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Role of apoptotic pathways in treating pancreatic cancer using natural compounds

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ABSTRACT

Pancreatic cancer is becoming most common cancer in the world wide having less treatment option with high death rate. Traditional compounds are chemical compounds isolated from natural/herbal plants. They have less side effects or no side effect and play an important role as anticancer agent in treatment. These having various natural compounds /substances that may involve in the action of different molecular pathways in apoptotic pathway like curcumin, capsaicin, triptolide, EGCG, ursolic acid etc. These natural compounds having ability to suppress development of the pancreatic cancer by the mechanism of signaling pathways such as K-Ras, NFκB, MAPK, P12K, AKT, P53, JAK & STAT. This review deals with use of natural compounds as a source of anticancer with potential mechanisms of apoptotic pathways.

Keywords- Natural compounds, Anticancer, Apoptotic pathway, Heterogeneous disease.

INTRODUCTION

Pancreatic cancer is one of the leading cause of cancer-related death, and many genetic and environmental risk factors have been associated with it (Ouyang, 2014). In many developing countries, pancreatic cancer was the eighth leading death cause from cancer in men and tenth leading death cause from cancer in women, respectively. The patients with pancreatic cancer had less survival rate about 9% of patients surviving 5 years after diagnosis. (Bayraktar *et al*. 2010; Sieg *et al*. 2011) In 2021, it was estimated that 60,430 patients will be diagnosed with pancreatic cancer and 48,220 patients with pancreatic cancer, most of them dying within first year of diagnosis. (Seer. cancer gov).

Cancer is one of the heterogeneous diseases and one of the major issues of health, especially for the public health system throughout the world (Javad *et al*. 2019). Pancreatic cancer is 12th most common and major cancerous tumors with high occurrence rate in the world. There are very rare cases of success with, chemotherapy or radiotherapy in treating

pancreatic cancer patients in advanced stage. Natural products/herbal medicines represent exciting adjunctive treatments as the alternative medicine.

Natural products are chemical compounds or substances which are produced by living organisms/environmental. With the development of modern technology, more and more plant extracts have been found to be useful for medical practice in the treatment of cancer and other diseases (Ouyang, 2014). Resveratrol, curcumin, Triptolide, Capsaicin and many more are the furthest developed examples of natural compounds for the treatment of pancreatic cancer, but many different compounds are also currently being evaluated for their therapeutic properties. This review deals with use of natural compounds as a source of anticancer with potential mechanisms of apoptotic pathways at advance level to treat pancreatic cancer in preclinical and clinical trials.

NATURAL PRODUCTS IN PANCREATIC CANCER TREATMENT AND THEIR MOLECULAR TARGETS IN APOPTOTIC RESISTANCE

Pancreatic cancer is becoming one of leading cause of cancer-related death, and many genetic and environmental risk factors have been associated with it. Some natural compounds like Curcumin, capsaicin, EGCG, Resveratrol, Triptolide, Ginsenosides etc having high level resistance to conventional chemotherapies and radiotherapies have not yet resovled in pancreatic cancer. Proto-oncogene expression, inactivation of tumor suppressor genes triggered by genetic mutations, and dys regulation of key signaling pathways (eg. NFκB, MAPK, PI3K/AKT, and JAK/STAT) have been implicated in pancreatic cancer's intractability (Li *et al*. 2010). Since chemotherapy and radiotherapy work mainly by inducing apoptosis (programmed cell death), thus defects cause in the apoptotic pathway can also cause cancer cell resistance (Kalthoff *et al*. 2003). The different molecular mechanisms that are involved in the apoptotic resistance pathways of pancreatic cancer are given below.

Molecular Heterogeneity Involved in Apoptotic Pathways-

1.K-Ras

In the Ras protein family, K-Ras is a small cytoplasmic GTP binding protein. (Shen *et al*. 2012). Mutation of K-ras (a proto-oncogene), which is observed in over 95% of pancreatic cancer cases, prevents efficient GTP hydrolysis, leaving the Ras protein in an active, GTP-bound state (Dhillon *et al*. 2007). K-Ras regulates several effects on pathways, producing anti-apoptotic effects through PI3/AKT activation, and pro-apoptotic effects through activation of Raf and MAPK in different circumstances.

2.Constitutively active NFκB

The NFκB family proteins, a class of redox-sensitive transcription factors, are activated in many malignancies; including breast, prostate, colon, and pancreatic cancers (Barkett M and Gilmore TD, 1999; Acharya *et al*. 2010). NFκB activation is linked to initiation and progression of cancer via regulation of its target genes involved in cell growth, proliferation, anti-apoptosis, angiogenesis, and metastasis (Acharya *et al*. 2010). NFκB is in a complex with its inhibitory protein IκB α, which masks the nuclear translocation domain of NFκB, thus restricting it to the cytosol and ultimately inhibiting its DNA binding activity. In addition, NFκB has been shown to inhibit TRAIL-induced apoptosis in human pancreatic cancer cells (Khanbolooki *et al*. 2006). Extensive evidence indicates that constitutive activation of NFκB is associated with AR and invasion (*Shah et al*. 2001; Arlt *et al*. 2003; Acharya *et al*. 2010). Enhanced accumulation of NFκB in cell nuclei and a concomitant decrease in cytosolic NFκB in Gem-treated cells suggests that the protein plays an important role in AR to Gem (Arora *et al*. 2011).

3.PI3K/AKT

Survival signals such as cytokines, growth factors, and hormones activate phosphatidylinositol 3-kinase (PI3K), which activates AKT by phosphorylation. Activated AKT interferes with the apoptotic machinery, including Bcl-2 family members, NFκB, and caspase 9 (Westphal and Kalthoff, 2003). In pancreatic carcinogenesis, AKT1, as an oncogene that prevents cell cyclear rest, promotes angiogenesis, and inhibits apoptosis (Zavoral *et al*. 2011). AKT2 is selective for the insulin receptor signaling pathway, is expressed in up to 60% of pancreatic cancer tumors (Roy *et al*. 2010). Inhibition of AKT2 has been reported to decrease NFκB activity and Bcl-2 expression while increasing Bax expression. Elevated levels of AKT reduce sensitivity of cells to pro-apoptotic stimuli through phosphorylation of substrates such as Bad andcaspase-9 (Westphal and Kalthoff, 2003). Different Studies have also shown that PI3K is required for

growth and survival of pancreatic cancer cells. Alteration of the PI3K/AKT pathway is an important mediator of chemo resistance to Gem (Long *et al*. 2011). Thus, the activated PI3K/AKT may be a potential target for the treatment of pancreatic cancer by apoptotic pathways. (Westphal and Kalthoff, 2003; Roy *et al*. 2010)

4.MAPK

An important role plays by Mitogen-activated protein kinases (MAPKs) in cell proliferation, differentiation, transformation, survival, and death. The Ras/Raf/MAPK pathway is a complicated pathway that regulates many cellular activities including gene expression, mitosis, movement, metabolism, and apoptosis (Dhillon *et al*. 2007; Cagnol and Chambard, 2010; Zavoral *et al*. 2011). MAPK path-ways are strongly implicated in pancreatic cancer treatment and prevention since K-ras is activated in about 90% of patients' tumors (Westphal and Kalthoff, 2003). The Ras/Raf/MAPK path-way is activated through a sequential phosphorylation cascade, which amplifies and transduces signals from the cell membrane to nucleus. Abnormalities in MAPK signaling play an important role in the pathology of cancer as well as for sensitivity to drugs (Dhillon *et al*. 2007). ERK signaling is activated by numerous extracellular signals, including growth factors, cytokines, and other external mitogenic signals, which are of particular relevance to cancer (Olson and Hallahan, 2004; Dhillon *et al*. 2007)

5. p53

The p53 gene encodes a 53-kDa nuclear phosphor protein is to be a tumor suppressor. The p53 protein is a transcription factor that regulates genes involved in apoptosis and can act upon mitochondrial proteins such as in Bax, Bak, Bcl-2, Bcl-XL to promote the release of cytochrome c and apoptosis (Schuler *et al*. 2001). It also induces cell cycle arrest and apoptosis in response to cellular stresses (e.g.- ionizing radiation, ultraviolet light, growth factor deprivation, reactive oxygen species (ROS)) and DNA damage induced by various cytotoxic agents (Ghaneh *et al*. 2002; Zhang *et al*. 2011).The p53 gene is mutated in over 50% of human pancreatic cancer cases. Accumulating evidence shows that p53 status has a significant impact on drug sensitivity (Nio *et al*. 1998).

6.JAK/STAT

The signal transducers and activators of transcription (STAT)family of transcription factors play a crucial role in regulating the expression of genes involved in cell survival, proliferation, chemo resistance, and angiogenesis, such as COX-2, matrix metallo-proteinase, Bcl-XL, cyclin D1, and VEGF (Ihle, 1996; Toyonaga *et al*. 2003; Yu and Kim, 2012). IL-6, epidermal growth factor receptor (EGFR), Janus-activated kinases (JAK) and Src family kinases are responsible for the activatation of STAT3. Aberrant signaling of the JAK/STAT pathway has been demonstrated in pancreatic cancer (Sahu and Srivastava, 2009; Thoennissen *et al*. 2009) and specific inhibitors of JAK2and/or STAT3 have been shown that it suppress the growth of cell in pancreatic cancer (Thoennissen *et al*. 2009). The JAK/STAT pathway act as potential therapeutic target in treating the pancreatic cancer.

NATURAL COMPOUNDS AND PANCREATIC CANCER

Herbal remedies have been used in the treatment of cancer for thousands of years in numerous countries, including Egypt, China, Japan and other countries. Some have come to be accepted as forms of complementary and altenative medicines in western countries (Saad *et al*. 2005). Epidemiological research have shown that flavonoids from fruit and vegetable as well as citrus limonoids could be helpful in reducing the risk of pancreatic cancer (Pericleous *et al*. 2014).

Recent study has shown that regular green tea drinking in women is associated with 32% reduction of pancreatic cancer risk; lower temperature of tea may be attributed to reduced risk of pancreatic cancer for human (Wang *et al*. 2012). In addition, accumulate evidence has demonstrated that the use of curcumin is beneficial in the prevention and treatment of pancreatic cancer (Johnson J and de Mejia, 2011; Preicleous *et al*. 2014). In the study for patients of pancreatic cancer with liver metastasis, Chinese herbal medicines were found to be a protective factor (Ouyang *et al*. 2011). Therefore, the role of HM/NP in the prevention or in the treatment of pancreatic cancer becomes as an alternative approach. They have been accrued with suitable advantages, like suppression of tumor progression, improving the efficacy and lessening the side effects of chemotherapy and radiotherapy, and improving immune system function. Unlike western medicines, which generally consist of purified compounds, Herbal Medicinal /Natural products may be comprised of different herbs and components acting simultaneously on the cellular mechanisms and molecular targets. The extracted

compounds from medicinal plants and herbs have multiple effects, like increasing the efficacy of and decreasing the toxicity of chemotherapeutic agents. There are several types of Herbal medicinal/natural products which may improve ability to overcome apoptotic resistance in pancreatic cancer (Lin *et al*. 2014).

1. Curcumin

Curcumin has the potential to suppress development of pancreatic cancer and it is also known as diferuloymethane and isolated from curcum longa. Curcumin is also associated with increased apoptosis via inhibition of pathways such as those of NF-jB, SP1,STAT3, Notch-1, COX-II, ATM/Chk1 and WT1 (Glienke *et al*. 2009; Sahu *et al*. 2009) .Curcumin treatment may also enhance IL-8 receptors CXCR1 and CXCR2 on cell surfaces, suggesting that it inhibits proliferation of pancreatic cancer cells by inhibiting NF-jB and IL-8 receptor internalization(Hidaka *et al*. 2002). In addition, a further derivative of curcumin, GO-Y030, has been found to inhibit STAT3 at small doses, where curcumin itself had less or no effect (Hutzen *et al*. 2009).

2. Capsaicin

Capsaicin is one of the compound having homovanillic acid derivative like in chili peppers plants that mammals perceive as spicy and has been shown to anticancer effects on various cancer cells and has historically used in different disease treatment through different mechanisms. In human pancreatic cancer cells, capsaicin induced apoptosis through significant down-regulation of Bcl-2, survive in, and release of the cytochromec and apoptosis inducing factor. Moreover, JNK activation and increased Bax expression have also been observed after exposure of capsaicin (Zhang *et al*. 2008) demonstrated that inhibition of PI3K and AKT was also involved in capsaicin's apoptotic effects on pancreatic cancer both in vivo and in vitro (Zhang *et al*. 2013). Capsaicin has been reported to disrupt thioredox in/apoptosis signal-regulating kinase 1 (ASK1) interaction and activate MKK4/MKK7 as well as their downstream effectors, thereby leading to apoptosis in pancreatic tumor cells.

3. Triptolide

Triptolide, is a diterpene triepoxide from the Chinese plant i.e. Tripterygium wilfordii Hook F. This compound can inhibit the growth of pancreatic cancer cells in vitro and metastasis of tumors in vivo. Different studies have reported that it induces through the inhibition of Hsp70 expression in pancreatic cancer cell can cause death (Phillips *et al*. 2007). Down-regulation of COX-2 and decreased TRAIL resistance have been implicated in triptolide-induced apoptosis (Borja *et al*. 2010; Ma *et al*. 2013).

4. Green Tea Catechins and Epigallocatechin Gallate (EGCG)

Green tea catechins can also inhibit growth of various types of cancer by targeting different signalling pathways. It inhibits phosphorylation of AKT and p53 which are leading to apoptosis and suppression of pancreatic tumour growth (Zhang *et al*. 2011). Reactive oxygen species are involved in EGCG-induced cell death, as EGCG dose-dependently induces reactive oxygen species generation in pancreatic cancer cells, and activates the JNK and cell cycle arrest, which is leading to apoptosis (Qanungo *et al*. 2005; Hariharan *et al*. 2008) . In addition, EGCG significantly inhibits pluri potency maintenance factors such as Nanog, c-Myc and Oct-4 of pancreatic CSC, thus inhibiting self-renewal potency of pancreatic CSCs (Tang *et al*. 2012).

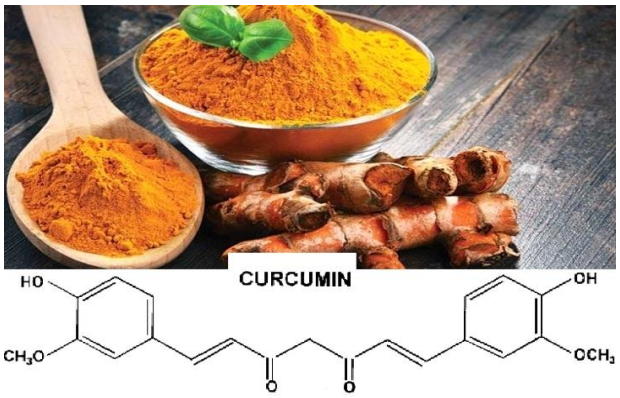

Fig.1.Curcumin

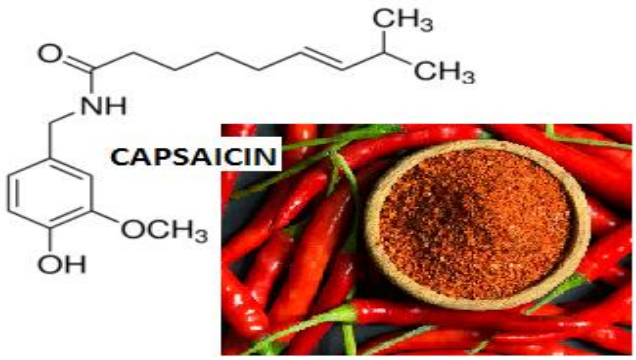

Fig.2. Capsaicin

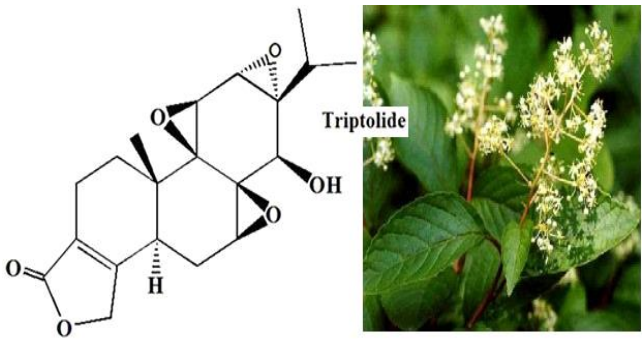

Fig.3. Triptolide

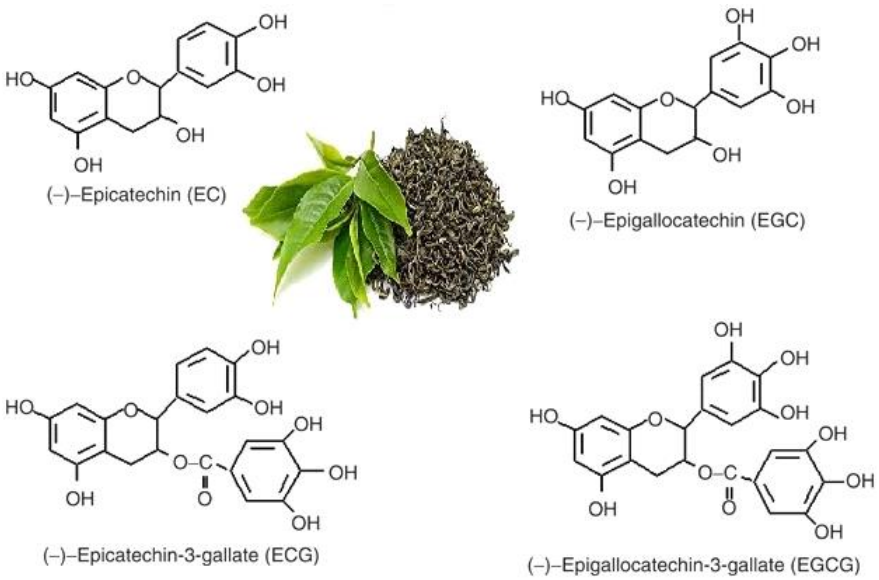

Fig.4. Green Tea Catechins and Epigallocatechin Gallate (EGCG)

5. Celastrol

Celastrol, is a triterpenoid also isolated from T. wilfordii and has anti-cancer activity against in variety of tumor cells in vitro and in vivo. Celastrol can enhance TRAIL-induced apoptosis via up- regulation of TRAIL receptor DR5 and DR4 expression in AsPC-1 cells (Sung *et al*. 2010). Synergistic effects of TRAIL plus celastrol were recorded in several normally resistant pancreatic cancer cell lines (Chakravarthy *et al*. 2013). It has been demonstrated that the anti-pancreatic cancer activity of celastrol also involves disruption of Hsp90–Cdc37 interaction in the super chaperone complex (Zhang *et al*. 2008).

6. Ginsenosides

Ginsenosides is also known as triterpene glycosides because it is one of the main bioactive components of ginseng. In human pancreatic cancer cells, treatment of BxpC-3 with ginsenoside Rh2 (GnsRh2) resulted in decrease in levels of Bcl-2/Bak and survivin (Tang *et al*. 2013). Two types of ginsenosides has been discovered i.e. 25-OCH3-PPD [20(S)- 25-methoxyl-dammarane-3b,12b,20-triol and 25-OHPPD [20(R)-dammarane-3b,12b,20,25-tetrol], that target MDM2 proteins and leading to up-regulation of p53 and down-regulation of Bcl-2 and Bax, and thereby favoring apoptosis (Wang *et al*. 2009).

7. Resveratrol

Resveratrol induces apoptosis through the mitochondria dependent pathway in pancreatic cancer cellsand it generate moderate reactive oxygen species (ROS) which increased when the resveratrol treatment is combined with ionizing radiation (Shankar *et al*. 2007) and it also induce apoptosis in INS-1E insulinoma cells through inhibiting AKT signalling

(Sun *et al*. 2008) and, resveratrol-induced cell cycle arrest has been associated with up-regulation of the cell cycle molecules such as p21/CIP1, p27/KIP1 and expression of cyclin D1 inhibites, in MIA PaCa-2,ASPC-1 and PanC-1 pancreatic cancer cells (Mo *et al*. 2011). Through inhibition of PI3KCI/AKT and MEK/ERK are targeted by FOXO phosphorylation , signalling in pancreatic cancer cells and eventually silences FOXO protein abrogated resveratrol induced by cell cycle arrest and apoptosis (Roy *et al*. 2011).

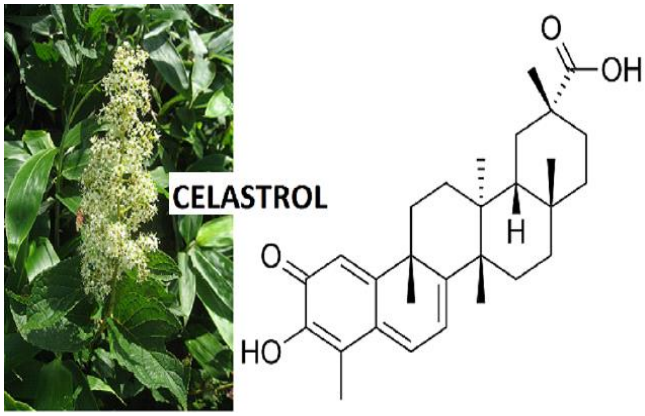

Fig.5. Celastrol

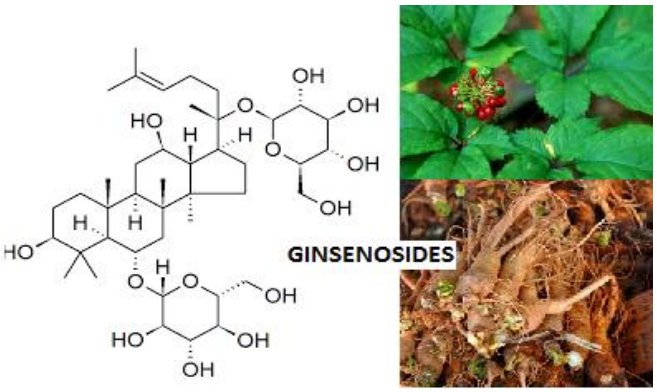

Fig.6. Ginsenosides

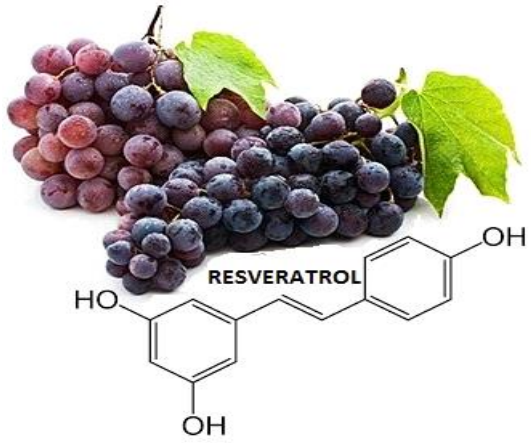

Fig.7. Resveratrol

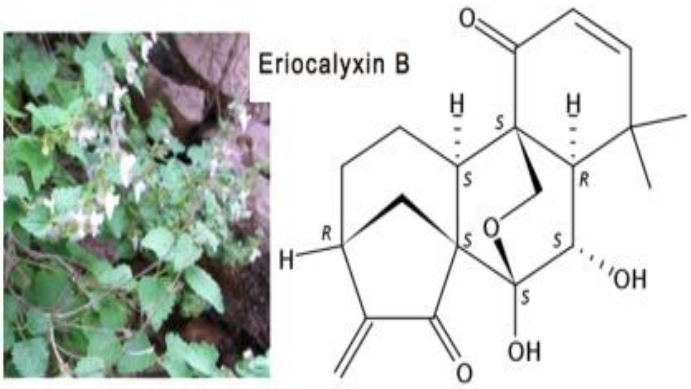

Fig.8: Eriocalyxin B (Eri B)

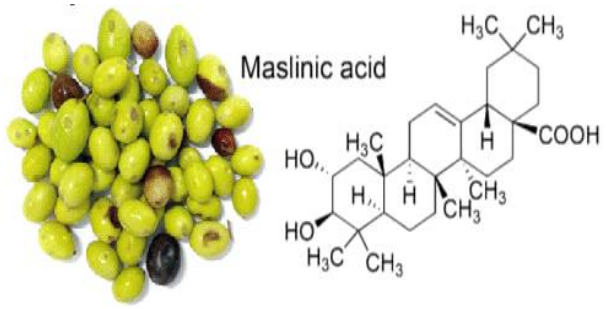

Fig.9. Ursolic Acid and Maslinic Acid

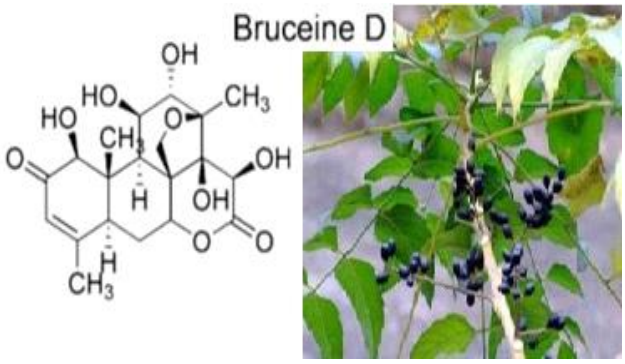

Fig.10. Bruceine D (BD).

8. Eriocalyxin B

Eriocalyxin B (Eri B) is extracted from the Isodon eriocalyx plant, anent-kaurane diterpenoid with the potential of developed into a broad-spectrum anticancer agent. Some Research Shows that reduction of the Bcl-2/Bak ratio and activation of p38 (ERK1/2)/p53pathways and caspase cascade are involved in the induction of apoptosis pathway in pancreatic cancer cells by Eriocalyxin B (Li *et al*. 2012). In some studies has shown that Eri B treatment also induces ROS through inhibition of thiol-containing antioxidant systems (glutathione and thioredoxin systems), thereby activating ASK1 (MAPK family member) and inhibiting the NFB pathway.

9. Ursolic Acid and Maslinic Acid

Ursolic acid is also know as pentacyclic triterpenoid compound which is extracted from different types of herbal plants & vegetables. Ursolic Acid has been reported for inhibit cell growth and induce apoptosis in human Gem-resistant pancreatic cancer cells through the PI3K/AKT/NFB and JNK pathways (Li *et al*. 2012). Maslinic acid, which is derived from dry olive-pomace oil, has shown inhibiting TNF induced IK degradation, p65 phosphorylation, and nuclear translocation, as well as expression of NFB-regulated genes including COX-2, survivin, IAP-1, Bcl-2, XIAP and Bcl-xL(Wang *et al*. 2009).

10. Bruceine D (BD)

In some studies explained that bruceine D, a quassinoid found in abundance in Brucea javanica, possesses potent anti-pancreatic cancer activity. Some previous research studies showed that bruceine D induced pancreatic cancer cell apoptosis by lowing the Bcl-2/Bak ratio and activating the p38 pathway (Lau *et al*. 2009; Liu *et al*. 2012). In addition, BD treatment significantly inhibited the NFB pathway and its target genes, including Bcl-2 and XIAP. Moreover, the enhancement of ROS production through inhibiting glutathione level and increasing the expression of NADPH oxidase p22phox, p67phox were also involved in BD-induced apoptosis (Lau *et al*. 2010).

CONCLUSION

Cancer is one of the leading causes of mortality worldwide and it is imperative to develop novel approaches to treat such type of diseases. Generally, natural agents are considered safe while treating or prevention diseases (Javad *et al*. 2019*)*; Although there have been great improvement in recent decades in the treatment of many common cancers in clinic (e.g. breast and prostate cancer), pancreatic cancer still remains a major challenge and remains the most lethal cancer diagnosis (Siegel *et al*. 2012). Many mechanisms contribute to intractability of pancreatic cancer, including genetic mutations, tumor micro environment and cancer stem cells. Above all, AR is the most critical factor limiting the efficacy of chemotherapeutic agents in patients with pancreatic cancer. By understanding the corresponding mechanisms and new break by overcome AR should improve clinical outcomes. Given the different mutations and signaling pathways involved in the pathology and AR of pancreatic cancer, there may not a single therapeutic agent capable of controlling it. There is a great variety of HM/NPs targeting different cancer-related proteins and pathways, making them an attractive direction for development into adjuvant therapeutics for pancreatic cancer. Thus, natural products/herbal medicines play an important role in prevention and treating of pancreatic cancer by different approach. (Lin Li and Po Sing Leung, 2014).

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REFERENCES

Acharya A, Das I, Chandhok D, Saha T. (2010) Redox regulation in cancer: a double-edged sword with therapeutic potential. *Oxid Med Cell Longev*, 3:23–34

Arora S, Bhardwaj A, Srivastava SK, Singh S, McClellan S, Wang B, *et al*. (2011) Honokiol arrests cell cycle, induces apoptosis, and potentiates the cytotoxic effect of gemcitabine in human pancreatic cancer cells. *PLoS ONE*, 6:e21573

Barkett M, Gilmore TD (1999) Control of apoptosis by Rel/NF-kappaB transcription factors. *Oncogene*, 18:6910–6924.

Bayraktar S, Bayraktar UD, Rocha-Lima CM (2010) Recent developments in palliative chemotherapy for locally advanced and metastatic pancreas cancer. *World J Gastroenterol*, 16:673–682

Borja-Cacho D, Yokoyama Y, Chugh RK, Mujumdar NR, Dudeja V, Clawson KA, *et al*. (2010) TRAIL and triptolide: an effective combination that induces

apoptosis in pancreatic cancer cells. *J Gastrointest Surg*, 14:252–260

Cagnol S, Chambard JC (2010) ERK and cell death: mechanisms of ERK-induced cell death—apoptosis, autophagy and senescence. *FEBS J*, 277: 2–21

Chakravarthy R, Clemens MJ, Pirianov G, Perdios N, Mudan S, Cartwright JE, *et al*. (2013) Role of the eIF4E binding protein 4E-BP1 in regulation of the sensitivity of human pancreatic cancer cells to TRAIL and celastrol-induced apoptosis. *Biol Cell*, 105:414–29

Dhillon AS, Hagan S, Rath O, Kolch W. (2007) MAP kinase signalling pathways in cancer. *Oncogene* , 26:3279–3290.

Downward J. (1998) Ras signalling and apoptosis Curr Opin Genet Dev, 8:49–54

Ghaneh P, Kawesha A, Evans JD, Neoptolemos JP (2002) Molecular prognostic markers in pancreatic cancer. *J Hepatobiliary Pancreat Surg*, 9:1–11.

Glienke W, Maute L, Wicht J, Bergmann L (2009) Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and down regulation of survivin/BIRC5 gene expression. *Cancer Invest*, 28:166–171.

Hariharan D, Saied A, Kocher (2008) HM Analysis of mortality rates for pancreatic cancer across the world. *HPB*, 10:58–62.

Hidaka H, Ishiko T, Furuhashi T, Kamohara H, Suzuki S, Miyazaki M, *et al*. (2002) Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface.*Cancer*, 95:1206–1214.

Hutzen B, Friedman L, Sobo M, Lin L, Cen L, De Angelis S, *et al*. (2009) Curcumin analogue GO-Y030 inhibits STAT3 activityand cell growth in breast and pancreatic carcinomas. *Int. J. Oncol*, 35:867–872.

Ihle JN. (1996) STATs: signal transducers and activators of transcription. *Cell*, 84:331–334.

Johnson J, de Mejia EG. (2011) Dietary factors and pancreatic cancer: the role of food bioactive compounds. *Mol Nutr Food Res*, 55:58–73

Khanbolooki S, Nawrocki ST, Arumugam T, Andtbacka R, Pino MS, Kurzrock R, *et al*. (2006) Nuclear factor-kappaB maintains TRAIL resistance in human pancreatic cancer cells. *Mol Cancer Ther*, 5:2251–2260.

Lau ST, Lin ZX, Leung PS. (2010) Role of reactive oxygen species in brucein Dmediated p38-mitogen-activated protein kinase and nuclear factor-kappaB signalling pathways in human pancreatic adenocarcinoma cells. *Br J Cancer*, 102:583–593.

Lau ST, Lin ZX, Liao Y, Zhao M, Cheng CH, Leung PS, *et al*. (2009) Induces apoptosis in pancreatic adenocarcinoma cell line PANC-1 through the activation of p38-mitogen activated protein kinase. *Cancer Lett*, 281:42–52.

Li C, Yang Z, Zhai C, Qiu W, Li D, Yi Z, *et al*. (2010) Maslinic acid potentiates the antitumor activity of tumor necrosis factor alpha by inhibiting NF-kappaB signaling pathway. *Mol Cancer*, 9:73

Li J, Liang X, Yang X (2012) Ursolic acid inhibits growth and induces apoptosis in gemcitabine-resistant human pancreatic cancer via the JNK and PI3K/Akt/NFkappaB pathways. *Oncol Rep* 28:501–510.

Li J, Wientjes MG, Au JL (2010) Pancreatic cancer: Pathobiology, treatment options, and drug delivery. *AAPS J*, 12:223–232

Li L, Yue GG, Lau CB, Sun H, Fung KP, Leung PC, *et al*. (2012) induces apoptosis and cell cycle arrest in pancreatic adenocarcinoma cells through caspase- and p53-dependent pathways. *Toxicol Appl Pharmacol*, 262:80–90.

Lin Li, Po Sing Leung* (2014) Use of herbal medicines and natural products: An alternative approach to overcoming the apoptotic resistance of pancreatic cancer . *The Internt J.of Bioche. & Cell Bio.*, 53:224–236

Long J, Zhang Y, Yu X, Yang J, LeBrun DG, Chen C, *et al*. (2011) Overcoming drug resistance in pancreatic cancer. *Expert Opin Ther Targets*, 15:817–828

Ma JX, Sun YL,Wang YQ,Wu HY, Jin J, YuXF. (2013) Triptolide induces apoptosis and inhibits the growth and angiogenesis of human pancreatic cancer cells by downregulating COX-2 and VEGF. *Oncol Res*, 20:359–68.

Mo W, Xu X, Xu L, Wang F, Ke A, Wang X, *et al*. (2011) Resveratrol inhibits proliferation and induces apoptosis through the hedgehog signaling pathway in pancreatic cancer cell. *Pancreatology*, 11:601–609.

Nio Y, Dong M, Uegaki K, Hirahara N, Minari Y, Sasaki S, *et al*. (1998) p53 expression affects the efficacy of adjuvant chemotherapy after resection of invasive ductal carcinoma of the pancreas. *Anticancer Res*, 18:3773–3779

Olson JM, Hallahan (2004) AR. p38 MAP kinase: a convergence point in cancer therapy. *Trends Mol Med*, 10:125–9.

Ouyang L*,a,Luo† Y,a, Tian M*,a, Zhang*SY, Lu‡ R, Wang§ JH *et al* (2014) Plants natural products from traditional compounds to new emerging drugs in cancer therapy, *cell prolif*, 47:506-515

Ouyang H, Wang P, Meng Z, Chen Z, Yu E, Jin H, *et al*. (2011) Multimodality treatment of pancreatic cancer with liver metastases using chemotherapy, radiation therapy, and/or Chinese herbal medicine. *Pancreas*, 40:120–5

Pericleous M, Rossi RE, Mandair D, Whyand T, Caplin ME. (2014) Nutrition and pancreatic cancer. *Anticancer Res*, 34:9–21

Phillips PA, Dudeja V, McCarroll JA, Borja-Cacho D, Dawra RK, Grizzle WE, *et al*. (2007) Triptolide induces pancreatic cancer cell death via inhibition of heat shock protein 70. *Cancer Res*, 67:9407–9416.

Pramanik KC, Srivastava SK (2012) Apoptosis signal-regulating kinase 1-thioredoxin complex dissociation by capsaicin causes pancreatic tumor growth suppression by inducing apoptosis. *Antioxid Redox Signal*, 17:1417–32.

Qanungo S, Das M, Haldar S, Basu A (2005) Epigallocatechin-3- gallate induces mitochondrial membrane

depolarization and caspase- dependent apoptosis in pancreatic cancer cells. *Carcinogenesis*, 26:958–967.

Roy SK, Chen Q, Fu J, Shankar S, Srivastava RK (2011) Resveratrol inhibits growth of orthotopic pancreatic tumors through activation of FOXO transcription factors. *PLoS One* 6, e25166

Roy SK, Srivastava RK, Shankar S (2010) Inhibition of PI3K/AKT and MAPK/ERK pathways causes activation of FOXO transcription factor, leading to cell cycle arrest and apoptosis in pancreatic cancer. *J Mol Signal*, 5:10

Saad B, Azaizeh H, Said O. (2005) Tradition and perspectives of arab herbal medicine:. *Evid Based Complement Alternat Med*, 2:475–479.

Sahu R, Batra S, Srivastava S (2009) Activation of ATM/Chk1 by Curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. *Br. J. Cancer* , 100:1425–1433.

Sahu RP, Srivastava SK. (2009) The role of STAT-3 in the induction of apoptosis in pancreatic cancer cells by benzyl isothiocyanate. *J Natl Cancer Inst*, 101:176–93

Schuler M, Green DR. (2001) Mechanisms of p53-dependent apoptosis. *Biochem Soc Trans*, 29:684–8

Seer.cancer gov/statfacts/html/pancreas.html

Siengel R, Naishadham D, Jemal (2012) A Review Cancer Statistics, 2012,*CA cancer J Clin*, 62:10-29

Shah SA, Potter MW, Hedeshian MH, Kim RD, Chari RS, Callery MP (2001) PI-3 kinase and NF-kappaB cross-signaling in human pancreatic cancer cells. *J Gastrointest Surg*, 5:603–12.

Shankar S, Suthakar G, Srivastava RK (2007) Epigallocatechin-3-gallate inhibits cell cycle and induces apoptosis in pancreatic cancer. *Front. Biosci*, 12:5039–5051.

Sharifi-Rad J,*Ozleyen A, Tumer TB,*Adetunji CO, Omari NE, Balahbib A *et al* (2019) Natural Products and Synthetic Analogs as a Source of Antitumor Drugs Biomolecules, 9,679,*doi:10.339/biom9110679*

Shen L, Kim SH, Chen CY. (2012) Sensitization of human pancreatic cancer cells harboring mutated K-ras to apoptosis. *PLoS ONE*, 7:e40435

Sun W, Wang W, Kim J, Keng P, Yang S, Zhang H, *et al*. (2008) Anti-cancer effect of resveratrol is associated with induction of apoptosis via a mitochondrial pathway alignment. *Adv. Exp. Med. Biol*, 614:179–186.

Sung B, Park B, Yadav VR, Aggarwal BB. (2010) Celastrol, a triterpene, enhances TRAILinduced apoptosis through the down-regulation of cell survival proteins and up-regulation of death receptors. J Biol Chem, 285:11498–11507

Tang SN, Fu J, Nall D, Rodova M, Shankar S, Srivastava RK (2012) Inhibition of sonic hedgehog pathway and pluripotency maintaining factors regulate human pancreatic cancer stem cell characteristics. *Int. J. Cancer*, 131:30–40.

Tang XP, Tang GD, Fang CY, Liang ZH, Zhang LY. (2013) Effects of ginsenoside Rh2 on growth and migration of pancreatic cancer cells. *World J Gastroenterol*, 19:1582–1592

Thoennissen NH, Iwanski GB, Doan NB, Okamoto R, Lin P, Abbassi S, *et al*. (2009); Cucurbitacin B induces apoptosis by inhibition of the JAK/STAT pathway and potentiates antiproliferative effects of gemcitabine on pancreatic cancer cells. *Cancer Res*, 69:5876–5884

Toyonaga T, Nakano K, Nagano M, Zhao G, Yamaguchi K, Kuroki S, *et al*. (2003) Blockade of constitutively activated Janus kinase/signal transducer and activator of transcription-3 pathway inhibits growth of human pancreatic cancer. *Cancer Lett*, 201:107–116.

Wang J, Zhang W, Sun L, Yu H, Ni QX, Risch HA, *et al*. (2012) Green tea drinking and risk of pancreatic cancer: a large-scale, population-based case–control study in urban Shanghai. *Cancer Epidemiol*, 36:e354–358.

Wang W, Rayburn ER, Zhao Y, Wang H, Zhang R. (2009) Novel ginsenosides 25-OH-PPD and 25-OCH3-PPD as experimental therapy for pancreatic cancer: anticancer activity and mechanisms of action. *Cancer Lett*, 278:241–248.

Westphal S, Kalthoff H (2003) Apoptosis :targets in pancreatic cancer. *Mol Cancer*; 2:6.

Yu JH, Kim H. (2012) Role of janus kinase/signal transducers and activators of transcription in the pathogenesis of pancreatitis and pancreatic cancer. *Gut Liver* 6:417–422

Zavoral M, Minarikova P, Zavada F, Salek C, Minarik M. (2011) Molecular biology of pancreatic cancer. *World J Gastroenterol*, 17:2897–2908

Zhang L, Pang E, Loo RRO, Rao J, Go VLW, Loo JA, *et al*. (2011) Concomitant inhibition of HSP90, its mitochondrial localized homologue TRAP1 and HSP27 by green tea in pancreatic cancer HPAF-II cells. *Proteomics*, 11:4638–4647.

Zhang JH, Lai FJ, Chen H, Luo J, Zhang RY, Bu HQ, *et al*. (2013) Involvement of the phosphoinositide 3-kinase/Akt pathway in apoptosis induced by capsaicin in the human pancreatic cancer cell line PANC-1. *Oncol Lett*, 5:43–48

Zhang R, Humphreys I, Sahu RP, Shi Y, Srivastava SK. (2008) In vitro and in vivo induction of apoptosis by capsaicin in pancreatic cancer cells is mediated through ROS generation and mitochondrial death pathway. *Apoptosis* 13:1465–1478

Zhang T, Hamza A, Cao X, Wang B, Yu S, Zhan CG, *et al*. (2008) A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. *Mol Cancer Ther*, 7:162–170.

Zhang Y, Chen AY, Li M, Chen C, Yao Q. (2008) Ginkgo biloba extract kaempferol inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. *J Surg Res*; 148:17–23.