vitro Gene Expression Profile to Screen of Natural Herbals for Breast Cancer Treatment. Front Oncol, 2021. **11**: p. 684351.
153. Li, R., et al., Natural Products: A Promising Therapeutics for Targeting Tumor Angiogenesis. Front Oncol, 2021. **11**: p. 772915.
154. Singh, R.P. and R. Agarwal, *Tumor Angiogenesis: A Potential Target in Cancer Control by Phytochemicals.* Curr Cancer Drug Targets, 2003. **3**(3): p. 205-217.
155. Panda, S.K., et al., Anticancer Activities of Mushrooms: A Neglected Source for Drug Discovery. Pharmaceuticals (Basel), 2022. **15**(2).
156. Wu, X., et al., Nano-Herb Medicine and PDT Induced Synergistic Immunotherapy for Colon Cancer Treatment. Biomaterials, 2021. **269**: p. 120654.
157. Xu, L., et al., Inhibition of NLRP3 Inflammasome Activation in Myeloid-Derived Suppressor Cells by Andrographolide Sulfonate Contributes to 5-FU Sensitization in Mice. Toxicol Appl Pharmacol, 2021. **428**: p. 115672.
158. Laurella, L.C., et al., Sesquiterpene Lactones as Promising Candidates for Cancer Therapy: Focus on Pancreatic Cancer. Molecules, 2022. **27**(11).
159. Wang, Y., P. Camateros, and W.Y. Cheung, A Real-World Comparison of FOLFIRINOX, Gemcitabine Plus nab-Paclitaxel, and Gemcitabine in Advanced Pancreatic Cancers. J Gastrointest Cancer, 2019. **50**(1): p. 62-68.
160. Long, J., Z. Liu, and L. Hui, *Anti-Tumor Effect and Mechanistic Study of Elemene on Pancreatic Carcinoma.* BMC Complement Altern Med, 2019. **19**(1): p. 133.
161. Geng, Y., et al., Xanthatin Suppresses Pancreatic Cancer Cell Growth via the ROS/RBL1 Signaling Pathway: In Vitro and In Vivo Insights. Phytomedicine, 2023. **119**: p. 155004.
162. Wang, H., et al., Umbelliprenin Induces Autophagy and Apoptosis While Inhibits Cancer Cell Stemness in Pancreatic Cancer Cells. Cancer Med, 2023. **12**(14): p. 15277-15288.
163. Ma, L.M., et al., Terpenoids From Nardostachys jatamansi and Their Cytotoxic Activity Against Human Pancreatic Cancer Cell Lines. Phytochemistry, 2022. **200**: p. 113228.
164. Wu, J.Y., K.C. Siu, and P. Geng, Bioactive Ingredients and Medicinal Values of Grifola frondosa (Maitake). Foods, 2021. **10**(1).
165. Liu, Y., J. Wu, and H. Hao, Antitumor Immunostimulatory Activity of the Traditional Chinese Medicine Polysaccharide on Hepatocellular Carcinoma. Front Immunol, 2024. **15**: p. 1369110.
166. Murakami, T., et al., *Role of the Tumor Microenvironment in Pancreatic Cancer.* Ann Gastroenterol Surg, 2019. **3**(2): p. 130-137.

167. Ji, C.F., Y.B. Ji, and D.Y. Meng, *Sulfated Modification and Anti-tumor Activity of Laminarin.* Exp Ther Med, 2013. **6**(5): p. 1259-1264.
168. Liu, D., H. Zhu, and C. Li, Galectins and Galectin-Mediated Autophagy Regulation: New Insights Into Targeted Cancer Therapy. Biomark Res, 2023. **11**(1): p. 22.
169. Yuan, P., et al., Structure and Anti-Tumor Activities of Exopolysaccharides from Alternaria mali Roberts. Molecules, 2019. **24**(7).
170. Bian, Y., et al., A Pectin-Like Polysaccharide From Polygala tenuifolia Inhibits Pancreatic Cancer Cell Growth In Vitro and In Vivo by Inducing Apoptosis and Suppressing Autophagy. Int J Biol Macromol, 2020. **162**: p. 107-115.
171. Rui, X., et al., Anti-Tumor and Anti-Angiogenic Effects of Fucoidan on Prostate Cancer: Possible JAK-STAT3 Pathway. BMC Complement Altern Med, 2017. **17**(1): p. 378.
172. Zong, S., et al., Synergistic Antitumor Effect of Polysaccharide From Lachnum sp. in Combination With Cyclophosphamide in Hepatocellular Carcinoma. Carbohydr Polym, 2018. **196**: p. 33-46.
173. Liu, X., et al., CRIP1 Fosters MDSC Trafficking and Rsets Tumour Microenvironment via Facilitating NF-kappaB/p65 Nuclear Translocation in Pancreatic Ductal Adenocarcinoma. Gut, 2023. **72**(12): p. 2329-2343.
174. Tao, H., et al., Corn Silk Crude Polysaccharide Exerts Anti-Pancreatic Cancer Activity by Blocking the EGFR/PI3K/AKT/CREB Signaling Pathway. Food Funct, 2020. **11**(8): p. 6961-6970.
175. Ding, M., et al., Structural Characterization of the Polysaccharide From the Black Crystal Region of Inonotus obliquus and its Effect on AsPC-1 and SW1990 Pancreatic Cancer Cell Apoptosis. Int J Biol Macromol, 2024. **268**(Pt 2): p. 131891.
176. Zhang, L., et al., RN1, a Novel Galectin-3 Inhibitor, Inhibits Pancreatic Cancer Cell Growth In Vitro and In Vivo via Blocking Galectin-3 Associated Signaling Pathways. Oncogene, 2017. **36**(9): p. 1297-1308.
177. Wu, P.P., et al., Triptolide Induces Apoptosis in Human Adrenal Cancer NCI-H295 Cells Through a Mitochondrial-Dependent Pathway. Oncol Rep, 2011. **25**(2): p. 551-557.
178. Clawson, K.A., et al., Triptolide and TRAIL Combination Enhances Apoptosis in Cholangiocarcinoma. J Surg Res, 2010. **163**(2): p. 244-249.
179. Giri, B., et al., Pre-Clinical Evaluation of Minnelide as a Therapy for Acute Myeloid Leukemia. J Transl Med, 2019. **17**(1): p. 163.
180. Borja-Cacho, D., et al., TRAIL and Triptolide: An Effective Combination That Iduces Apoptosis in Pancreatic Cancer Cells. J Gastrointest Surg, 2010. **14**(2): p. 252-60.
181. Chugh, R., et al., A Preclinical Evaluation of Minnelide as a Therapeutic Agent Against Pancreatic Cancer. Sci Transl Med, 2012. **4**(156): p. 156ra139.
182. Zhao, X., et al., Triptolide Inhibits Pancreatic Cancer Cell Proliferation and Migration via Down-Regulating PLAU Based on Network Pharmacology of Tripterygium wilfordii Hook F. Eur J Pharmacol, 2020. **880**: p. 173225.
183. Noel, P., et al., Triptolide Targets Super-Enhancer Networks in Pancreatic Cancer Cells and Cancer-Associated Fibroblasts. Oncogenesis, 2020. **9**(11): p. 100.
184. Hu, J., et al., Clinical Efficacy and Safety of Traditional Medicine Preparations Combined With Chemotherapy for Advanced Pancreatic Cancer: A Systematic Review and Meta-Analysis. Front Oncol, 2022. **12**: p. 828450.
185. Kuo, Y.T., et al., Complementary Chinese Herbal Medicine Therapy Improves Survival of Patients With Pancreatic Cancer in Taiwan: A Nationwide Population-Based Cohort Study. Integr Cancer Ther, 2018. **17**(2): p. 411-422.
186. Hashem, S., et al., Targeting Cancer Signaling Pathways by Natural Products: Exploring Promising Anti-Cancer Agents. Biomed Pharmacother, 2022. **150**: p. 113054.
187. Xu, Z., et al., Alizarin, a Nature Compound, Inhibits the Growth of Pancreatic Cancer Cells by Abrogating NF-kappaB Activation. Int J Biol Sci, 2022. **18**(7): p. 2759-2774.
188. Suhail, M., et al., Targeting a Transcription Factor NF-kappaB by Green Tea Catechins Using In Silico and In Vitro Studies in Pancreatic Cancer. Front Nutr, 2022. **9**: p. 1078642.
189. Kingston, D.G., *A Natural Love of Natural Products.* J Org Chem, 2008. **73**(11): p. 3975-3984.
190. Dai, H., et al., PUM1 Knockdown Prevents Tumor Progression by Activating the PERK/eIF2/ATF4 Signaling Pathway in Pancreatic Adenocarcinoma Cells. Cell Death Dis, 2019. **10**(8): p. 595.
191. Fathi, F., et al., Exploring Gunnera tinctoria: From Nutritional and Anti-Tumoral Properties to Phytosome Development Following Structural Arrangement Based on Molecular Docking. Molecules, 2021. **26**(19).
192. Alhakamy, N.A., et al., Apamin-Conjugated Alendronate Sodium Nanocomplex for Management of Pancreatic Cancer. Pharmaceuticals (Basel), 2021. **14**(8).
193. Duan, H., L. Li, and S. He, *Advances and Prospects in the Treatment of Pancreatic Cancer.* Int J Nanomedicine, 2023. **18**: p. 3973-3988.
194. Najm, A., et al., Chitosan and Cyclodextrins-Versatile Materials Used to Create Drug Delivery Systems for Gastrointestinal Cancers. Pharmaceutics, 2023. **16**(1).

 doi:10.20944/preprints202407.2469.v1

195. Shakeel, F., et al., Hepatoprotective Effects of Bioflavonoid Luteolin Using Self-Nanoemulsifying Drug Delivery System. Molecules, 2021. **26**(24).
196. Dasari, N., G.S. Guntuku, and S. Pindiprolu, *Targeting Triple Negative Breast Cancer Stem Cells Using Nanocarriers.* Discov Nano, 2024. **19**(1): p. 41.
197. Wei, Y., et al., The Emergence of TRP Channels Interactome as a Potential Therapeutic Target in Pancreatic Ductal Adenocarcinoma. Biomedicines, 2023. **11**(4).
198. Han, X., et al., Overexpression of miR-135b-5p Promotes Unfavorable Clinical Characteristics and Poor Prognosis via the Repression of SFRP4 in Pancreatic Cancer. Oncotarget, 2017. **8**(37): p. 62195-62207.
199. Hu, Y., et al., The Role of Reactive Oxygen Species in Arsenic Toxicity. Biomolecules, 2020. **10**(2).
200. Xia, Y., et al., *Drug Repurposing for Cancer Therapy.* Signal Transduct Target Ther, 2024. **9**(1): p. 92.
201. Liu, T., et al., Management of Advanced Pancreatic Cancer through Stromal Depletion and Immune Modulation. Medicina (Kaunas), 2022. **58**(9).
202. Oloulade, B.M., et al., Cancer Drug Response Prediction With Surrogate Modeling-Based Graph Neural Architecture Search. Bioinformatics, 2023. **39**(8).
203. van der Wijst, M.G.P., et al., An Integrative Approach for Building Personalized Gene Regulatory Networks for Precision Medicine. Genome Med, 2018. **10**(1): p. 96.