Imperial Journal of Interdisciplinary Research (IJIR)
Vol-3, Issue-8, 2017
ISSN: 2454-1362, http://www.onlinejournal.in

A Review on Selective Herbs for the Management of Pancreatic Cancer

*J.Nisha[1] , S.T. Immanuel Moses Keerthy[2], N.Anbu[3]
[1]PG scholar, Dept of Maruthuvam ,Government Siddha Medical College, Arumbakkam, Chennai – 600106.
[2]Field officer, Dept of epidemiology, The Tamil Nadu Dr.M.G.R.Medical University, Guindy, Chennai-600032.
[3]Head of the department, Dept of Maruthuvam , Government Siddha Medical College, Arumbakkam, Chennai– 600106.

Abstract : *Pancreatic cancer is a very devastating disease which arises when cells in the pancreas, begin to multiply out of control and form a mass. These cancerous cells have the ability to invade other parts of the body. The usage of herbs and spices as medicaments for the treatment of various diseases dates back even still prior to the Stone Age period. Though mankind was in the customary usage of medicinal herbs down the timeline, unfortunately traditional medical field lacks sufficient scientific evidences. Diverse research groups involved in the research regarding the management of pancreatic cancer have come out with their surprising research findings that the commonly used herbs such as Commiphora mukul (Gum Guggul), Curcuma longa (Turmeric), Beta vulgaris (Beet root), Crocus sativus (saffron), Momordica charantia (Bitter melons) possess antimicrobial and antitumor properties due to the potent phytochemicals such as carotenoids, curcumins, catechins and lignans respectively, which provide significant protection against cancer. This review discusses recent scientific data on the antitumour and chemopreventive activities of some herbs and spices against pancreatic cancer.*

Key words: *Pancreatic cancer, Medicinal herbs, Siddha medicine, Traditional herbs*

Introduction

The pancreas is a vital part of the digestive system and a critical controller of blood glucose levels . It appears as a long flattened gland located in the upper left part of the abdomen behind the stomach. It plays a vital task in metamorphosing the food we consume into fuel for the body's cells. The pancreas is about 6 inches long and the head of the pancreas is connected to the duodenum through the pancreatic duct. The narrow end of the pancreas, called the tail, extends to the left side of the body [1,2].The pancreas has two main functions: an exocrine function and an endocrine function.

Types of Pancreatic Cancer

Pancreatic cancer is classified according to which part of the pancreas is affected: the part that makes digestive substances (exocrine) or the part that makes insulin and other hormones (endocrine).

Exocrine Pancreatic Cancer

Although there are several different types of exocrine pancreatic cancer, 95% of cases are due to pancreatic adenocarcinoma. Other less common exocrine pancreatic cancers include:
Adenosquamous carcinoma, Squamous cell carcinoma, Giant cell carcinoma, Acinar cell carcinoma, Small cell carcinoma. The exocrine pancreas makes up 95% of the pancreas, consequently most pancreatic cancers arise here.

Endocrine Pancreatic Cancer

Other cells of the pancreas make hormones that are released directly into the bloodstream (endocrine system). Cancerous tumors arising from these cells are called pancreatic neuroendocrine tumors or islet cell tumors. Endocrine pancreatic cancers are uncommon, and are named according to the type of hormone produced: Insulinomas (from an insulin-producing cell), Glucagonomas (from a glucagon-producing cell), Somatostatinomas (from a somatostatin-making cell), Gastrinomas (from a gastrin-producing cell), VIPomas (from vasoactive intestinal peptide-making cell). Some pancreatic islet cell tumors do not secrete hormones and are known as non-secreting islet tumors of the pancreas [3].

Causes of Pancreatic Cancer

Pancreatic cancer occurs when cells in the pancreas grow, divide, and spread uncontrollably, forming a malignant tumor. The exact cause of pancreatic cancer is unknown.Cigarette smoking is the major risk factor for pancreatic cancer: Smoking roughly doubles the risk for pancreatic cancer when compared to non-smokers. Cigarette smoking is estimated to account for 25–29% of pancreatic cancer incidence, with reported odds

ratios ranging from 1·6 to 5·4 [4]. Age, race, and family history are other risk factors for pancreatic cancer [5].

Several genetic syndromes are associated with an increased risk of pancreatic cancer, including hereditary pancreatitis, hereditary non-polyposis colorectal cancer, ataxiatelangiectasia, Peutz-Jeghers syndrome, familial breast cancer, and familial atypical multiple-mole melanoma [6]. In epidemiological studies of pancreatic cancer, a protective role has been noted for diets high in fruits and vegetables [7] Research efforts aimed at quantifying risk factors and identifying individuals at high risk are critical to the eventual prevention of this disease.

Disease burden

Pancreatic cancer is one of the leading causes of cancer mortality with higher incidence and mortality found in the developed countries. The five year survival rate of Pancreatic cancer is estimated to be 5%. Of late, Cancer has overcome the rate of killing people more on a global scale than the diseases such as AIDS, malaria and TB combined. However, many of the 600,000 deaths occurring each month attributed to cancer can be prevented with growing governmental support and funding for prevention, detection and treatment programmes. The prevalence of cancer is escalating at a rapid pace in developed countries, particularly in Northern America,Australia and New Zealand and in Northern and Western Europe. Howbeit, the aftermath of cancer in the emergent nations like India is shooting at an alarming rate. More than 70% of all cancer deaths already occur in low- and middle-income countries and these regions are projected to account for two thirds of all cases of cancer worldwide by 2050 (an increase of 15% since 1975[8] . In addition to the impact on loss of life, the economic impact of cancer is huge. Currently it is estimated that the disease costs economies across the world an estimated $290 billion in 2010 - $154 billion of which were medical costs [9].

Current conventional treatment

Doxorubicin (Adriamycin) is the current, first drug of choice for the chemotherapy of a wide variety of carcinomas, sarcomas and cancers of hematological origin [10]. However, there are serious side-effects associated with the use of this potent anticancer drug [11].Nausea, vomiting, neutropenia, alopecia and heart arrhythmias are common at the beginning of the therapy. The potential for developing cardiotoxicity leading to cardiomyopathy and congestive heart failure increases dramatically when the cumulative drug dose reaches >550 mg/m2 upon continued use. Further, at high doses, doxorubicin loses its efficacy against multidrug resistant tumors, such as breast cancer.

Need for Siddha medicine

For more than several hundreds of years, traditional system of medicine has been anchored on plants and herbs which have proved to be a panacea and cure for divers minor and grave ailments thus keeping the body healthy. There are several millions of herbs around the globe and among them some have become rather well known, nevertheless massive number of effective medicinal plants and herbs have not come to the limelight of human attention yet. Herbal remedies have proven effective in helping the body maintain good health during pregnancy and in healing serious illnesses such as cancer and heart disease when they do occur.

Cancer is the third leading cause of death worldwide, only preceded by cardiovascular disease, infectious and parasitic disease [12] [13]

Recent studies found that several plant constituents are very effective in the treatment of pancreatic cancer such as common polyphenols like apigenin, baicalenin, kaempherol, luteolin and quercetin [14] and curcumin from *Curcuma longa* L. (turmeric) [15]; essential oil terpenes, linalool found in several aromatic plants [16], thymoquinone from *Nigella sativa* (black cumin seed)[17], extracts of *Allium sativum* (garlic) [18] and antioxidants from *Morus alba L.*(white mulberry), *Phyllanthus emblica L.* (Indian gooseberry) and *Piper rostratum Roxb* (Thai herb)[19]are observed to alleviate the detrimental side effects associated with doxorubicin chemotherapy including cardiotoxicity. Additionally, the following anticancer plant constituents were found to act synergistically with doxorubicin in in vitro and/or in vivo animal model studies: polyphenols from *Camellia sinensis* (green tea; catechins) [20], *ngifera indica* (mango; mangiferin) [21] , *Semecarpus anacardium* (nut kernel; catechol) [22], extracts of the fruits of *Phyllanthus emblica* L. (Indian gooseberry) and *Terminalia bellerica* (beleric) [23] and *Morinda citrifolia* (Noni) [24] and seeds of *Vitis vinifera* (Grape) [25]. The above findings of synergistic activity of anticancer plant products with cancer drug doxorubicin shows significant results [26].Few other plants listed below have showcased their medicinal potentiality against pancreatic cancer, while carefully scrutinizing the research articles for the purpose of selecting plants against pancreatic cancer.

Commiphora mukul

Commiphora mukul is an Indian plant which has its habitat in Rajasthan, Madhya Pradesh, Assam, Andhra Pradesh, Karnataka. It belongs to the family Burseraceae. It is commonly called in English as Indian Bdellium, Gum Guggul. In

siddha or in Tamil language it is called as Erumaikan, Kungiliyam ; in Ayurveda it is known as Guggul, Devadhoop, Kaushika; in Unani medicine it is named as Muqallal yahood, Muql, Bu-e-Jahudaan. It is also found in other regions such as Afghanistan, the Arabian Peninsula and north east Africa in rocky dry areas. Widely used in the treatment of a wide array of ailments including bone fractures, lipid disorders, inflammation and arthritis for centuries, the gum resin is a part of the holistic Indian medicine[27-30].

The dry oleo-gum resin exudates obtained from cracks and fissures of *Commiphora* (*Erumaikan*) bark is a complex mixture of different compounds. Many groups have studied the phytochemistry of *C. mukul* and found gums (32%), oleo-gum resin (38%) and essential oils (1%). The commercial product also contains minerals (20%), foreign organic matter (4%) and other compounds (5%). The complex dry oleo-gum resin mixture includes steroids, sterols, terpenes, cembrenoids, flavones, tannins, ferrulates and lignans [31] Fractionation of gum-resin is necessary for identification of individual bioactive components [32].

The anticarcinogenic effects of guggul sterone (*Erumaikan*) against pancreatic cancer have been studied deeply. *Erumaikan* has been found to modulate various steps of cancer. Induction of apoptosis and repression of proliferation, invasion, angiogenesis and metastasis are the mechanisms of anticancer activity. Inhibition and suppression of the molecular targets are specifically responsible for its anticancer activity. An extensive literature has been published on the potential use of this gum guggul in the treatment of various types of cancers. Dose-dependent treatment with Erumaikan suppresses growth and inhibits proliferation of a variety of tumour cells including those of human leukaemia, head and neck carcinoma, multiple myeloma, lung carcinoma, melanoma, breast carcinoma and ovarian cancer cell lines. Erumaikan at a concentration of 25 mM induces S-phase arrest of the cells in the cell cycle through down-regulation of the much-required cyclin D1 and cdc2 and through up-regulation of cyclin-dependent kinase inhibitors p21 and p27 in a time-dependent manner. This causes inhibition of DNA synthesis and thus further proliferation of U937 leukaemia cells by 80% within 24 h.

In apoptosis, Erumaikan not only suppresses progression of cancer by repressing the proliferation of cancerous cells, but also induces apoptosis in a wide variety of cells. Both mitochondria-dependent and mitochondriaindependent mechanisms are responsible for the apoptotic action of guggulsterone [33]. The next stage in the progression of tumours is invasion. When chemotherapy is ineffective, the cancerous cells penetrate into the normal tissue in the vicinity. This leads to recurrence of the tumour. Erumaikan was found to down-regulate the expression of the MMP-9 enzyme, which further caused inhibition of invasion of these cancerous cells [34]. Guggul sterone also induced apoptosis and cell cycle arrest, which further inhibited invasion of cells in head and neck squamous cell carcinoma

Curcuma longa

Botanical name: *Curcuma longa***,** Tamil name: *Manjal.* In a recent research study, they evaluated the clinical biological effects of curcumin (diferuloylmethane), a plant-derived dietary ingredient with potent nuclear factor-nB (NF-nB) and tumor inhibitory properties, against advanced pancreatic cancer. They administered some patients with 8 g curcumin by mouth daily until disease progression, with restaging every 2 months. Serum cytokine levels for interleukin (IL)-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cell expression of NF-nB and cyclooxygenase-2 were monitored. As a result, 25 patients were enrolled, with 21evaluable for response. Circulating curcumin was detectable as drug in glucuronide and sulfate conjugate forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Two patients showed clinical biological activity. One had ongoing stable disease for >18 months; interestingly, one additional patient had a brief, but marked, tumor regression (73%) accompanied by significant increases (4- to 35-fold) in serum cytokine levels(IL-6, IL-8, IL-10, and IL-1receptor antagonists). No toxicities were observed. Curcumin down-regulated expression of NF-nB, cyclooxygenase-2, and phosphorylated signal transducer and activator of transcription 3 in peripheral blood mononuclear cells from patients (most of whom had baseline levels considerably higher than those found in healthy volunteers).Whereas there was considerable interpatient variation in plasma curcumin levels, drug levels peaked at 22 to 41ng/mL and remained relatively constant over the first 4 weeks. Oral curcumin is well tolerated and, despite its limited absorption, has biological activity in some patients with pancreatic cancer. [35].

Camillia sinenesis

Botanical name: *Camillia sinenesis.* Tamil name : *Theyilai;* The anticancer effects of tea have been well studied and researched. Green tea contains bioactive chemicals such as catechins and polyphenols, which renders beneficial medicinal effects. The (-) epigallocatechin gallate (EGCG) in tea is now widely agreed as a cancer preventive in Japan [36]. A recent human study [37] showed that black tea, containing L-theanine, a precursor of the non-peptide antigen ethylamine, could primed

peripheral blood T cells to mediate a memory response on re-exposure to ethylamine, and secreted interferon-γ (IFN-γ) in response to bacteria. Such priming may enhance innate immunity to bacteria and other microbes, as well as tumors that share nonpeptide antigens with bacteria. Bukowski and colleagues [37] proposed that it might be possible to further purify Ltheanine from tea, and use it as a drug to boost the defense against infection [38].

Beta vulgaris

Botanical name: *Beta vulgaris*. Tamil name : *Senkilangu*;Many variety of cytotoxic plant extracts and phytochemicals are known to act synergistically with anticancer drug doxorubicin (D), but their clinical application is not clearly known regarding safety concerns of such combinational therapy. A recent study supports the postulation that dietary constituents with known anticancer activity of red beetroot (*Senkilangu*) extract when used in right combination and dose could enhance the therapeutic efficacy of potent chemotherapeutic drugs (like doxorubicin), reduce theirtoxic side-effects through dosage reduction and impede development of cancer cell resistance to drug treatment [39,40].The multi-organ cancer treatment potential of *Senkilangu* extract–doxorubicin combination is noteworthy. Favorable clinical trials in humans could lead to expedited review process by regulatory agencies and quick approval of doxorubicin–red beetroot extract combination chemotherapy, since the latter is already approved for use in humans as a safe food colorant (designated as food color E162)).

Crocus sativus

Botanical name: *Crocus sativus*; Tamil name: *Kumkumapoo.* Saffron has three main pharmacogically active metabolites: (a) crocins, the water-soluble carotenoids that give the saffron color, (b) Picrocrocin is responsible for the bitter taste and (c) Saffranal is the volatile oil that gives the characteristic odor and aroma of saffron. In vivo and in vitro,saffron and its components possess anti-carcinogenic and antitumor activities [41-50]. In experimental models, saffron extract could inhibit and/or retard tumorgenesis in vivo [41-47]. Several hypotheses on the main constituents in saffron and their mechanism(s) of anti-carcinogenic and tumor effects have been proposed. One mechanism was that the active constituents inhibited cellular DNA and RNA synthesis, but not protein synthesis [43] . A second proposed mechanism suggested that the active ingredients inhibited the free radical chain reaction [49,50], while other proposals included the metabolic conversion of naturally occurring carotenoids to retinoids that exert antitumor effects [50](90), the interaction of carotenoids with topoisomerase II [45], and the induction of apoptosis

Momordica charantia

Momordica charantia (Bitter melon), Tamil Name: *Pagarkai* is a commonly consumed vegetable in the Asian and African continents [51,52] and there is a growing interest in bitter melon because of its beneficial effects against diabetes, obesity, hyperlipidemia and so on [53]. Bitter melon has been evaluated in human population in several clinical trials for its antidiabetic effects and has plenty of human safety data 54. Besides its antidiabetic effects, bitter melon extract and its bioactive compounds have shown anticancer efficacy against leukemia, breast, prostate and colon cancers [55-59]. A direct correlation has been established in recent studies between diabetes and pancreatic cancer (60), and the use of antidiabetic drug metformin has been associated with reduced risk and improved survival in diabetic patients with pancreatic cancer [61].

Taken together, based on above-described studies showing: (i) strong antidiabetic and anticancer effects of bitter melon, (ii) a direct correlation between diabetes and pancreatic cancer (iii) and that bitter melon constituents activate AMPK, in this study, we examined, for the first time, the anticancer activity of bitter melon juice (BMJ) and the involvement of AMPK activation in its efficacy against human pancreatic carcinoma cells. [62].

642. Ocimum sanctum

Common known : Holy Basil; Tamil name : *Tulasi .Tulasi* is a medicinal herb found in the semitropical and tropical parts of India. It has been used for ages in the diverse medicinal systems like Ayurveda, Unani and especially in *Siddha* to treat diverse ailments including infections, skin and liver disorders and as an antidote for snake and scorpion bites [63]. It has been used as an anti-inflammatory,immunomodulatory, anti-infective, anti-stress, antipyretic, antitussive, anti-diabetic[64], cardioprotective, neuroprotective and hepatoprotective agent [65,66]. Though it is reported that all parts of this plant is supposed to possess therapeutic properties and used in medicinal treatment, especially the leaves have been most widely studied and researched. The leaves of *Tulasi* are the source of an essential oil which has numerous medicinal properties. Both ethanolic and essential oil of *Tulasi* extracts have previously been shown to have antioxidant effects [68,69].

In a recent research study conducted by Shimizu et al, the effect of Ethanolic extract of *Tulasi* and essential oil of *Tulasi* on pancreatic cancer cell cycle progression was evaluated . Thus they reported that ethanolic extract and the essential oil of *Tulasi* inhibit the proliferation,

motility and invasive ability of pancreatic cancer cells. Intraperitonally injected aqueous extracts decreased the tumorigenicity of orthotopically implanted the human pancreatic cancer cell lines (AsPC-1), significantly. This was associated with significant increase in the expression of pro-apoptotic genes with a concomitant decrease in the level of genes that inhibit apoptosis or promote pancreatic cancer cell proliferation or metastasis. Taken together, these results suggest that the extract or essential oil of *tulasi* leaves and the components present in them could be potentially useful as novel agents for the therapy and/or prevention of human pancreatic cancer cells. These results will form the basis for future studies to investigate the effect of individual components of *Tulasi* leaves for the treatment of pancreatic cancer [70].

Conclusion

Cancer is a hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Intensive researches during the few decades have exhibited much about the hidden biological mechanism of cancer. The present allopathic drugs used to treat most types of cancers are those which blocks cell signalling, including growth factor signalling (e.g., epidermal growth factor); prostaglandin production (e.g., COX-2); inflammation drug resistance gene products (e.g., multi-drug resistance) cell cycle proteins , angiogenesis , invasion (e.g., matrix metalloproteinases),antiapoptosis , e.g., and cellular proliferation. Large volume of research findings has suggested that medicinal plants navigate their course of action according to the newly identified therapeutic targets. However, the prime objective of this review is to illuminate more light on the concept of anticancer effects of plants, including their various types of combinational therapy with the conventional medicines.

References

[1] Baetens, D., Malaisse-Lagae, F., Perrelet, A., Orci, L., "Endocrine pancreas: three-dimensional reconstruction shows two types of islets of Langerhans". *Science*., December 1979, 206 (4424):1323-5.

[2] Frank, A., Deng, Sh. et al., "Transplantation for type I diabetes: comparison of vascularized whole-organ pancreas with isolated pancreatic islets". *Annals of surgery,* 2004, 240: 631-643.

[3]Types of pancreatic cancer fact sheet Pancreatic Cancer UK, June 2014.

[4]Fryzek, J. P., Garabrant, D. H., Greenson, J. K., Schottenfeld, D., "A review of the epidemiology and pathology of pancreas cancer". *Gastrointest Cancer,* 1997; 2: 99–110.

[5] Hruban R. H, Petersen G. M, Ha P. K, Kern S. E., Genetics of pancreatic cancer: from genes to families. *Surg Oncol Clin N Am*, 1998; 7:1–23.

[6] Becker, A. E., Hernandez, Y. G., Frucht, H., & Lucas, A. L. "Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection". *World journal of gastroenterology*: WJG, 2014, 20(32), 11182.

[7] Ji B.T, Chow W. H, Gridley, G, et al., "Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai, China".*Cancer Epidemiol Biomarkers* Prev, 1995; 4: 885–93.

[8] Bray, F. et al. "Predicting the future burden of cancer". *Nat. Rev. Cancer*. 2006 6:63-74.)

[9] WEF report http://www.world---heart-federation.org/fileadmin/user_upload/documents/Advocacy/Resources/Articles__Series__Reports/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf. (9 November 2011)

[10] Lown, J. W., "Anthracycline and anthraquinone anticancer agents, Current status and recent developments*". Pharmacol Ther*, 1993; 60: 185–214.

[11] Carvalho C, Santos, R. X, Cardoso, S, Correia, S, Oliveira, P. J, Santos, M. S, Moreira, P. I. "Doxorubicin: the good, the bad and the ugly effect". *Curr Med Chem*, 2009;16: 3267–85.

[12] Mathers, C.D., Boschi-Pinto, C., Lopez, A.D., and Murray, C. J. L. "Cancer incidence, mortality and survival by site for 14 regions of the world". *World Health Organization*, p3, 2001.

[13] Briand, L. C., Daly, J., and Wüst, J., "A unified framework for coupling measurement in object oriented systems", *IEEE Transactions on Software Engineering*, 25, 1, January 1999, pp. 91-121

[14] Psotova J, Chlopcikova S, Miketova P, Hrbac J, Simanek V."Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes". Part III. Apigenin,baicalenin, kaempherol, luteolin and quercetin. *Phytother Res*, 2004, 18: 516–21.

[15] Teiten M. H, Eifes, S, Dicato, M, Diedrich, M. "Review: Curcumin –the paradigm of a multi-target natural compound with applications in cancer prevention and treatment". *Toxins*, 2010; 2: 128–62.

[16] Ravizza, R, Gariboldi, M. B, Molten,i R, Monti, E." Linalool, a plantderived monoterpene alcohol, reverses doxorubicin resistance in human breast adenocarcinoma cells". *Oncol Rep* 2008; 20: 625–30.

[17] Effenberger, K, Schobert, R. "Combinational effects of thymoquinone on the anti-cancer activity of doxorubicin". *Cancer Chemother Pharmacol*, 2010; 67: 867–74.

[18] Alkreathy H, Damanhouri, Z. A, Ahmed, N, Slevin, M, Ali, S. S and Osman, A. M. M. "Aged garlic extract protects against doxorubicininduced cardiotoxicity in rats". *Food Chem Toxicol*, 2010, 48:951–6.

[19]Wattanapitayakul, S. K, Chularojmontri, L, Herunsalee, A, Charuchongkolwongse, S, Niumsakul, S, Bauer, J. A. "Screening of antioxidants from medicinal plants for cardioprotective effect against doxorubicin toxicity". *Basic Clin Pharmacol Toxicol*, 2005; 96: 80–7.

[20] Liang, G, Tang, A, Lin, X, Li, L, Zhang, S, Huang, Z, et al., "Green tea catechins augment the antitumor activity of doxorubicin in an in vivo mouse model for chemoresistant liver cancer". *Int J Oncol*, 2010, 37: 111–23.

[21] Sarkar A, Sreenivasan Y, Ramesh, G. T, Manna, S. K., "D-Glucoside suppresses tumor necrosis factor-induced activation of nuclear transcription factor kB but potentiates apoptosis". *J Biol Chem*, 2004, 279:33768–81.
[22] Nair PKR, Melnick S, Wnuk SF, Rapp M, Escalon E, Ramachandran C." Isolation and Characterization of an anticancer catechol compound from Semecarpus anacradium". *J Ethnopharmacol*, 2009, 122: 450–6.
[23] Pinmai K, Chunlaratthanabhorn S, Ngamkitidechakul C, Soonthornchareon N, Hahnvajanawong C., "Synergistic growth inhibitory effects of Phyllanthus emblica and Terminalia bellerica extracts with conventional cytotoxic agents: Doxorubicin and cisplatin against human hepatocelluar carcinoma and lung cancer cells". *World J Gastroenterol*, 2008, 14: 1491–7.
[24] Wang MY, West BJ, Jensen CJ, Nowicki D, Chen SU, Palu AK,et al. Morinda citrifolia (Noni): A literature review and recent advances in Noni research. Acta Pharmacol Sin, 2002,12: 1127–47.
[25]Sharma G, Tyagi, A. K, Singh, R. P, Chan, D. C, Agarwal, R. "Synergistic anticancer effects of grape seed extract and conventional cytotoxic agent doxorubicin against human breast carcinoma cells". *Breast Cancer Res Treat*, 2004; 85:1–12.
[26] Kapadia, G. J. Rao, G. S., Ramachandran, C, Iida, A., Suzuki, N., & Tokuda, H., et al. "Synergistic cytotoxicity of red beetroot (Beta vulgaris L.) extract with doxorubicin in human pancreatic, breast and prostate cancer cell lines." *Journal of Complementary and Integrative Medicine* 2013 Jun 26;10(1):113-22.
[27] Saeed, M. A, Sabir, A. W.. "Antibacterial activities of some constituents from oleo-gum-resin of Commiphora mukul". *Fitoterapia*, 2004, 75: 204–208.
[28] Sultana, N, Atta, Ur. R, Jahan S. ""Studies on the constituents of Commiphora mukul. Z". *Nat Sect B J Chem Sci*, 2005, 60:1202–1206.
[29] Sharma, P. K, Sharma, J. D. "Potent amoebicides from plant extracts – an in vitro assessment with the gum-oleo-resin of Commiphora wightii", *Curr Sci*, 1996, 71: 68–70.
[30] Newton, S. M, Lau, C, Gurcha, S. S, Besra, G. S, Wright, C. W., "The evaluation of forty-three plant species for in vitro antimycobacterial activities; isolation of active constituents from Psoralea corylifolia and Sanguinaria canadensis". *J Ethnopharmacol*, 2002, 79: 57–67.
[31]Ramawat KG, Mathur M, Dass S, Sutha S., Guggulsterone: a potent natural hypolipidemic agent from Commiphora wightii – problems, perseverance, and prospects. In Biactive Molecules and Medicinal Plants, Ramawat KG, Merillon, JM (eds). Springer-verlag: Berlin; 2008, 101–121.
[32] Shah, R, Gulati, V, Palombo, E. A. "Pharmacological properties of guggulsterones, the major active components of gum guggul". *Phytotherapy research*, 2012, Nov 1; 26(11): 1594-605.
[33]Singh, S. V, Choi, S, Zeng Y, Hahm, E. R, Xiao D. 2007. "Guggulsteroneinduced apoptosis in human prostate cancer cells is caused by reactive oxygen intermediate-dependent activation of c-Jun-NH2-terminal kinase". *Cancer Res* , 2007, 67: 7439–7449.
[34]Shishodia S, Aggarwal, B. B., "Guggulsterone inhibits NF-kB and IkBa kinase activation, suppresses expression of antiapoptotic gene products, and enhances apoptosis". *J Biol Chem* , 2004, 279: 47148–47158.
[35] Dhillon, N, Aggarwal, B. B, Newman, R. A, Wolff, R. A, Kunnumakkara, A. B, Abbruzzese, J. L, Ng, C. S, Badmaev, V, and Kurzrock R., "Phase II trial of curcumin in patients with advanced pancreatic cancer". *Clinical Cancer Research*. 2008 Jul 15;14(14): 4491-9.
[36] Fujiki, H, Suganuma, M, Imai, K., Nakachi, K, "Green tea: cancer preventive beverage and/or drug", *Cancer letters* 2002: 188(1), 9-13.
[37] Kamath, A. B. Wang, L, Das, H, Li, L., Reinhold, V. N, Bukowski, J. F., "Antigens in tea-beverage prime human Vγ2Vδ2 T cells in vitro and in vivo for memory and nonmemory antibacterial cytokine responses." Proceedings of the National Academy of Sciences, 2003, 100(10) : 6009-6014.
[38] Lai P. K, Roy. J, "Antimicrobial and chemopreventive properties of herbs and spices". *Current medicinal chemistry*, 2004, Jun 1;11 (11):1451-60.
[39] Ulrich-Merzenich, G, Panek, D, Zeitler, H, Vetter, H and Wagner, H., "Drug development from natural products: exploiting synergistic effects". *Indian J Exp Biol*, 2010;48:208–19.
[40]Kapadia, G. J, and Rao, G. S. Anticancer effects of red beet pigments. In: Neelwarne B, editor. Red beet biotechnology: metabolites for food and pharmaceutical applications. New York, NY: Springer, 2013:125–54.
[41]Nair, S. C. Salomi, M. J.; Pannikar, B and Pannikar, K. R. J., "Modulatory effects of Crocus sativus and Nigella sativa extracts on cisplatin-induced toxicity in mice". *Ethnopharmacol*, 1991, 31, 75.
[42] El Daly, E. S., "Protective effect of cysteine and vitamin E, Crocus sativus and Nigella sativa extracts on cisplatin-induced toxicity in rats"., *J Pharm Belg*, 1998, 53(2), 93.
43].Nair, S.C.; Pannikar, B.; Pannikar, K.R. "Antitumour activity of saffron (Crocus sativus) ". *Cancer Lett*, 1991, 57(2), 109 .
[44] Nair, S.C; Varghese, C.D; Pannikar, K.R; Kurumboor, S.K; Parathod, R.K.. "Effects of saffron on Vitamin A levels and its Antitumour activity on the growth of solid tumours in mice", *Int J Pharmacog*., 1994, 32(2), 105 .
[45]. Nair, S.C., Salomi, M.J.,Varghese., C.D; Pannikar., B; Pannikar., K.R. *BioFactors.*, 1992, 4(1), 51 .
[46]. Garcia-Olmo, D.C., Riese, H.H., Escribano, J., Ontañon, J., Fernandez, J.A., Atienzar, M., Garcia-Olmo D. *Nutr. Cancer*, 1999, 35(2), 120.
[47].Chang, V.C., Lin, Y.L., Lee, M.J., Show, S.J., Wang, C.J. *Anticancer Res*., 1996, 765, 3603 .
[48]. Abdullaev, F.I., Riveron, N. L., Rotenburd, B. V., Kasumov, F.J.,Perez, L. I., Hernandes, J.M.; Espinosa, A. J.J. "Saffron as chemopreventive agent. In Food of 21st Century: Food and Resource Technology Environment", T Wenyi, Ed.; Ligth Industry Press, China, 2000; 185.
[49]. Molnar, J., Szabo, D.; Pusztai, R.; Mucsi, I.; Berek, L.;, Ocsovski, I.; Kawata, E.; Shoyama, Y. *Anticancer Res.,* 2000, 20(2a), 861 .
[50]. Dufresne, C., Cormier, F., Dorion, S. *Planta Med.,* 1997, 63(2), 150.
[51].Krawinkel,M.B. et al. "Bitter gourd (Momordica charantia): a dietary approach to hyperglycemia". *Nutr. Rev*., 2006, 64331–337.
[52]. Nerurkar,P. et al. "Bitter melon: antagonist to cancer". *Pharm. Res*., 27, 2010 , 1049–1053.

[53].Leung,L. et al. "Anti-diabetic and hypoglycaemic effects of Momordica charantia (bitter melon): a mini review". *Br. J. Nutr.,* 102, 2009, 1703–1708.
[54]. Fuangchan, A. et al. "Hypoglycemic effect of bitter melon compared with metformin in newly diagnosed type 2 diabetes patients". *J.Ethnopharmacol*., 134, 2011, 422–428.
[55]. Takemoto, D.J. et al. "Purification and characterization of a cytostatic factor from the bitter melon Momordica charantia". *Prep. Biochem*., 1982, 12,355–375.
[56]. Grossmann, M.E. et al. "Eleostearic acid inhibits breast cancer proliferation by means of an oxidation-dependent mechanism". *Cancer Prev. Res.(Phila).,* 2, 2009, 879–886.
[57]. Kohno,H. et al. "Dietary seed oil rich in conjugated linolenic acid from bitter melon inhibits azoxymethane-induced rat colon carcinogenesis through elevation of colonic PPARgamma expression and alteration of lipid composition". *Int. J. Cancer,* 110, 2004 ,896–901.
[58]. Ray,R.B. et al. " Bitter melon (Momordica charantia) extract inhibits breast cancer cell proliferation by modulating cell cycle regulatory genes and promotes apoptosis". *Cancer Res*., 2010, 70, 1925–1931.
[59]. Ru,P. et al. "Bitter melon extract impairs prostate cancer cell-cycle progression and delays prostatic intraepithelial neoplasia in TRAMP model". *Cancer Prev. Res. (Phila).,* 4, 2011,2122–2130.
[60]. Li,D., "Diabetes and pancreatic cancer. Mol". *Carcinog* 2012,51, 64–74.
[61]. Sadeghi,N. et al. (2012) Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin. Cancer Res., 18, 2905–2912.
[62]. Kaur, M., Deep, G., Jain, AK., Raina, K., Agarwal, C., Wempe MF., Agarwal R. " Bitter melon juice activates cellular energy sensor AMP-activated protein kinase causing apoptotic death of human pancreatic carcinoma cells". *Carcinogenesis,* 2013 Mar 8;34(7):1585-92.)
[63]. Singh, S., Majumdar, D.K., Yadav, M.R., "Chemical and pharmacological studies on fixedoil of Ocimum sanctum" ,*Indian J.Exp.Biol*.34 ,1996, pp1212–1215.
[64]. Bhat, M.,.Zinjarde, S.S .,.Bhargava, S.Y.,.Kumar, A.R ., Joshi, B.N., "Antidiabetic Indian plants:agood source of potent amylase inhibitors", *Evid.Based Complement.Alternat.Med*.23, 2008 pg 16 .
[65]. Samy, R.P.,.Pushparaj, P.N , Gopalakrishnakone, P., " Acompilation of bioactive compounds from Ayurveda",*Bioinformation* 3(2008)100–110.
[66]. Samson, J.,.Sheeladevi, R .,.Ravindran, R., "Oxidative stress in brain and antioxidant activity of Ocimum sanctum in noise exposure,*Neurotoxicology*" 28 ,2007,679–685.
[67]. Kelm, M.A., Nair, M.G., Strasburg, G.M., DeWitt, D.L., "Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn",*Phytomedicine* 7,2000, pp 7–13.
[68]. Manikandan, p., Vidjaya, L.P., Prathiba, D., Nagini, S., "Combinatorial chemopreventive effect of Azadirachta indica andOcimum sanctum onoxidant–antioxidantstatus,cell proliferation,apoptosis and angiogenesis in arat forestomach carcinogenesis model",*Singapore Med.J*. 49 2008, pp 814–822.
[69]. Trevisan, M.T.M., Vasconcelos Silva, G.B., fundstein, p., Spiegelhalder, B., Owen, R.W., "Characterization of the volatile pattern and antioxidant capacity of essential oils from different species of the genus Ocimum"*J.Agric.Food Chem* Jun2006, 14;54(12), pp 4378-82
[70]. Shimizu, T., Torres, M,P., Chakraborty,. S, Souchek, JJ., Rachagani, S., Kaur, S., Macha, M., Ganti, AK., Hauke ,RJ., Batra, SK., "Holy Basil leaf extract decreases tumorigenicity and metastasis of aggressive human pancreatic cancer cells in vitro and in vivo: Potential role in therapy