THE MOLECULAR APPROACH OF NATURAL PRODUCTS AS PANCREATIC CANCER TREATMENT: A REVIEW

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ABSTRACT
Pancreatic cancer is one of the most feared types of cancer because of the high number of deaths from this disease. High cases of death are reported due to the ineffectiveness of the early detection process of this type of cancer and the low effectiveness of treatment. This review reports a natural product that has the potential to be used as an anticancer of the pancreas. Natural products are the focus of researchers due to the low risk of resistance and side effects of these products. The mechanism of action of natural products is also explored to ensure the activity of natural products as anticancer, including molecular mechanisms of action, cell cycle inhibitory activity, and promoting apoptosis. Natural products are ingredients that are widespread around us, very easy to find, and have a lot of evidence of their effectiveness as anticancer. It is hoped that this review will become the basis for researchers to conduct further exploration of natural products as pancreatic anticancer.

Keywords: Pancreatic cancer, Natural product, Cell cycle, Apoptosis.

INTRODUCTION
Cancer is a disease that is responsible for 1 in 8 deaths in the world. This disease has a high-risk factor, which is characterized by uncontrolled cell proliferation that attacks normal tissues and metastasizes to other organs.¹ Pancreatic cancer is the most deadly type of cancer and has become a serious problem. Pancreatic cancer is the third leading cause of death in the United States with less than 6 months of survival and only 8% survive more than 5 years.²,³ Based on data from the Chinese Oncology Institute, pancreatic cancer is the biggest cause of death from cancer. In 2015, there were 90,000 cases of pancreatic cancer occurred, and 70,000 cases ended in death.⁴ Meanwhile, in Japan, pancreatic cancer is the fourth most common cancer-causing death. Until 2019, there were 33,000 cases of death due to this disease.⁵ The high number of deaths due to pancreatic cancer is due to late detection of cancer, rapid cancer metastases, and inadequate treatment. Conventional treatment to stop pancreatic cancer can be done by surgery, radiation, chemotherapy, or a combination of these.⁶ However, the ineffectiveness of pancreatic cancer treatment methods is a problem in the world of health, for example, the resistance that occurs in many chemotherapies against pancreatic cancer cells.⁷ Basically be an effective way to treat cancer, but not useful for the treatment of pancreatic cancer. This is because 80-85% of pancreatic cancer patients when detected are at an advanced stage.⁸ Surgery is also less than optimal because only 10-20% of pancreatic cancer patients whose cancer cells are located can be determined correctly. Surely this is a difficulty in removing cancer cells. So far, the use of chemotherapy and radiotherapy are the options in the treatment of pancreatic cancer. The use of options is new hope in the treatment of pancreatic cancer.⁹⁻¹¹
5-Fluorouracil and gemcitabine are chemotherapy that is often used for the treatment of patients. This did not last long, it was reported that this chemotherapy drug is not effective for this type of pancreatic cancer in the metastatic phase.\(^{12}\) This occurs due to resistance mechanisms, so the effectiveness of chemotherapy decreases.\(^{13}\) The use of drugs in the treatment of cancer is now aimed at FOLFIRINOX (a combination of 5-FU, leucovorin/folinic acid, oxaliplatin, and irinotecan). This drug is reported to be able to inhibit the development of cancer cells and is more effective than the single use of gemcitabine.\(^{14}\) The use of chemotherapeutic agents began to be combined with radiotherapy. This combination shows substantial benefits, but as not had much effect on improving patient survival. The side effects of radiotherapy also need to be considered. The imbalance between effectiveness and side effects is a new problem in the treatment of pancreatic cancer.\(^{15}\) Therefore, adjunctive therapeutic approaches to treat pancreatic cancer are very important.\(^{16}\) The world of health began to develop a pancreatic cancer treatment. Treatment by knowing the molecular properties of pancreatic cancer cells is an effective thing that can be done.\(^{17}\) In addition, the use of natural products derived from plants has also been developed to become anticancer drugs in both natural and semi-synthetic forms.\(^{18}\) The use of natural products is expected to overcome the problem of chemotherapy resistance in the treatment of pancreatic cancer so that the therapy carried out becomes more effective.\(^{19}\) Several studies have reported that the secondary metabolite content of plants has an anticancer effect with good effectiveness and low side effects.\(^{20}\) Natural products combined with conventional chemotherapy and radiotherapy, can increase the efficacy of anticancer therapy and reduce side effects. In this context, the use of natural ingredients as a complementary approach, to treating pancreatic cancer is very promising.\(^{21}\) This article will be very useful for the world of health. This article provides information on natural ingredients and their possible mechanism of action as pancreatic anticancer.

**EXPERIMENTAL**

Data on pancreatic cancer and herbal medicine were searched and collected for this miniature review and perspective. We used key search engines, namely, Google Scholar, PubMed, Science Direct, and SciFinder. The search keywords used comprised cancer, pancreatic cancer, herbal medicine, alternative medicine, in vitro and in vivo test of drug cancer, mechanism action of pancreatic cancer drug, Surgery, chemotherapy, and radiotherapy. The authors appraised, evaluated, and interpreted the selected articles. This perspective reflects the opinion of the authors concerning the use of foods and herbs as preventatives and corresponding therapies against pancreatic cancer.

**Molecular Mechanism of Pancreatic Cancer**

Pancreatic cancer treatment continues to be developed by looking at the molecular nature of pancreatic cancer. Molecular studies have become important for detecting and treating pancreatic cancer.\(^{22}\) It is known, that pancreatic cancer is the result of the accumulation of mutated genetics including, oncogenes, tumor suppressor genes, and genome maintenance genes. The complex genetic problems that occur in pancreatic cancer such as mutations in K-Ras, CDKN2A, TP16, TP53, DPC4, and TGF-β which are the main driving genes for pancreatic cancer are interesting to study so that effective therapies can be found in the treatment of pancreatic cancer.\(^{23}\) The first genetic change found in pancreatic cancer patients was a change in the K-Ras (Kirsten Rat Sarcoma Virus) gene. More than 85% of early-stage pancreatic cancers result from mutations in this gene.\(^{24}\) K-Ras is a group of RAS GTP-binding proteins that have multiple functions, such as proliferation, differentiation, and survival. Activation of the mutated K-Ras leads to the formation of other oncogene kinases.\(^{25}\) Experiments to directly inhibit the activation of K-Ras have been carried out, but have not yielded clinically effective results.\(^{26}\) Therefore, efforts to inhibit signalization in the downstream pathway are prioritized, such as inhibition of the Raf, MEK, and Akt pathways.\(^{27}\) The role of the K-Ras gene in influencing the formation of other genes that will promote the growth of pancreatic cancer cells can be seen in Fig.-1. Phosphoinositide 3-kinase (PI3K) affects cell functions such as cell proliferation, cell transformation, apoptosis, tumor growth, and angiogenesis through its influence on downstream protein expression pathways.\(^{28}\) Phosphoinositide 3-kinases (PI3Ks) are a family of Lipid kinases that release intracellular signaling cascades that regulate and influence various cellular processes. Overexpression of the PI3K pathway leads to increased phosphorylation phosphatidyl – inositol - 4,5 - biphosphat (PIP2) to phosphatidyl – inositol - 3,4,5 - triphosphate (PIP3). The formation of PIP3 causes phosphorylation of phosphatidyl – inositol - dependent kinase-1 (PDK1) and causes phosphorylation of PKB so that PKB
becomes active.\textsuperscript{29,30} This protein is a central mediator in signal transduction of the PI3K pathway, which can be seen in Fig.-2. The ligand stimulates activation of the tyrosine receptor kinase (RTK) or G-protein coupled receptor (GPCR), p110 subunit at PI3K catalyzes phosphorylation PIP2 becomes PIP3 which is the second messenger.\textsuperscript{31} This protein will regulate the function mobile via multiple activation of a protein that has a homologous lipid-binding domain and a pleckstrin (PH) domain. PIP3 will phosphorylate PDK1 via the PH domain. PDK1 will phosphorylate residue tyrosine from PKB so that PKB becomes active.\textsuperscript{32} The PI3K-PKB pathway is regulated by activity phosphatase enzymes. The enzyme is PTEN which plays the role in dephosphorylation PIP3 becomes PIP2. Mutations that occur on this phosphatase enzyme will reduce phosphatase activity so that may lead to tumor progression. Gene that code for phosphatase can is said to be an anthioncogene or tumor suppressor genes.\textsuperscript{33,34}

Tumor suppressor genes also play an important role in the formation of pancreatic cancer. This gene is usually active to prevent the proliferation of damaged cells, but mutations result in impaired gene function. There are several types of examples of tumor suppressor genes that undergo mutations, including TP16, TP53, DPC4, and TGF-β. TP16 was a mutated gene in about 95\% of pancreatic cancer cases.\textsuperscript{36} This gene plays a role in inhibiting the complex between Cyclin D-CDK4 and Cyclin D-CDK6 which in turn will have an impact on cell proliferation. Inactivation of TP16 will certainly be very beneficial for the growth of cancer cells, especially pancreatic cancer.\textsuperscript{37} The tumor suppressor gene TP53 is a gene that often undergoes mutations. Approximately 70\% of pancreatic cancer cases are affected by this gene. TP53 is involved in the cell cycle, if it is not activated it will skip the examination phase of the cell cycle which will have an impact on the formation of cells with mutated genes.\textsuperscript{38} DPC4 and TGF-β are other types of tumor suppressor genes. These genes are mutated in 55\% of pancreatic cancer patients. DPC4 and TGF-β work together to regulate cell proliferation in specific regions of DNA. Mutations in this gene cause uncontrolled proliferation and growth of cells, leading to pancreatic cancer.\textsuperscript{39}

\textbf{Pancreatic Cancer Treatment}

Treatment for cancer cases generally depends on the severity of cancer, for example, the difference between therapy in the early phase and therapy in the metastatic phase.\textsuperscript{40} Knowledge of the stage of cancer will be very useful in determining the right therapy for the patient. There are 3 types of general therapy commonly used to treat cancer cases, namely surgery, radiotherapy, and chemotherapy.\textsuperscript{41} The scheme of pancreatic cancer treatment therapy according to the severity phase can be seen in the Fig.-3. Surgery is the right choice to treat pancreatic cancer. This method provides a high cure rate and improves patient survival. However, this method is not recommended for patients who are in the metastatic phase. The surgical method is increasingly difficult to do due to the delay in cancer detection and the rapid change of cancer to the metastatic phase.\textsuperscript{42}
Patients using surgical therapy by the National Comprehensive Cancer Network (NCCN) are recommended to receive adjuvant chemotherapy accompanied by radiotherapy to reduce treatment failure. 5-Fluorouracil or leucovorin, gemcitabine, use of fluoropyrimidine chemoradiation in combination with gemcitabine is the first recommendation for adjuvant therapy. Administration of adjuvant therapy to obtain optimal results is recommended for 12 weeks after surgery. Treatment of metastatic pancreatic cancer patients should use chemotherapy, radiotherapy with additional chemotherapy is the second solution. Gemcitabine is a well-known chemotherapy for treating pancreatic cancer, although with a high risk of side effects. Therefore, the use of chemotherapy such as gemcitabine should be combined with other chemotherapy to reduce the risk of side effects.

The study of the combination of 5-Fluorouracil and Fluoropyrimidine given to patients with metastatic pancreatic cancer turned out to give the same good results as using gemcitabine monotherapy. The combination of 5-Fluorouracil and Fluoropyrimidine with gemcitabine was also investigated and the results were more effective than the first combination but increased the intensity of side effects such as neutropenia and thrombocytopenia. This combination of chemotherapy drugs has become the main choice in the treatment of pancreatic cancer in the world. Gemcitabine and erlotinib as targeted combinations at the EGFR receptor have been tested with good results. But the side effects of this combination are unavoidable, events such as skin rashes are a problem experienced by patients. The combination of gemcitabine and platinum analogues such as cisplatin has not shown any effect on pancreatic cancer, although some investigators have had good results. Gemcitabine given alone or in combination is a good chemotherapy treatment for pancreatic cancer patients. In addition to gemcitabine irinotecan, oxaliplatin, fluorouracil, and
leucovorin, or what is known as FOLFIRINOX are combination chemotherapy agents that are as good as gemcitabine. FOLFIRINOX is very effective for pancreatic cancer patients with metastases. Unfortunately, FOLFIRINOX also causes many side effects such as thrombocytopenia, neutropenia, diarrhea, and alopecia.\textsuperscript{53,54}

**Natural Products as Pancreatic Cancer Treatment**

It has been explained that pancreatic cancer is an aggressive type of cancer, it can be seen from the low cure rate and the average survival rate of patients is only under 5 years. This is due to the slow diagnosis of the disease due to non-specific disease symptoms and the rapid process of metastasis from cancer cells.\textsuperscript{55} Surgery with or without chemotherapy is the best solution that can be done in the early stages of cancer, but it is not appropriate for cancer that has entered the metastatic phase.\textsuperscript{56} Chemotherapy is the mainstay of treatment for metastatic pancreatic cancer. Giving monotherapy such as gemcitabine or a combination of gemcitabine with other chemotherapy such as FORFIRINOX is the recommended treatment option.\textsuperscript{57} The use of conventional chemotherapy such as gemcitabine as monotherapy or in combination with other chemotherapy tends to have the potential to cause considerable side effects. Common side effects include neutropenia, thrombocytopenia, skin rash, nausea and vomiting.\textsuperscript{58} The risk of chemotherapy resistance is also a separate problem that needs to be considered in the treatment of pancreatic cancer. Chemotherapy resistance in cancer cells will reduce the efficiency of chemotherapeutic agents in inhibiting the development of cancer cells.\textsuperscript{59} Therefore, it is necessary to search for alternative drugs that can inhibit the development of pancreatic cancer cells.\textsuperscript{60} Natural products are the right choice to be developed into anti-pancreatic cancer drugs through research conducted in vitro and in vivo as evidence of their efficacy and usefulness.\textsuperscript{61} Natural products that have been tested and researched have anti-pancreatic cancer activity in vitro and in vivo as well as their mechanism of action in inhibiting cancer cells, so they can be considered as alternative treatments as shown in Table-1. Inhibition of the cell cycle and promotion of apoptosis become an effective approach as a form of anti-pancreatic cancer activity of the sample.\textsuperscript{62} Aberrant cell cycle activity is one of the signs of cancer formation. Cell cycle aberrations result from mutations in the signaling pathways of genes encoding cell cycle proteins. The proliferation of cancer cells depends on the development of 4 phases, namely G0/G1, S, G2, and M which are regulated by the activity of cyclin-dependent kinase (CDKs) and Cyclin proteins as shown in Fig.-4.\textsuperscript{63} CDK is a key protein in this process, a serine/threonine derivative protein. Kinases that actively affect the cell cycle. The G1 phase was influenced by CDK 4, CDK 6, and CDK, the S phase by CDK 2, and CDK 1 in the G2-M phase.\textsuperscript{64} In the cell cycle process, CDK will interact with Cyclin and form a complex. There are 4 types of cyclins, each of which plays a role in a different phase of the cell cycle.\textsuperscript{65} The G1 phase is mediated by the interaction between cyclin D with CDK 4 and CDK 6. The cell cycle phase changes to the S phase when cyclin E interacts with CDK2. During the S phase, cyclin A will begin to interact with CDK2. Changes in the type of cyclin and CDK will occur again when entering the end of the G2 phase to the M phase. At that time cyclin A will interact with CKD1, then cyclin A will be enabled by cyclin B.\textsuperscript{66–68} The process of programmed cell death or better known as apoptosis is a popular method used by researchers to test the anticancer effects of medicinal substances, especially natural products.\textsuperscript{69} The process of apoptosis in pancreatic cancer cells can be studied in two types. The first type is a direct pathway that involves the activity of caspase 8 in producing caspase 3 causing apoptosis, can be seen in Fig.-5.\textsuperscript{70} The production of caspase 8 occurs due to signalization derived from the activity of the ligand with the death receptor. Frequently acting ligands such as TNFα, FasL, and TRAIL. This binding leads to the formation of DISC (death-inducing signaling complex) between FADD (Fas-associated death domain protein) and procaspase 8.\textsuperscript{71} The second type is the indirect type. The release of caspase 3 as an effector protein that causes apoptosis occurs through the effect of signaling on mitochondria.\textsuperscript{73} tBID derived from cleaved BID as a result of caspase 8 activity will increase the release of cytochrome c and other apoptotic factors from the mitochondria to the cytoplasm. cytochrome c will form a complex with Apaf-1 (apoptotic protease activating factor-1) thereby releasing the initiator caspase, namely caspase 9.\textsuperscript{74} The release of initiator caspase will stimulate the formation of effector, namely caspase 3, causing apoptosis, for more details can be seen in Fig.-6.\textsuperscript{75} Apoptotic activity in cancer cells does not run smoothly as expected. There are types of proteins that inhibit the occurrence of apoptosis that cannot be controlled, such as bcl-2 family, IAP family,
PI3K/Akt, and NF-kB. Several types of these proteins in cancer cells become inhibitors of apoptosis. Therefore, researchers are trying to find drug compounds that work in inhibiting the activity of these proteins so that the process of apoptosis can occur. Some research has been identified in Table-1.

Fig.-4: Protein Regulation in Cell Cycle

Fig.-5: Types of Cell Mechanism to Induce Caspase 3 to Lead Apoptosis

Fig.-6: Molecular Mechanism of Apoptosis Process in Cell Line
### Table-1: Pharmacology Activity of Natural Products as Antipancreatic Cancer

<table>
<thead>
<tr>
<th>Sample</th>
<th>Experimental model</th>
<th>Anticancer/anticarcinogenic effects</th>
<th>Molecular mechanism of action (↓Down regulated;↑ Up regulated)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction dichlorometane brown algae Fraction ethyl acetat brown algae</td>
<td>Mia PaCa-2, PANC-1, BXPC-3, PANC-3,27 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell viability, proliferation, and induced apoptotic cell death</td>
<td>NFkB ↓, EGFR ↓, VEGF ↓, Akt ↓, KRas ↓, Bel 2 ↓, Stat 3 ↓</td>
<td>79</td>
</tr>
<tr>
<td>Xylarione and 5-methyl mullein from Aegle marmelos</td>
<td>Mia PaCa-2 pancreatic cancer cell (in vitro)</td>
<td>Cytotoxic effect, inhibited cell cycle, and induced apoptotic cell death</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>Crocin from Crocus sativus</td>
<td>BxPC-3 pancreatic cancer cell (in vitro)</td>
<td>Inhibited of cell viability, cell cycle, and induced apoptotic cell death</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>Flavonoide Genistein</td>
<td>Mia PaCa-2, PANC-1 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell viability, proliferation, and induced apoptotic cell death</td>
<td>Cytochrome C ↑, Bax ↑, Caspase 3 ↑, Caspase 9 ↑, Bel 2 ↓, Stat 3 ↓, Cyclin D ↓, Survivin ↓</td>
<td>82</td>
</tr>
<tr>
<td>Isoprenoid farnesol and geraniol</td>
<td>Mia PaCa-2 pancreatic cancer cell (in vitro) PC-1 hamster pancreatic adenocarcinoma (in vivo)</td>
<td>Cytotoxic effect, inhibited cell cycle, and induced 5 apoptotic cell death</td>
<td>-</td>
<td>83</td>
</tr>
<tr>
<td>Agarwood essential oil from Aquilaria crassna</td>
<td>Mia PaCa-2 pancreatic cancer cell (in vitro)</td>
<td>Inhibited of cell viability, cell migration, and induced apoptotic cell</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>Extract methanol Petunia punctate</td>
<td>PANC-1 pancreatic cancer cells (in vitro)</td>
<td>Cytotoxic effect and induced apoptotic cell death</td>
<td>Caspase 3 ↑</td>
<td>85</td>
</tr>
<tr>
<td>Flavonoid apigenin</td>
<td>Mia PaCa-2, PANC-1, AsPc-1 BxPc-3 pancreatic cancer cell (in vitro)</td>
<td>Cytotoxic effect, inhibited cell cycle, and induced apoptotic cell death</td>
<td>Akt ↓, CDK 4 ↓, MIMP-9 ↓, GAPDA ↓</td>
<td>86</td>
</tr>
<tr>
<td>Rottlerin</td>
<td>PANC-1 pancreatic cancer cell (in vitro) Balb C nude mice (in vivo)</td>
<td>Inhibited of cell proliferation, angiogenesis, metastasis, and induced apoptotic cell death</td>
<td>Akt ↓, Notch ↓, Shh ↓, CDK 2 ↓, CDK 6 ↓, COX 2 ↓, VEGF ↓, VEGFR ↓, IL-8 ↓, MMP-2 ↓, MMP-9 ↓, Bel 2 ↓, Cyclin D1 ↓, Caspase 3 ↑, Bax ↑</td>
<td>87</td>
</tr>
<tr>
<td>Britannin</td>
<td>AsPc-1, PANC-1 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell viability, proliferation, and induced apoptotic cell death</td>
<td>FOXO ↑, ROS ↑, Caspase 3 ↑, Akt ↓</td>
<td>88</td>
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<tr>
<td>Narigenin from Citrus fruit</td>
<td>SNU-123 pancreatic cancer cell (in vitro)</td>
<td>Cytotoxic effect and induced apoptotic cell death</td>
<td>Prdx-1 ↓, ROS ↑, ASK-1 ↑, p 38 ↑, p 53 ↑</td>
<td>89</td>
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<tr>
<td>Brucein D from Brucea javanica fruit</td>
<td>PANC-1 SW1990, CAPAN 1 pancreatic cancer cell (in vitro)</td>
<td>Inhibited of cell viability and induced apoptotic cell</td>
<td>Caspase 3 ↑, Caspase 8 ↑, Caspase 9 ↑, p 38-MAPK ↑, Bel 2 ↓</td>
<td>90</td>
</tr>
<tr>
<td>Extract methanol</td>
<td>Achyranthes aspera</td>
<td>Mia PaCa-2, PANC-1, pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell proliferation and induced apoptotic cell death</td>
<td>MMP-1 ↓, MMP-2 ↓, TIMP 2 ↓, VEGF A ↓, VEGF B ↓</td>
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<tr>
<td>Extract methanol</td>
<td>Achyranthes aspera</td>
<td>Mice mode of PACA (in vivo)</td>
<td>Inhibited of cell proliferation and induced apoptotic cell death</td>
<td>Caspase 3 ↑, Akt ↓</td>
</tr>
<tr>
<td>Flavonoid apigenin</td>
<td></td>
<td>AsPc-1, PANC-1, Mia PaCa-2 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell viability, cell cycle, and induced apoptotic cell death</td>
<td>IKK-β ↓, NF-Kβ ↓, TNF-α ↓, Caspase 3 ↑, p50 ↑, p65 ↑</td>
</tr>
<tr>
<td>Brusatol</td>
<td></td>
<td>PANC-1 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of proliferation and induced apoptotic cell death</td>
<td>Bax ↑, Caspase 3 ↑, Caspase 3 ↑, Bcl 2 ↓, Stat 3 ↓, NF-Kβ ↓, p38-MAPK ↑</td>
</tr>
<tr>
<td>Rauwolfa vomitoria</td>
<td></td>
<td>Mia PaCa-2, PANC-1, AsPc-1, BxPC-3 pancreatic cancer mouse models (in vivo)</td>
<td>Cytotoxic effect, inhibited cell cycle, and induced apoptotic cell death</td>
<td>Caspase 8 ↑, Caspase 3 ↑</td>
</tr>
<tr>
<td>Toosendanin</td>
<td></td>
<td>PANC-1, AsPc-1 pancreatic cancer cells (in vitro)</td>
<td>Inhibited of cell viability, cell migration, and induced apoptotic cell death</td>
<td>Akt ↓, Mtor ↓</td>
</tr>
<tr>
<td>Fraction ethyl acetate of Orostachys japonicus</td>
<td></td>
<td>PANC-1 cells (in vitro)</td>
<td>Inhibited cell cycle and induced apoptotic cell death</td>
<td>CDK4 ↓, Cyclin D1 ↓, Cyclin B1 ↓, Caspase 8 ↓, Caspase 3 ↓, Caspase 9 ↓, p38 ↑, ERK ↑, JNK ↑</td>
</tr>
<tr>
<td>Corn silk crude polysaccharide</td>
<td></td>
<td>BxPC-3, SW1990, PANC-1 cell line (in vitro)</td>
<td>Induce pancreatic cancer cell apoptosis, arrest the cell cycle in S phase, and impede pancreatic cancer cell migration and invasion</td>
<td>Caspase 3 ↑, Bax ↑, Bcl-2 ↓, p21 ↑, Chk2 ↑, CDK2 ↓, EGFR ↓, PI3K ↓, Akt ↓, CREB ↓</td>
</tr>
<tr>
<td>The fractions of saponin-enriched extract of Helicteres hirsuta stem</td>
<td></td>
<td>MIAPaCa-2 PC, BxPC-3 and CFPAC-1 cells (in vitro)</td>
<td>Inhibited cell cycle and induced apoptotic cell death</td>
<td>-</td>
</tr>
<tr>
<td>Broussoflavonol B from Broussonetia kazinoki Siebold</td>
<td></td>
<td>PANC-1 cell (in vitro)</td>
<td>Sample reduced cell proliferation, induced cell cycle arrest, and inhibited cell migration, and invasion of human pancreatic cancer PANC-1 cells (p53 mutated)</td>
<td>FoxM1 ↓, Cyclin D1 ↓, Cyclin B1 ↓, MMP2 ↓, ERK ↓</td>
</tr>
<tr>
<td>β-sitosterol</td>
<td></td>
<td>MIAPaCa-2 and BXPC-3 cells (in vitro) Female BALB/c mice (nu/nu; 5-weeks-old; 19–23 g weight) (in vivo)</td>
<td>Inhibited the growth of PC cell lines by inhibiting proliferation, inducing G0/G1 phase arrest, and apoptosis. BS inhibited migration and invasion and downregulated epithelial–mesenchymal transition (EMT) markers and AKT/GSK-3β signaling pathways</td>
<td>NF-Kb ↓, Bcl-2 ↓, Bax ↑, Akt ↓, GSK ↓</td>
</tr>
<tr>
<td>Cucurbitacin B</td>
<td></td>
<td>ASPC-1, BxPC-3, HPAC, MiaPaCa-2 cells (in vitro)</td>
<td>Cucurbitacin B arrested pancreatic cancer (PC) cells in AFAP1-AS1 ↓, EGFR ↓, and Akt ↓</td>
<td>-</td>
</tr>
<tr>
<td>Natural Product</td>
<td>Cell Lines / Animal Model (Methodology)</td>
<td>Effects</td>
<td>Changes in Protein Expression</td>
<td>Notes</td>
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<tr>
<td>Britannin</td>
<td>PANC-1, BxPC-3 and MIA CaPa-2 cell lines (in vitro) Male BALB/c-nu mice (4 w of age) (in vivo)</td>
<td>In vitro anti-proliferation effects, anti-migration effects, and induced apoptosis</td>
<td>P-P65 ↓, P65 ↑, P50 ↑</td>
<td>103</td>
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<tr>
<td>Monensin</td>
<td>PANC-1 and MiaPaCa-2 cells (in vitro)</td>
<td>Monensin suppresses cell proliferation and migration, cell cycle progression, and induces apoptosis</td>
<td>E2F ↓, STAT ½ ↓, NfkB ↓, AP-1 ↓, Elk-1 ↓, EGFR ↓, RAF 1 ↓, ERK ↓</td>
<td>104</td>
</tr>
<tr>
<td>Olive Biophenols</td>
<td>MIA PaCa-2, BxPC-3, and CFPAC-1 cells (in vitro)</td>
<td>Reduce Proliferation, Influence the Cell Cycle, and Induce Apoptosis</td>
<td>Bax ↓, Bcl-2 ↓, Bak ↓, EGR-1 ↓, ADAMTS-1 ↓, c-FOS ↑</td>
<td>105</td>
</tr>
<tr>
<td>Eucalyptus microcorys leaf extract derived</td>
<td>MIA PaCa-2 cell (in vitro)</td>
<td>Reduces the viability of MIA PaCa-2 cells by inducing apoptosis, and arresting cell cycle</td>
<td>Bax ↑, Bak ↑, PARP ↑, Procaspe 3 ↑, Bcl-2 ↓</td>
<td>106</td>
</tr>
<tr>
<td>Crocin</td>
<td>BXPC3 and Capan-2 cell (in vitro)</td>
<td>Reduced cell viability and induced apoptosis</td>
<td>Cyclin D1 ↓, CDK 4 ↓, Bcl-2 ↓, p16 ↑, caspase 3 ↑, caspase 9 ↑, Bax ↑</td>
<td>107</td>
</tr>
<tr>
<td>Skullcapflavone I</td>
<td>PANC-1 cell (in vitro)</td>
<td>Reduced cell viability and induced apoptosis</td>
<td>E-cadherin ↑, N-cadherin ↓, vimentin ↓, TGF-β1 ↓, p-FAK ↓, p-AKT ↓, p-GSK-3β ↓ and p-p38 ↓</td>
<td>109</td>
</tr>
<tr>
<td>Paeonol</td>
<td>Panc-1 and Capan-1 cell lines (in vitro)</td>
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NATURAL PRODUCTS AS PANCREATIC CANCER TREATMENT

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Ethanolic extract of *Equisetum arvense* AsPC-1 cell (in vitro) Reduce Proliferation - 125

Ruscogenin is a saponin found in the root of *Ophiopogon japonicus* BxPC-3, SW1990, PANC-1, and AsPC-1 cells (in vitro) Influenced iron and ROS level ROS ↑, transferrin ↑, ferroportin ↓ 126

CONCLUSION

Pancreatic cancer is a dangerous type of cancer that is difficult to treat. Various attempts have been made to find methods and compounds that are effective in inhibiting the development of cancer cells. Surgery, chemotherapy and radiotherapy are the usual ways of treating pancreatic cancer. But these methods are starting to be less effective to use, such as surgery can only be used in the early stages of cancer, while radiotherapy and chemotherapy have decreased effectiveness due to chemoresistance and side effects that arise during therapy. Products derived from natural ingredients with fewer side effects are an alternative developed as pancreatic cancer drugs. Various tests and research on natural products were conducted to determine antiproliferative activity, cell cycle inhibition, apoptosis and molecular mechanisms in vitro and in vivo. This article summarizes some natural products that have been tested so that they can be used as a reference for pancreatic cancer treatment and further testing is needed to improve existing results.

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REFERENCES


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