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Mini Review

Pancreatic Cancer-What, How and Why of Plant-bioactives and Probiotic Therapy

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Abstract

Pancreatic Cancer records 98% mortality till date owing to advanced age, elusive early diagnostic biomarkers and tools and side-effects of conventional therapies that are mostly only palliative. Primary defense in the form of chemoprevention is a potential tackling strategy. Plant bioactives-based dietary therapy is safe, natural and less expensive considering that dietary and lifestyle risk factors, especially- smoking, obesity, high- fat diet and/certain hereditary factors are associated significantly with the onset and mortality of pancreatic cancer. A variety of plant phenolics including curcumin and green tea extract, whole grains, isothiocyanates, capsaicin, micronutrients, carotenoids and vitamins, medicinal plants and their related actives and probiotics have been established to prevent onset and metastasis of PC using various model organisms as well as preliminary clinical trials. Further epidemiological studies using well-designed and disciplines-integrated clinical trials to identify susceptible populations and establish efficacy of plant bioactives based dietary therapy will contribute to reducing the mortality associated with PC.

Keywords: Pancreatic Cancer; Plant Bioactives; Probiotics; Chemoprevention; Synthetic Mimics

Abbreviations

PC: Pancreatic Cancer; PDAC: Pancreatic Ductal Adeno Carcinoma; BOP: N-nitrosobis (2-oxopropyl) Amine; EGCG: (-) Epigallocatechin Gallate; GTE: Green Tea Extract; LDHA: Lactate Dehydrogenase; WG: Whole Grains; HDI: Human Development Index; HSP: Heat Shock Protein; PPI: Proton Pump Inhibitor; ROS: Reactive Oxygen Species

Introduction

Pancreatic cancer is presently the seventh leading cause of global cancer deaths, with almost 98% mortality, as inferred from GLOBOCAN- 2018 [4]. Rates are 3-4 folds higher in HDI countries, highest being in Europe, North America and Australia/New Zealand, also with the presently available intervention technologies it is forecast that PC will surpass breast cancer, as the third leading cause of cancer deaths across the world. It is noteworthy to highlight that high-quality cancer registry data, the basis for planning and implementing evidence-based cancer control programs, are not available in most low- and middle-income countries. The present mini-review attempts to highlight one of the most fatal malignancies known and how plant bioactives-based dietary interventions could pave way for natural and safer therapies.

Why plant-based therapies -*Chemoprevention*

Despite advances in molecular understanding of PC, the clarity on the etiology has been elusive. However, several risk factors are linked to a higher risk of pancreatic neoplasia -tobacco smoking the most well-established risk factor, has an estimated two-fold risk of pancreatic malignancy in smokers compared to non-smokers [23]. Besides, Type II diabetes, excess alcohol consumption, diet rich in red meat, sugar and saturated fat, high body mass index, gallstones, *Helicobacter pylor*i infection, chronic pancreatitis, a family history of pancreatic cancer, and known germline mutations are some of the identifiable risk factors for PC. The risk was found to decrease with increased consumption of fresh fruits and vegetables, fiber, natural foods and Vitamin C [8,9,33]. The facts that markers of early detection of PC, especially of PDAC, are lacking and screening programs ambiguous even in high risk populations, makes surgical and radiotherapy resurrection rarely feasible after PC is diagnosed. The location of the tumor in the retroperitoneum, the advanced age of patients, and the systemic effects of the disease limit the options for local therapy. Chemotherapy is palliative and with known disadvantages. The molecular and cellular features of ductal pancreatic tumors are aggressive and underlay multiple levels of thera-

peutic resistance. Stromal proliferation reduced vascular density and immune suppression also contribute to therapeutic resistance [20]. The need therefore is to explore and establish less toxic and burdensome natural products, such as phytochemical bioactives from plants and probiotics as chemopreventive and/or prophylactic agents. Natural products have demonstrated promise against variety of cancer models. 'Primary prevention' is the first level of defense i.e. to reduce the incidence of the cancer by focussing on lifestyle, disorders, dietary interventions and special agents. Phytochemicals are safe, cost-effective, and mostly have high oral bioavailability. The past few decades of molecular and epidemiological research on understanding of the malignancy and therapies and thereby importantly early diagnosis techniques and technologies, have unraveled valuable information and data that would aid in screening and establishing plant-based dietary agents through well-designed clinical trials [2].

Plant bioactives as dietary therapeutic agents

Phenols

Quercetin (tea, whole grains), trans-resveratrol (trans-3,5,4′-trihydroxy-trans-stilbene- red grapes, peanuts, berries, pine) and genistein (soybean) markedly decrease pancreatic tumour growth specifically and prevent metastasis by causing apoptosis although through distinct mechanisms, including interesting synergistic enhanced effects on combination therapy, as studied *in-vivo* in mouse models and *in-vitro* in human and rat pancreatic carcinoma cell-lines [17]. In Asian folk medicine, dried roots of *Poligonum cuspidatum* (Japanese Knotweed), a rich source of trans-resveratrol, were used for treating inflammation or hyperlipidemia. Green Tea Extract (GTE) suppresses pancreatic tumour growth in HPAF-II cells, by altering the expression of 32 proteins, especially the Heat Shock Proteins involved in drug resistance, motility and metabolism [3]. Green tea flavonoid- EGCG, changes the metabolism of PC cells by suppressing the expression of an enzyme (LDHA) associated with cancer, in a manner similar to the known LDHA inhibitor oxamate [14], thereby suppressing human pancreatic carcinoma cell growth and invasion. Further, combination of EGCG with other bioactives such as gingerol (from ginger), curcumin (from turmeric; detailed in section below), quercetin, vitamin C, amino acids, sulphoraphane and indole-3-carbinol (from cruciferous vegetables like broccoli) or known natural and/or conventional chemotherapeutic agents enhance the efficacy to suppress tumour growth and progression as shown by pre-clinical and initial clinical studies on EGCG as adjuvant in cancer therapy. Besides, green tea/GTE has anti-inflammatory and anti-oxidative holistic effects thereby aiding digestion, preventing diabetes, maintaining respiratory, cardiovascular and liver health and boosting general immunity [25]. Cocoa polyphenol, specifically the Catechins, is a promising chemopreventive agent for inhibiting PDAC development [27].

Curcumin

Curcumin, a hydrophobic polyphenol from turmeric-the rhizome of the herb *Curcuma longa* and other curcuminoids have been popular in traditional therapeutic preparations. Curcumin shows anti-carcinogenic effects in human pancreatic cancer MIA PaCa-2 cells; it inhibits farnesyl protein transferase, while suppressing NF-κB expression and reducing IL-8 bioactivities. Rel A, the p65 subunit of NF-κB, is constitutively activated in approximately 67% of human pancreatic adenocarcinomas, but not in normal pancreatic tissues. Curcumin inhibits Rel A- DNA binding activity and potentiates apoptotic cell death induced by chemotherapy medication Paclitaxe in MDAPanc-28 pancreatic cancer cells [30]. Further, Curcumin suppresses pancreatic carcinoma growth in murine xenograft models and inhibits tumor angiogenesis. When coupled with the chemotherapy medication Gemcitabine, curcumin has been observed to have synergistic chemosensitizing antiproliferative effects in pancreatic cancer cell-lines and orthotopic mice models. Clinical trials on tropical pancreatitis and PC subjects have indicated positive effects on oxidative stress markers and tumour regression markers [1] and high oral doses were found to be safe. Omega- 3-Fatty acids potentiate the activity of curcumin in PC [30] therapy. Modulating multiple cellular signaling pathways and interacting with numerous molecular targets, curcumin has the potential to act against a large number of cancers.

Isothiocyanates (ITCs)

Cruciferous vegetables are a rich source of glucosinolates, which are converted to isothiocyanates (ITCs) by the enzyme myrosinase and released when plant cells are damaged by cutting or chewing. Benzyl ITCs and sulphoraphane have protective effects against BOP-related initiation of PC in hamsters and inhibit processes in cancer progression specifically in human PC cell-lines, but not in normal cells. They suppress tumour angiogenesis and promote apoptosis [3]. Benzyl ITCs also sensitize human PC cells to radiation therapy and chemotherapy. Specific structure-function based studies of ITCs and toxicology after long-term administration of ITCs in different species are needed to establish clinical translational studies. Epidemiological studies have suggested an inverse association between long-term intake of ITC-rich cruciferous vegetables and bladder cancer risk and survival, in opposition to reports on initiation of bladder cancer in rats, nevertheless, not in any other species [28].

Capsaicin

Capsaicin suppresses caerulin-induced carcinogenesis in transgenic mice and pancreatic tumor growth both *in-vitro* and *in-vivo* in mice models with 20 ppm dose for eight weeks. It induces ROS through inhibition of mitochondrial complexes, leading to apoptosis, specifically targeting PC cells, one of the proofs being its inability to generate any ROS or induce apoptosis in healthy pancreatic epithelial (HPDE-6) cells [3].

Selenium

A study of the UK EPIC cohort indicated that high intake of selenium was associated with a reduced risk of PC and the findings have been confirmed by two further studies which have described an inverse association between biomarkers of selenium and PC [21].

Carotenoids and Vitamins

Norell., *et al.* 1986 [19], reported that a low risk was associated with frequent consumption of fruits and vegetables, particularly carrots and citrus fruits for almost daily intake. This is further confirmed by case-control studies where significant benefits were shown for consumption of fruit and vegetables such as citrus, melon, berries, dark green vegetables, tomatoes, beans, peas, deep yellow vegetables, all being carotenoids and water soluble vitamins-rich [21]. Tomato-rich diet with high lycopene content may help reduce PC risk. Selenium, magnesium, vitamin C, vitamin E, β-carotene and β-cryptoxanthin have been shown to reduce PC risk [6]. Vitamin D and its analogues are potential candidates for preventing or treating PC [5]. Accordingly, sunlight exposure is also associated with reduced risk of PC and greater mortality with increasing distance from the equator. However, Liu *et al.* reported in 2013 that Vitamin D supplementation in PC was beneficial only in case of deficiency [13]. Tocotrienols from the Vitamin E family selectively inhibit the HMG-CoA reductase pathway through post-translational degradation and suppress the activity of transcription factor NF-κB in PC cell-lines [32].

Traditional medicinal-plant actives

Derived from the dry fruits of *Gardenia jasminoides Ellis*, Genipin has long been used in traditional Chinese medicine for its anti-inflammatory and hepato-protective effects. In preclinical studies, it has been shown to be capable of inhibiting uncoupling protein 2, inducing autophagy, and potentiating cytotoxicity of gemcitabine [31] in PC therapy. C 1-OH of Genipin is the principal active group identified [35]. Thymoquinone from the spice *Nigella sativa* and Cucurbitacin B from the oriental medicinal plant *Trichosanthes kirilowii Maximowicz* used as an anti-inflammatory and anti-diabetic agent, are anti-proliferative and chemosensitizing to conventional chemotherapeutic agents (Gemcitabine and Oxaliplatin) as shown *in vitro* and *in vivo* using an orthotopic model of PC. There are numerous such natural products both from Ayurveda and other traditional streams, known to exert PC therapy benefits [36]. The need is to scientifically validate their functions with systematic structure-function studies and clinical studies.

The bottleneck is the systemic delivery and bioavailability of the bioactives, which are being extensively researched [22]. Synthetic analogues with effective bioavailability and potent antitumour activities are being explored. EGCG and GTE based formulations such as Polyphenon E are well tolerated by healthy individuals, with mild adverse effects [30]. Nutrigenomics studies with various epidemiological populations would establish the efficacies and identify target populations for chemoprevention, considering that there were sporadic reports of green tea not being able to significantly reduce pancreatic cancer risk in a Japanese cohort study [15].

Whole grains

Higher intake of whole grains (WG) effect reduction of PC risk as seen in case-control and cohort studies, while refined grains do not show these benefits. WG are rich in micro and macronutrients including dietary fibre, minerals, vitamins and trace elements. A significant inverse association between dietary fiber intake and PC risk was observed in a recent meta-analysis of epidemiological studies [12]. WG cereals and pseudo cereals also contain a variety of antioxidant phenolics and are a natural source of probiotics [11] that can be tapped to formulate natural chemopreventive agents. Further WG render lower glycaemic load and low fat to the diet, both associated with lowering risk of PC. Supplementation of WG with folate is also found to further enhance their beneficial effects [21].

Probiotics as therapeutic agents:

Gut-microbes play important role in maintaining homeostasis. The ITCs can also be generated by intestinal microflora [28]. Further, *L. acidophilus* and *Bifido* sp. alleviate genotoxicity of dietary nitroso compounds implicated in PC progression. *L. plantarum* KLAB2 contain anti-mutagenic fractions that act against nitroso compounds affecting *S. enterica* TA 100 cells, thus lowering carcinogenicity by reducing bioavailability of the potent toxins. *L. rhamnosus* can detoxify aflatoxin B1. The role of probiotics on allevia-

tion of NCDs is well-established [29]. The probiotics balance can be specifically modulated by dietary prebiotic components such as dietary fibre and oligosaccharides from plant sources. As mentioned in section above, WG of millets such as pearl millet and finger millet are natural sources of probiotics. Moreover, specific probiotic supplements are now established for NCDs. A review by Wright and Samson, 2016 [34], suggest that supplemental probiotics may also be a beneficial addition to treatment plans for pancreatic cancer patients. Probiotics have been attributed to improve gut barrier function by restoring 'gut-barrier effect' and reduce post-operative and infectious complications (jaundice) in PC patient population [10,18], also those chronically treated with PPIs. Various human clinical trials report that probiotics are safe and beneficial for various patient populations, including the critically ill, patients with infections and pediatric patients; however, large prospective trials in pancreatic cancer patients are lacking [10,16,24]. The different mechanisms of action for probiotics involve induction of antibacterial secretion, such as mucins from human epithelial cells and defensins from Paneth cells in the small intestine, modulation of fecal microbiota, strengthening of epithelial junction proteins, maintenance of epithelial cellular polarization, and reduction of cell apoptosis in the gut lining [7,26,34]. Hence, probiotics based therapy for PC prevention and treatment are potential areas for further exploration, especially their role in preventing metastasis.

Conclusion

The plethora of dietary and lifestyle risk factors associated with onset and progression of PC and the fatality of the cancer, calls for chemoprevention as primary defense. Advanced age, insufficient early diagnostic markers and tools, side effects of conventional therapies are bottlenecks that can be overcome using plant bioactives-based dietary interventions and probiotics as they are safer, natural and cost-effective. Plant phenols including curcumin and GTE, ITCs, micronutrients, capsaicin, carotenoids and Vitamins C, D, E and probiotics are a few of nature's gifts that have been reported to curb onset and progression of PC in animal models, cell-lines and preliminary clinical trials. Establishing this line of chemoprevention calls for global identification of susceptible cohorts, well-designed and nutrigenomics integrated phase –II and III clinical trials and further scientific validation of the immense global traditional knowledge base of medicinal plant-based therapies.

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Conflict of Interest

None to declare.

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