ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Pancreatic Cancer, Ascites, Diet, Bioactives and Ayurveda Efficacy: Mini Review and a Case Report

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Abstract

Background: Pancreatic cancer (PC) remains one of the deadliest malignancies, often associated with late diagnosis, resistance to chemotherapy, and complications such as malignant ascites. Ayurveda and functional foods have shown promise in both adjuvant and recovery roles, amid interest in integrative oncology. We review a case study and the literature to find promising action pathways. **Materials and Methods**: We analyzed the anti-carcinogenic activity of the four most important herbs using literature, which were used sans chemo- or radio-therapy or allopathic drugs to improve the well-being and prolong life without pain of a 80 year old male PC patient in Pune city by 6 months. **Results and Discussion**: The use of Ayurvedic herbs and their bioactives includes (1) Licorice (*Glycyrrhiza glabra* – glycyrrhizin, isoliquiritigenin, and licoflavone (A)), (2) Giloy/Heart-leaved moonseed (*Tinospora cordifolia* – berberine, octacosanol, and polysaccharides), (3) Fennel (*Foeniculum vulgare* – anethole and flavonoids), and (4) Ash gourd (*Benincasa hispida* – Cucurbitacin, Terpenoids, and Vitamin C). These are known in the literature to cause apoptosis in cancer cell lines, improve oxidative status by blocking free radicals, boost immunity, and wound healing. **Conclusion**: The said herbs seem promising medicines in addressing PC, including ascites. Their integration with the current treatments of chemotherapy and radiotherapy demands research.

Keywords: Herbs, spices, neoplasm, oncology, phytochemicals

Asian Pac. J. Health Sci., (2025); DOI: 10.21276/apjhs.2025.12.4.04

Introduction

Cancer is a top global cause of mortality and leading global burden of diseases.[1] Pancreatic cancer (PC) is among the most lethal malignancies, ranking as the 7th leading cause of cancer-related mortality globally.[2] The 5-year survival rate remains low – 5%.[3] This could be due to delayed diagnosis, aggressive tumor biology, and resistance to conventional therapies such as chemotherapy and radiation, besides complications such as malignant ascites that impair the quality of life and prognosis.[4] Thus, pancreatic ductal adenocarcinoma (PDAC) may be the 3rd most deadly cancer in USA, as metastatic disease is frequent and treatment responses are limited.[5] Modern oncology primarily targets tumor eradication through cytotoxic or targeted agents. However, pancreatic tumors – particularly PDAC – are notorious for their fibrotic stroma, poor vascularization, and immune evasion, besides chemotherapy-resistance and adverse drug reactions (ADR), which diminish the drug penetration and efficacy.[5,6] Despite medical advancements, the burden of PC continues to rise, especially in low- and middle-income countries where access to specialized care is limited.

This scenario necessitates exploration of complementary, affordable, and integrative therapies that align with local health practices. Ayurveda – the traditional Indian system of medicine – along with functional nutrition, offers a multidimensional approach targeting inflammation, digestion, immunity, and detoxification.[7] Various botanicals traditionally used in Ayurvedic and oncology approaches may attenuate cancer progression through mechanisms such as anti-angiogenesis, immunomodulation, and apoptosis induction.[8,9] Herbs, bioactives, and other traditional medicine systems are also being explored globally for higher efficacy, ADR reduction.[10-12] This review investigates the scientific basis and therapeutic promise of such agents, in terms of their bioactives and especially pharmacological action on PDAC and its common sequela, ascites.

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How to cite this article: Kulkarni H, Ghate U. Pancreatic Cancer, Ascites, Diet, Bioactives and Ayurveda Efficacy: Mini Review and a Case Report. Asian Pac. J. Health Sci., 2025;12(4):20-24.

Source of support: Nil.

Conflicts of interest: None.

Received: 11/06/2025 **Revised:** 22/06/2025 **Accepted:** 15/07/2025

Rationale for Integrative Oncology

Allopathic drugs usually target a single protein as the disease driver with a single drug molecule, as exemplified by the molecular docking approach for initial screening of the potential remedy.[13] Ayurveda, on the other hand, approaches cancer as a systemic derangement of multiple health components such as digestion (*Agni* in vernacular), accumulation of toxins (*Ama*), and disturbed homeostasis (*Tridosha* imbalance-3 humors).[14] Hence, diet and lifestyle are important regulations in Ayurveda and other medicinal systems, which may not be tightly considered in modern medicine.[15] Further, chemotherapy and radiotherapy are prohibitively costly and impose family and social burden, including on the national budget, and cause severe ADR, including loss of innate immunity and enhances susceptibility to infections and other ailments, pushing people increasing to complementary and alternative medicine (CAM), to the extent of 25% of patients in USA by 2010.[16]

In the USA, the Integrative Medicine Service at Memorial Sloan Kettering Cancer mentions cases of PC treated with herbs such as *Boswellia* and Turmeric, and that about 1/3rd of cancer

patients adopt CAM, whereas about 50% Americans consume dietary supplements.[17] In Japan, traditional Kampo medicine – which shares commonalities with Ayurveda – has also been used as adjuvant care in pancreatic and gastric cancers with moderate success.[18] These cases, while anecdotal, underscore the potential of plant-based and dietary interventions to improve symptoms, treatment tolerance, and quality of life.[19]

Materials and Methods

Previous study mentioned a case of an 80-year-old pancreatic patient who survived 10 months with little pain or weight loss or other health issues and recovered in a few days from COVID-19, also soon, based solely on Ayurvedic treatment, as chemotherapy or radiotherapy was not advisable.[1] This survival is 2 times longer than usual, with the median survival duration of 5 months.[3] The incremental period of 5 months is commendable, given the old age, and this may be due to the Ayurveda regimen's efficacy. The patient had a normal, healthy life, and no medical issues ever, such as diabetes or hypertension, and was 6' tall, with a body mass index of about 26. He had minor surgery 9 months before his death and was fitted with a bile duct stent, as he had experienced stiff belly and breathing difficulty. PC was then detected in April 2020 when the doctors estimated balance life of 3–4 months. Ayurveda treatment started soon with a diet such as daily Ash gourd consumption of 40–100 g fresh weight, in curry form. Ascites developed 8 months later in December and lasted a little over 1 month. The patient was admitted to the hospital for only one night stay in his life when he breathed his last soon after discharge of his abdominal fluid only once. Modern family physicians did not advise its discharge before. His swollen belly made his life a bit uncomfortable, and he had been tired in the last 2 weeks at home. However, he had comfortable, painless treatment for 9 months at little cost and was walking till his last day on January end. This event triggered this article, aimed at sharing the strength of traditional medicine for the wide global benefit, especially of the elders from the developing world. The research method involves a literature review of phytochemicals found in the main herbs prescribed in the treatment and comparison with evidence elsewhere for post-facto analysis.

Results- Focal Herbs Their Mechanisms of Action

In this case, the treatment comprised consuming decoction 2 times daily, consisting of many herbs but with larger quantities (10 g each) of the three herbs below to be boiled for 40–45 min to reduce the water volume from two glasses to one glass (150 mL).

a. Licorice (*Glycyrrhiza glabra* – "Jyesthmadh – Marathi and Mulethi – Hindi")
b. Heart-leaved moonseed (*Tinospora cordifolia* (TC), vernacular – "Giloy – Hindi/Guduchi – Sanskrit/Gulvel – Marathi")
c. Fennel (*Foeniculum vulgare* – "Badishep – Marathi/Sounf – Hindi").

In the diet, daily consumption of Ash gourd (*Benincasa hispida* – "Kohala") was recommended – about 100 g/day.

Licorice

Licorice and its derivatives may prevent carcinogen-induced DNA damage and may suppress it too.[20] Glycyrrhizic acid inhibits lipoxygenase and cyclooxygenase, and protein kinase C. Further, it downregulates the epidermal growth factor receptor. Licorice polyphenols cause cancer cells' apoptosis. Moreover, licorice alleviates radiotherapy- and chemotherapy-induced adverse reactions in cancer treatment.[21] The anticancer effects involve modulating various signalling pathways, such as the phosphatase and tensin homolog/phosphatidylinositol 3-kinase/protein kinase B pathway, the mitogen-activated protein kinase, and the mammalian target of rapamycin/signal transducer and activator of transcription 3 (STAT3), causing apoptosis, oxidative stress, and inflammation.[22] Furthermore, licorice induced the G0/G1 growth phase cycle arrest of tumor cells, leading to the down-regulation of CDK4-Cyclin D1 complex, spiralling into an increased protein abundance of PD-L1. Furthermore, licorice mitigation of the outgrowth of non-small cell lung cancer tumor relied on increased antigen presentation and improved $CD8^+$ T cell infiltration.[23] Isoliquiritigenin in licorice downregulates the levels of Bcl-2 while increasing the expression of Bax and caspase-3 in the MKN28 cell line, leading to apoptotic cell death.[24] Licoflavone A, a flavonoid of glycyrrhiza, also had anti-proliferative properties in three different gastric cancer cell lines, namely MKN-45, SGC-7901, MGC-803, and vascular endothelial growth factor (VEGF)-stimulated MKN-45 cells.[25] While this is promising, caution is also raised against over-indulgence in licorice to avoid any side effects.[26]

Heart-Leaved Moonseed

"TC" is the strongest immunomodulatory herb (climber) in Ayurveda, and it contains the bioactive "Berberin."[27] Berberine and TC are found to attenuate the colon cancer cells differently, namely multiple cell signalling pathways, including differentiation, proliferation, and the transition between epithelial and mesenchymal tissue (EMT), using real-time polymerase chain reaction.[28] Expression levels of a panel of 44 chosen genes in the human colon adenocarcinoma-7 cell line were evaluated. Of these, the majority of distinct genes (33, i.e., 67%) with varying roles in cell cycle, differentiation, and EMT were downregulated by berberine administration in a time- and dose-dependent manner, indicating that TC can arrest metastasis.

In vivo anticancer potential of TC stem bark polysaccharide against breast cancer is demonstrated.[29] Albino Wistar rats were induced with breast cancer using 7,12-dimethylbenz [a] anthracene (DMBA). Polysaccharide-treated animals were able to restore the DMBA-suppressed red blood cell, white blood cell, and platelet count. Tumor markers carcinoembryonic antigen and cancer antigen 15.3 did not increase in the polysaccharide treatment group compared to the DMBA-induced breast cancer group and the level of the normal group. TC phytochemicals, namely palmative, quercetin, rutin, arabinogalectin, diterpenes, etc., may also arrest cancer tumor spread.[30] TC aqueous extract (TCE) induced apoptosis in AW13516 cells in a concentration-dependent manner, starting from a low concentration of 5 μg/mL.[31] The caspase activity assay confirmed it, thus arresting EMT and further spread. The ability of B16-F10 melanoma cells was also significantly reduced in an *in vitro* study in Kerala state, India, when the polysaccharide fraction was injected intraperitoneally in mice previously injected with the melanoma cells.[32] A novel approach shown is the taming of neutrophils via potent immunomodulation by TC.[33] TC could attenuate Ehrlich ascites carcinoma (EAC) in mice, also.[34] Declined glutathione (GSH) activity was seen in the EAC mice receiving 50 mg/kg TCE in a time-dependent manner,

accompanied by enhanced lipid peroxidation (LPx) peaking at 6 h. TCE's cytotoxic effect on tumor cells can be understood from the reduction in the GSH concentration and parallel increase in LPx.

Berberine exhibited anticancer properties in mice inflicted with EAC by inhibiting topoisomerase II and addressed ascites carcinoma also.[35] The authors argue that octacosanol, a long-chain aliphatic alcohol, inhibits matrix metalloproteinase activity, nuclear factor kappa B (NF-κB) translocation to the nucleus, and VEGF synthesis by cancer cells into ascites fluid (in vivo). Octacosanol is an antiangiogenic drug that inhibits tumor spread and growth, increases pro-apoptosis and senescence, and arrests apoptosis reversal, with therapeutic effect on neuroblastoma. The study said that TC can protect both MCF-7 breast cancer and chemically produced liver cell carcinoma patients. NF-κB inhibition, p53 activation, and mitochondrial apoptosis are also key to TC anti-carcinogenic activity.TC hexane fraction showed apoptosis against Ehrlich ascites tumor (EAT) in mice.[36] It inhibited the proliferation of EAT cells by blocking cell cycle progression in the G1 phase. The constitutive expression of caspase-activated DNase in both the nucleus and cytoplasm was associated with the apoptosis of EAT cells. Furthermore, the expression of pro-apoptotic gene, bax, was increased, and the expression of anti-apoptotic gene, Bcl-2, was decreased. TCE treatment was seen to arrest the majority of cells in the G0/G1 phase and modulated the expression of the DNA clamp sliding protein (proliferating cell nuclear antigen) and cyclin D1.[37] Further, the study showed that TCE-treated cells differed by morphology and the expression of the neuronal cell-specific differentiation markers in neuroblastoma cells, namely neurofilament 200, MAP-2, and NeuN.

Fennel

Not just herbs but regular diet elements such as spices and vegetables contain bioactives that can tame or help to alleviate cancer, including pancreatic cancer.[38] A common condiment, such as fennel, is anti-carcinogenic.[39] The bioactive anethole in fennel seed suppresses tumor necrosis factor transcription factor NF-activation in KBs. Anethole, an aromatic essential oil inhibits the cellular responses induced by these cytokines, thus preventing cancer. It showed that cancer-bearing mice's liver and tumor tissue had more malondialdehyde and much less catalase activity and GSH. However, the ascites fluid's total protein content decreased. Fennel's methanol extract significantly reduced the growth of breast cancer cells (MCF-7) and liver cancer cells (HepG) via modifying LPx, blocking free radicals, and activating the antioxidant defence system was activated. Fennel seed extract in 75% ethanol reduced cell viability, induced apoptosis, and effectively inhibited cell migration in hepatocellular carcinoma cells during an in vitro study in China.[40] Fennel seed and its extract showed high oxidative DNA damage prevention ability.[41]

Ash Gourd

It is a common fruit–vegetable used to make a sweetmeat called "Petha" in northern India and is added to a routine spicy curry called "Sambar" in southern India. It has one of the highest anti-inflammatory powers, so it can be helpful in cancer treatment through antioxidant action.[42,43] Cucurbitacin, a tetracyclic triterpenoid derived from species of the Cucurbitaceae family, exhibits anticancer effects by suppressing Janus kinase 2 activity and STAT3 in the cancer cell lines from the breast, prostate, and nasopharynx.[44] Ash gourd also aids in the absorption of bile acids and supports the growth of beneficial gut bacteria, which in turn boosts short-chain fatty acids (SCFA) levels, the study claims. These SCFAs are known for their various health benefits, including enhancing gut barrier function, reducing inflammation, and potentially exerting anticancer effects. Further, phytochemicals in Ash gourd address cancer as flavonoids inhibit the carcinogens' activity and prevent the metastasis of malignant cells, while terpenes of essential oils block the action of carcinogens. Ash gourd (100 g serving) has 14% of recommended daily intake of Vitamin C which is vital incancer treatment and prevention, by improving the immunity; stimulating collagen synthesis; wound healing post cancer surgery, preventing metastasis, inhibiting tumor-causing viruses; meet the Vitamin-C deficit, which is normally linked with cancer patients; improving chemotherapy sensitivity and decreasing chemotherapy toxicity.[45] Terpenoids, the main active ingredients in Ash gourd, are known to be anti-carcinogenic in multiple pathways, including apoptosis.[46] Alnusenol and multiflorenol, 2 triterpenes in Ash gourd, inhibited the histamine release.[47] Histamine is implicated in tumorogenesis and can be useful in immunotherapy, though its action is two-way and dose-dependent, so it needs careful management.[48] Table 1 depicts a summary of the anticancer effects of the herbs/vegetables described above.

Finally, gut microbiome modulation is also an important action of the phytochemicals that helps in cancer treatment, including immunotherapy.[49] This is crucial in PC as microbiota-derived tryptophan metabolite indole-3-acetic acid (3-IAA) is found at a higher level in patients with a positive response to the treatment.[50] Fecal microbiota transplantation, short-term dietary manipulation of tryptophan, and oral 3-IAA administration increase the efficacy of chemotherapy in humanized gnotobiotic mouse models of PDAC. Myeloperoxidase oxidizes 3-IAA, which, in combination

Table 1: Bioactives and the action of ayurvedic herbs in pancreatic cancer

Herb	*Bioactive compounds*	*Mechanism of action*	*Key outcomes*
Licorice	Glycyrrhizin, isoliquiritigenin, licoflavone A	Downregulated the Bcl-2 levels, enhance Bax and caspase-3 in the MKN28 cell line, LOX, COX	Apoptosis, tumor reduction, EMT, and metastasis arrested#
Heart-leaved moonseed	Berberine, octacosanol, polysaccharides	NF-κB inhibition, p53 activation, apoptosis-mitochondria, AW13516, taming neutrophils, LPx	Anti-inflammatory, tumor regression, inhibiting topoisomerase II, increased Bax, inhibited Bcl-2,
Fennel	Anethole, flavonoids	modifying lipid peroxidation, blocking free radicals, and inhibiting NF-KBs	Antioxidant, hepatoprotective, and ascites fluid's total protein decline
Ash gourd	Cucurbitacin, terpenoids, Vitamins C	boosts short-chain fatty acids, immunity, collagen synthesis, and wound healing	Diuretic, anti-angiogenic, anti-metastasis

LOX: Lipoxygenase, COX: Cyclooxygenase, EMT: Epithelial and mesenchymal tissue, NF-κB: Nuclear factor kappa B, Lpx: Lipid peroxidation

with chemotherapy, induces a downregulation of the reactive oxygen species (ROS)-degrading enzymes GSH peroxidase 3 and 7. This causes accumulation of ROS and the downregulation of cancer cells' autophagy, attenuating their metabolic fitness and proliferation. Thus, microbiota-derived metabolites with clinical implications are being identified in PDAC treatment, and it's vital to consider the nutritional interventions.

Conclusion

Diet is a key external factor to influences the treatment response, and its role in PDAC needs further research. Tobacco smoking is associated with about 30% of the PDAC cases and diabetes, besides other dietary factors, namely red meat, obesity, and less intake of methionine and folate. Notable content of Vitamin B6 and folate in Ash gourd may be useful in addressing cancer, as proposed in a Swedish study of 81,922 women over a 7-year period.[51] This article summarises the merit of traditional medicine and diet in Ayurveda, vide modern pharmacology parameters, and this can lead to its higher adoption and well-being, by reduced cost, hospitalization, and pain. Recent patents on herbs or bioactives used as combination drugs for PC show this.[52] Finally, nanotechnology and innovative approaches can improve the natural medicine strategy faster and with higher efficacy, as is being attempted widely.[53,54]

Acknowledgment

We thank our college principal and NGO management for the kind permission for this research and publication. We also thank the late Mr. Vasantkumar Ghate, Dr. Narendra Pendse, Dr. Asmita Wele, and Mr. Darshan Shankar for sharing useful data and insights and encouraging this article.

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