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Review Article

NUTRI- COGNOSY IN CANCER

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ABSTRACT

Cancer is a hyper proliferative disorder that is usually treated by chemotherapeutic agents that are toxic not only to tumour cells but also to normal cells, so these agents produce major side effects. And also, these agents are highly expensive and thus not affordable by most. Traditional medicines, functional foods and phytonutrients are generally free of the deleterious side effects and usually inexpensive. Protective elements in a cancer prevention diet include selenium, vitamin-E, vitamin-C, folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as the carotenoids (α-carotene, β-carotene, lycopene, lutein, anthocyanidins and cryptoxanthin). Major dietary factors now known to promote cancer development are polished grain foods and low intake of fresh vegetables, with general importance for an unhealthy lifestyle and obesity. The strategies of cancer prevention in human being may include consumption of functional foods like whole grains (brown rice, Oats, hand pounded rice, whole wheat and whole fine millets) and their by-products, as well some vegetables (bitter melon, garlic, onions, broccoli, and cabbage) and mushrooms. Intake of flax seed, especially its lignin fraction is also evident to lower cancer risk. In addition some beverages (green tea and decaffeinated coffee) may be protective. The current review is certainly a positive approach in the development of novel guidelines against cancer by using dietary functional foods to maintain good health.

Keywords: Functional foods, Bio- active compounds, Nutrients, Anticancer activity, Cancer and Tumour cells.

INTRODUCTION

According to the World Health Organization, cancer is a leading cause of death worldwide accounting for 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 [1].

American Institute for Cancer Research and the World Cancer Research Fund estimated that 30–40 percent of all cancers can be prevented by appropriate diets, physical activity, and maintenance of appropriate body weight [2]. Copious studies have demonstrated that natural products play critical roles against cancer [3-5].

Functional foods can be defined as those providing health benefits beyond basic nutrition and which have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis at effective levels. Several dietary constituents modulate the process of carcinogenesis and prevent genotoxicity. Foods may inhibit cancer by modifying the bioactivation / detoxification of foreign compounds, altering growth regulators such as intracellular cAMP (cyclic AMP) concentrations and/or serving as anti hormones.

According to Purnima et al., 2013, the most Indian foods potentially have anti carcinogenic properties and serve as functional foods including minor millets, allium plants, tomato, cruciferous vegetables, flax seeds and some native fruits as they are abundantly rich in vitamin C, vitamin A, vitamin E, selenium and dietary fibres [6]. Manchali et al., 2012 reported few anticancer vegetables such as broccoli, cauliflower, radish, kale, Brussels sprouts, watercress and cabbage. However, he also emphasized from his study that the lower incidences of many chronic diseases such as cancer and cardiovascular related ailments are associated with consumption of vegetables rich dietary regimes [7].

Bioactive phytochemicals (polyphenols, folic acid, selenium, isothiocyanates, and epicatechins) with anticancer from cereals, vegetables, fruits, mushrooms, tea, coffee, spices, and traditional medicinal herbs [8, 9]. Terrón et al., 2013 reported Phenols and anthocyanins in fruits and vegetables possess great potential of anticancer [10].

CANCER EVOLUTION MECHANISM

Various studies have explicated that the cancer progression within the human body was mainly due to exposure of certain factors like environmental pollution, cigarette smoking, large amount of alcohol consumption and unhealthy dietary patterns. Chronic inflammation, a major cancer initiator has emerged out as one of the leading causes of cancer progression. In this regard, cytokines [receptor activator for nuclear factor κ B ligand (RANKL) and tumour necrosis factor (TNF)], inflammatory enzymes of chemokines [urokinase plasminogen activator (uPA), matrix metalloproteinase (MMP), 5-lipoxygenase and cyclooxygenase-2], adhesion molecules and various growth factors have eventually been recognized as chronic inflammation markers.

The inflammation enhancers are primarily influenced by signal transducer and activator of transcription-3 (STAT-3) however, nuclear transcription factor kappa B (NF-κB) which is found in cytoplasm in its inactivated form, by the action of anchorin domain containing proteins i.e. 1κBα, 1κBβ, 1κBγ, 1κBε, p105, p100 and B cell lymphoma protein-3 [11, 12**]** these factors are activated by free radicals tumour promoters, carcinogens, X- rays and ultraviolet light. In activated form they induce about 200 genes expression that further cascade cellular transformation, metastasis and chemo resistance thereby causing cancer insurgence along with allied ailments as myocardial infarction, atherosclerosis, asthma, diabetes and inflammatory disorders [13]. Signal transducer and activator of transcription- 3 (STAT-3), a member of STAT family closely linked with umorigenesis is activated by epidermal growth factor (EGF) and interleukin-6 (IL-6) receptors and various growth factors thus leading to tumour growth. Along with inflammation, tumour progression requires cell transformation, decreased antioxidant activity, viral or bacterial invasion, angiogenesis and metastasis etc. Free radicals present within the body due to oxidation related complications are leading cause of malignancy. Baliga et al., 2011reported that high production of reactive oxygen and nitrosative species causes oxidative and nitrosative stress [14]. All along with, hydroxyl radical, superoxide anion radical, peroxynitrite (ONOO-), nitric oxide (NO) and hydrogen peroxide (H2O2) are causative agents of structural cell damage as in lipid and protein membranes system and DNA thus shifting healthy cells towards cancerous state as shown in Figure 1

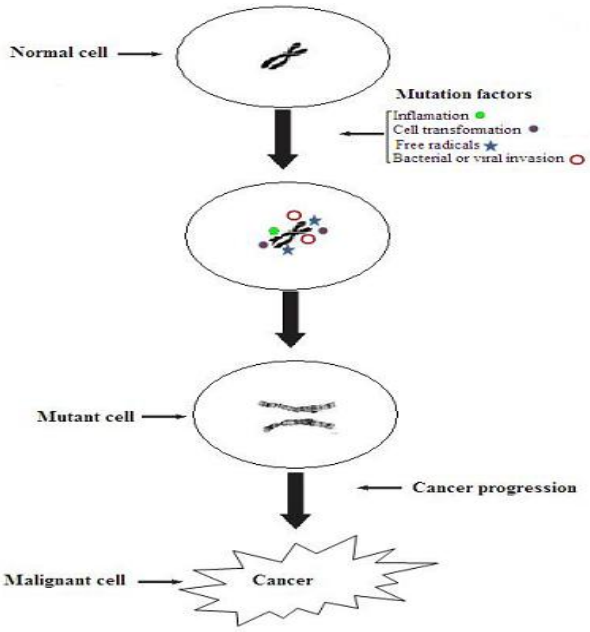

Fig. 1: Mechanism of cancer evolution

Source: Masood Sadiq Butt, Anti-oncogenic perspectives of spices/herbs: 2013

NATURAL FUNCTIONAL FOODS FOR CANCER PREVENTION

FUNCTIONAL PROPERTIES OF RICE VARIETIES

According to Huang et al (2012b) Rice (*Oryza sativa* L.) is one of the most important cereals for human nutrition which contributes 21% to human's nutrient intake and energy requirements 15. Wu et al., 2013 reported that Germinated brown rice is not only richer in the basic nutritional and bioactive components, but also a popular functional food, which exhibits many physiological effects, including anticancer, anti hypertension, anti diabetes etc. chronic diseases16. Deng et al (2013) found out from his studies that the pigmented rice contains a variety of flavones, tannin, phenolics, sterols, tocols, γ-oryzanols, amino acids, GABA, and essential oils, which has a lots of bioactivities including antitumor, antioxidant, antiatherosclerosis, hypoglycemic, and antiallergic activities [17]. Min et al., 2011 described that total proanthocyanidin was the highest in red rice bran, while total anthocyanin was highest in purple brans [18]. The dietary rice bran may exert beneficial effects against several types of cancer, such as leukemia, breast, lung, liver, cervical, stomach, and colorectal cancer [19, 20]. Rice bran is used as an anticancer functional food, based on their bioactive phytochemicals such as ferulic acid, tricin, γ-oryzanol, β-sitosterol, tocotrienols/ tocopherols, and phytic acid Similarly, the anticancer activity of cycloartenyl ferulate in rice bran showed the most prominent in vitro growth inhibition on human colorectal adenocarcinoma SW480 [21]. Red mold rice is always a functional food in Asian people, its extracts exhibit direct cytotoxic and proapoptotic effects on MCF-7 cells and could be considered as a potential functional food for breast cancer prevention[22].

GARLIC

Garlic (*Allium sativum* L.) is a multifaceted medicinal herb with antithrombotic, hypolipidemic, hypoglycemic, antiarthritic, antimicrobial and antitumor activities. Besides sulfurous compounds it also possessed arginine, oligosaccharides, flavonoids and selenium that may be responsible for maintaining good health [23]. The anticancer activity of garlic is mainly due to sulfur containing constituents that have effect on various

Drug metabolizing enzymes, free radical scavenging activity and anti-oncogenesis [24]. In addition, Thomson and Ali, 2003 described from his study that the organosulfur compounds of garlic especially S-allylcysteine disrupts the development of chemically induced tumours in various biological trials. Thus, garlic consumption may prevent from cancer mutiny [25].

European Prospective Investigation into Cancer and Nutrition (EPIC) reported garlic consumption reduce the colon cancer risk in both men and women of various countries. Meanwhile, women that consume higher amount of garlic depicted about 50 percent reduction in colon cancer incidences than that of those who consumed lesser amount [26]. Different garlic derivatives have been reported to modulate an increasing number of molecular mechanisms in carcinogenesis, such as DNA adduct formation, mutagenesis, scavenging of free radicals, cell proliferation and differentiation as well as angiogenesis. The growth rate of cancer cells is reduced by garlic, with cell cycle blockade that occurs in the G2/M phase[27]. In 1990, the U.S. National Cancer Institute initiated the Designer Food Program to determine which foods played an important role in cancer prevention [28]. They concluded that garlic may be the most potent food having cancer preventive properties. In rodents, garlic and its constituents have been reported to inhibit the development of chemically induced tumours in the liver [29], colon [30], prostate [31], bladder [32], mammary gland [33], oesophagus [34], lung [35], skin [36], and stomach37 in both rodent and human studies. Further, Diallyl trisulphide (DATS), an organo sulfur compound isolated from garlic, has been shown to have anticancer activity both in *in vitro* and *in vivo* investigations [38].

TOMATO

Nguyen et al (1999) states that Lycopene is an acyclic carotenoid found primarily in tomatoes and tomato products (about 80% of dietary lycopene) [39]. Other minor food sources include apricots, grapefruit, guava, watermelon, and papaya. Tomato lycopene levels vary widely among different varieties and stages of ripeness [40, 41]. The evidence in support of lycopene in prevention of chronic diseases comes from epidemiological studies[41-44] as well as tissue culture studies using human cancer lines [45, 46] animal studies 47 and also human clinical trials [48].

Giovannucci (1999) conducted a follow up met-analysis of 72 different studies in which, he showed that lycopene intake as well as serum lycopene levels were inversely related to several cancers including prostate, breast, cervical, ovarian, liver and other organ sites [42]. Several other studies since then demonstrated that with increased intake of lycopene and serum levels of lycopene, the risk of cancers were reduced significantly [49-51]. In an earlier research work, Rao et al (1999) studied the status of oxidative stress and antioxidants in prostate cancer patients and the results showed significant differences in levels of serum carotenoids, biomarkers of oxidation and prostate specific antigen (PSA) levels [52].

From the studies of Kucuk et al(2001), Kucuk et al(2002) it was observed that lycopene had reduced the levels of PSA as well as the growth of prostate cancer in newly diagnosed cancer patients receiving 15 mg of lycopene daily for 3 weeks prior to radical prostactomy [49, 53]. In line with this finding, Giovannucci et al (2002) also substantiated that regular consumption of lycopene rich food has been reported to be associated with 30 to 40% lower risk of prostate cancer43. In this connection, yet another study proved that feeding tomato sauce, providing 30 mg lycopene/day for 3 weeks preceding prostatectomy in men diagnosed with prostate cancer significantly elevated serum and prostate lycopene levels [54].

Nkondjock et al.(2005) suggested that a diet rich in tomatoes and tomato based products with high lycopene content may help to reduce the risk of pancreatic cancer[55]. Investigations have indicated that dietary lycopene (10 ppm) significantly reduced the lipid and protein oxidation and demonstrated an apparent protective effect against azoxymethane induced colonic preneoplastic lesions in rats [56]. Similarly, Heber et al., 2002 reported that studies of human and animal cells have identified a gene, connexin 43, whose expression is up regulated by lycopene and that allow direct intercellular gap junctional communication (GJC) [57]. GJC is deficient in many human tumours and its restoration or upregulation is associated with decreased proliferation.

SAFFRON

Saffron (*Crocus sutivus*) is dry stigma containing tetraterpenes class of phytochemicals having principal components i.e. glycoside picrocrocin that crystallizes and produces aldehyde and glucose by hydrolysis, yielding characteristic bitter flavor to saffron [58]. Chemical profiling revealed that crocetin and crocin as characteristic compounds of saffron responsible for cytotoxic ability on tumoral cells and inhibit the carcinomas of colon, skin and soft tissue tumour in combination with vitamin E and Cysteine. In addition, this combination retarded cisplatin induced toxicity in rats modelling system [59].

In an analogous research done by Nair et al., (1995) with saffron extract containing dimethyl-crocetin against human leukemia and murine tumour cell lines, it was noted that saffron extract reduced ascites tumour development and increased the life expectancy of mice up to 45-120 %. Additionally, it also prolongs progression of papilloma development and decreased squamous cell carcinoma. It was also noted that it has ability to decrease soft tissue sarcoma in treated mice. Furthermore, extract also inhibit nucleic acids synthesis in carcinoma development and thus concluded that dimethyl-crocetin interrupts interaction with DNA [60]. However, in an *in vitro* trial, Abdullaev (2002) examined cytotoxic activity of saffron extract in colony forming assay and showed antimutagenic and noncomutagenic behaviour. Moreover, saffron extract showed a dose dependent inhibition in HeLa cells [59].

Kashmiri saffron was investigated for its *in vitro* and *in vivo* xenograft tumour growth inhibition by isolated crocin. It was reported that crocin reduced cell viability in diffusion limited aggregation (DLA) cells with dose dependent activity. Furthermore, animals administrated with spice extract treatment before induction of cancer showed 58 %increase in lifespan, whereas, about 95.6 % reduction of solid tumour in crocin treated animals was observed after 31st day of subsequent to tumour inoculation. Crocin also showed significant impact on haematological aspects especially haemoglobin concentration and lymphocyte count [61].

BEVERAGES

Tea is derived from the leaf of Camellia sinensis, cultivated in Asia producing more than 91% of the world [62]. The world evoked the interest of its use in cancer prevention based on green tea polyphenols with strong antioxidants and the inhibition of carcinogenesis, e.g. oesophageal, stomach, bladder, kidney, urinary tract, colon, rectum, uterus, prostate, liver, lung, breast, pancreas, and skin cancer [63]. Ogunleye et al., 2010 reported that the most active polyphenol in green tea is epigallocatechin gallate; its regular drinkers demonstrated a 40% reduction in breast, prostate and ovarian cancer risk [64]. From the studies of Shi et al., 2012; Zhang et al., 2012 it is evident that the 30-40% polyphenols of green tea decreased risks of ovarian, breast, prostate, gastric, colorectal cancers, and adult leukemia in Chinese populations [62, 65, and 66].

Consumption of coffee is associated with a reduced risk of liver cancer [67], whereas, Caffeinated coffee intake was inversely associated with oral/ pharyngeal cancer mortality [68]

GINGER

Ginger (Zingiber officinale Rosc.), belonging to a tropical and sub-tropical family – Zingiberaceae, having originated in South-East Asia and introduced to many parts of the globe, has been cultivated for thousands of years as a spice and for medicinal purposes [69]. Some phenolic substances present in ginger, generally, possess strong anti-inflammatory and anti-oxidative properties and exert substantial anti-carcinogenic and anti-mutagenic activities [70 –72]. In a study, Unnikrishnan and Kuttan (1988) found that alcoholic extracts of the ginger were more cytotoxic to Dalton's lymphoma ascites tumour cells and human lymphocytes in vitro and Chinese hamster ovary cells and Vero cells in tissue culture than aqueous extracts [73]. The anti-H pylori effects of ginger and its constituents were tested in vitro by Mahady et al. (2003) [74]. It was found that gingerol inhibited the growth of H. pylori CagA+ strains (cytotoxin *associated gene A*) in vitro and this activity may contribute to its chemo preventive effects against colon cancer.

Some compounds present in ginger may exert cancer preventive effects by inducing apoptosis in cancerous or transformed cells. The oleoresin from the root of ginger contains [6]-gingerol, the major pharmacologically active component and lesser amounts of a structurally related vanilloid, [6]-paradol. Two studies such as Lee and Surh, 1998; Lee et al., 1998 suggested that these compounds suppress proliferation of human cancer cells through the induction of apoptosis and were found to exert inhibitory effects on the viability of human HL-60 (promyelocytic leukemia) cells [75, 76]. Results of the study show that the cell viability was decreased by 35% and 89% after 5 h of treatment with 20 lM and 100 lM [6]-paradol, respectively [75**]**.

The results of a study done by Kim et al. (2005) demonstrated that 6-gingerol inhibited angiogenesis of human endothelial cells and caused cell cycle arrest in the G1 (Growth 1)phase through the down-regulation of cyclin D1[**77]**. 6-Gingerol inhibited nitric oxide synthase expression in LPS (*lipopolysaccharide*s)-treated cell lines [78] as well as the EGF (Epidermal growth factor)-induced cell transformation and AP-1(Activator protein) activation in JB6 cells [79**]**. The inhibition of the AP-1 transcriptional complex by [6]-gingerol, in human skin keratinocytes cell lines was also reported by Davies et al. (2005) **[**80**]**. Nakamura et al. (2004) investigated the phase II detoxification enzyme induction of zerumbone (ZER), a sesquiterpene compound occurring in tropical ginger (Zingiber Zerumbet Smith), in rat normal liver epithelial cell line RL34. Exposure of cells to ZER resulted in significant induction of glutathione S-transferase and nuclear localization of the transcription factor Nrf2. This study also implied an antioxidant role for this detoxification system activation by ZER in the neutralization of lipid peroxidation in hepatocytes, providing a new insight for cancer prevention [81**]**.

CRUCIFEROUS VEGETABLES

Cruciferous vegetables (broccoli, cauliflower, cabbage, Brussels sprouts) contain sulforophane, which has anticancer properties. A case-control study done by Fowke et al (2003) in China found that intake of cruciferous vegetables, measured by urinary secretion of isothiocyanates, was inversely related to the risk of breast cancer; the quartile with the highest intake only had 50% of the risk of the lowest intake group [82]. Similarly, in the Nurses' Health Study a high intake of cruciferous vegetables (5 or more servings/week vs. less than two servings/ week) was associated with a 33% lower risk of non- Hodgkin's lymphoma [66]. According to the Health Professionals Follow-up Study conducted by Michaud et al., 1999, the bladder cancer was only weakly associated with low intake of fruits and vegetables, but high intake (5 or more servings/week vs. 1 or less servings/wk) of cruciferous vegetables was associated with a statistically significant 51% decrease in bladder cancer [83]. Also, prostate cancer risk was found to be reduced by cruciferous vegetable consumption in a population-based case control study carried out in western Washington State. Three or more servings per week, compared to less than one serving of cruciferous vegetables per week resulted in a statistically significant 41% decrease in prostate cancer risk [84]. Similar protective effects of cruciferous vegetables were also seen in a multi-ethnic case-control study [85]. A prospective study in Shanghai, China found that men with detectable amounts of isothio cyanates in their urine (metabolic products that come from cruciferous vegetables) had a 35% decreased risk of lung cancer. Among men that had one or two genetic polymorphisms that caused them to eliminate these isothiocyanates slower there was a 64% or 72% decreased risk of lung cancer, respectively [86].

CURCUMIN

Curcuma longa Linn or turmeric is a tropical plant native to South and South east tropical Asia. It is a rhizomatous herb that belongs to the family Zingiberaceae. The major species is genus Curcuma longa Linn which is of commercial value. The rhizomes, on maturity, are steeped in boiling water, sun dried and polished to obtain the turmeric sticks. The powder form is used in various dishes. Turmeric contains essential oils, fatty oils and 2-5% curcuminoid [87]. The ability of curcumin to induce apoptosis in a variety of cancer cell lines and its low toxicity have led to scientific interest in its potential

for cancer therapy as well as cancer prevention [88]. To date, most of the controlled clinical trials of curcumin supplementation in cancer patients have been Phase I trials. Phase I trials are clinical trials in small groups of people, which are aimed at determining bioavailability, safety, and early evidence of the efficacy of a new therapy [89]. A phase I clinical trial in patients with advanced colorectal cancer found that doses up to 3.6g/day for four months were well-tolerated, although the systemic bioavailability of oral curcumin was low [90]. When colorectal cancer patients with liver metastasis took 3.6g/day of curcumin orally for seven days, trace levels of curcumin metabolites were measured in liver tissue, but curcumin itself was not detected [91]. In contrast, curcumin was measurable in normal and malignant colorectal tissue after patients with advanced colorectal cancer took 3.6 g/day of curcumin orally for seven days [92]. These findings suggest that oral curcumin is more likely to be effective as a therapeutic agent in cancers of the gastrointestinal tract than other tissues. Phase II trials are clinical trials designed to investigate the effectiveness of a new therapy in larger number of people, and to further evaluate short-term side effects and safety of the new therapy. A phase II clinical trial in patients with advanced pancreatic cancer found that curcumin exhibited some anticancer activity in two out of 21 patients; however, bioavailability of curcumin was extremely poor [93]. Due to low systemic bioavailability and the fact that curcumin is hydrophobic, the authors proposed that intravenous administration of liposome-encapsulated curcumin be used in future clinical trials [93]

Curcumin has also been reported to affect the expression and activity of various proteins involved in cancer progression, particularly nuclear transcription factor-κB (NF-κB). In cancer tissues, upstream signals (growth factors, cytokines, and hypoxemia) can activate NF-κB, which in turn up regulates the expression of downstream proteins involved in anti-apoptosis (Bcl-2 and Bcl-xL), cell proliferation (cyclin D1 and c-myc), angiogenesis (vascular endothelial growth factor [VEGF] and interleukin-6), and metastasis (matrix metalloproteinases [MMP]), all of which can induce cancer progression [94]. Curcumin's NF-κB-inhibiting activity, together with its safety profile supported by its widespread use as a spice and traditional medicine for many years, therefore presents this compound as a promising new anticancer agent.

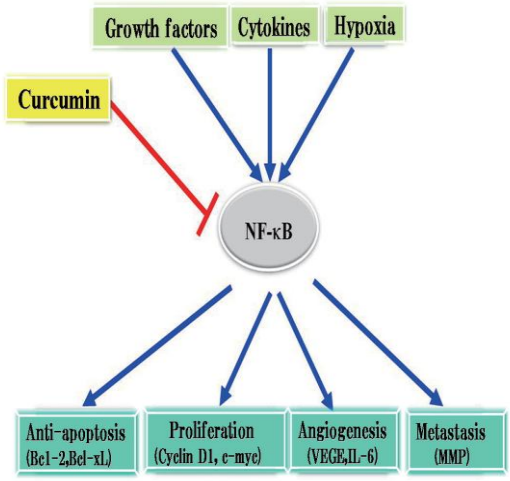

Fig. 2: Suppression of the nuclear factor-κB activation pathway by Curcumin

Source: Aggarwal: Suppression of the nuclear factor-κB activation pathway by spice-derived phytochemicals, 2004.

OMEGA 3:6 RATIO IMBALANCE

Omega 3 fats (alpha-linolenic acid, EPA, DHA) have been shown in animal studies to be protect from cancer, while omega 6 fats (linoleic acid, arachidonic acid) have been found to be cancer promoting fats. Long chain N-3 and N-6 fats have a different effect on the breast tumor suppressor genes BRCA1 and BRCA2. Treatment of breast cell cultures with N-3 fats (EPA or DHA) results in increased expression of these genes while arachadonic acid had no effect [95**]**. Flax seed oil and DHA (from an algae source) both can be used to increase the intake of N-3 fat, with DHA being a more efficient, sure source. While, non-vegetarians may depend on fishes like Shellfish and Fish* (Mackerel, Tuna, Salmon, Bluefish, Mullet, Sturgeon, Menhaden, Anchovy, Herring, Trout, Sardines) for omega-3.

Especially in India, sources of omega-3 from fish may be majorly obtained only from sardine variety as other varieties are scarcely found in Indian coastal catchment area.

ANNONA SQUAMOSA

The plant Annona squamosa traditionally known as custard apple possesses potent bioactive principles in all its parts. The effect of aqueous and organic extracts from defatted seeds of A. squamosa was studied on a rat histiocytic tumour cell line AK-5. Both the extracts caused significant apoptotic tumour cell death with enhance caspase-3 activity down regulation of antiapoptotic genes Bcl-2 and Bclxi and enhance the generation of intracellular ROS, which correlated well with the decreased levels of intracellular GSH. In addition DNA fragmentation and annexin – V staining confirmed that the extracts induced apoptosis in tumour cells through the oxidative stress. Aqueous extracts of A.Squamosa seeds possessed significant antitumor activity in vivo against AD-5 tumour [96]. In this study, organic and aqueous extracts from the defatted seeds of annona squamosa (custard apple) were tested on different human tumour cell lines for antiumoural activity. While organic and aqueous extracts induced apoptosis in MCF-7(Michigan Cancer Foundation-7) and K-562 cells while they failed to do so in COLO-205 cells. Treatment of MCF-7 and K-562 cells with organic and aqueous extracts resulted in nuclear condensation, DNA fragmentation, induction of reactive oxygen species (ROS) generation and reduced intracellular glutathione levels. In addition, down regulation of Bcl-2 and PS externalization by Annexin – V staining suggested induction of apoptosis in MCF-7 and K-562 cells by both the extracts through oxidative stress. On the contrary, COLO-205 cells showed only PS externalization but no change in ROS and glutathione levels. These observations suggest that the induction of apoptosis by A. squamosa extracts can be selective for certain types of cancerous cells [97].

FLAX SEED

Flax seed provides all of the nutrients from its small brown or golden hard-coated seed. It is an excellent source of dietary fiber, omega 3 fat (as alpha-linolenic acid), and lignans. The lignans in flax seed are metabolized in the digestive tract to enterodiol and enterolactone, which have estrogenic activity. In fact, flax seed is a more potent source of phytoestrogens than soy products, as flax seed intake caused a bigger change in the excretion of 2-hydroxyestrone compared to soy protein [98].

Branca and Lorenzetti, 2005 described Phytoestrogens as biologically active estrogenic compounds found in flaxseed that influence protein synthesis, cell proliferation, hormone metabolism, angiogenesis and intracellular enzymes [99]. Mammalian metabolites of flaxseed lignans i.e. enterodiol and enterolactone can serve as a protective approach to cope with pre-cancer cellular alterations. Like phytoestrogens, flaxseed lignans metabolize estrogens and are supposed to serve in prostate and breast cancer prevention strategies as an adjuvant in hormone replacement therapy [100-102]. Omega-6 and omega-3 fatty acids sources i.e. fats with natural or enriched higher concentration from corn oil and flaxseed oil, respectively, play a significant role in inhibiting development of chemically induced tumours in laboratory animals thus reducing chances of colon cancer initiation[103]. At a lower levels of oestradiol, reducing effect on the growth of oestrogen receptors and breast cancer cells of human have been demonstrated by n-3 fatty acid rich fractions of flaxseed cotyledon. Flaxseed cotyledons based diet fed to tumour induced mice (82g/kg) for a period of 8 weeks significantly lowered the cell proliferation process and reduced tumour growth area [104]. Mason et al., 2010 reported

that the dietary combination of flaxseed oil (8%) with primary anticancer drugs can significantly reduce breast tumour development ~89% as compare to primary drug treatment alone for a period of 4 weeks.

RESVERATROL

Resveratrol is a plant-derived polyphenol, phytoalexin that is found in red wine, grapes, peanuts, and mulberries [105]. The amount of resveratrol in natural foods ranges from 16 ng/g (bilberries) to 14.3 mg/L (red wines). In 1997, Jang and colleagues published a seminal paper reporting the ability of resveratrol to inhibit carcinogenesis at multiple stages. Their finding suggested that topical application of resveratrol reduced the number of skin tumours per mouse by up to 98% triggered research on resveratrol around the world [106]. Tessitore et al., 2000 suggests that even the concentration of resveratrol obtained from dietary sources, such as red wine, could be therapeutic in some cases. At higher doses, but pharmacologically achievable doses, protective effects of resveratrol are more frequently observed, and the results are more dramatic [107]. For example, Chen et al., 2004 suggested a daily dose of 40 mg per kg (body weight) increased the survival of mice with subcutaneous neuroblastomas from 0% to 70% [108].

A clinical trial was conducted in twenty colorectal cancer patients by Patel et.al. (2010)[109]. the patients were given either one or two 500-mg resveratrol caplets daily for 8 consecutive days prior to surgical Resection. During surgery, samples of tumour and normal colon tissue were obtained for analysis. Besides resveratrol, six metabolites were identified in the tissue, with resveratrol-3-O-sulfate glucuronide having had the maximal concentration in 14 out of the 20 patients. It was shown that consumption of resveratrol can reduce tumour proliferation by 5%. The results of this trial suggest that daily oral doses of 500 or 1,000 mg produce resveratrol levels in the gastrointestinal tract that are sufficient to elicit anti carcinogenic effects, showing resveratrol as a potential cancer chemo preventive agent.

CONCLUSION

As discussed herein, functional foods are considered as one of the most promising dietary agents for the prevention and treatment of many diseases and consequently, it is being studied extensively worldwide. Overall, our review shows that bio- active compounds from various functional foods can kill a wide variety of tumour and cancer cell types through diverse mechanisms. Furthermore, its ability to kill tumour cells makes bio- active compounds an attractive candidate for drug development. Although numerous animal studies and clinical trials have been done, additional studies are needed to gain the full benefit from various functional foods. Once, if this is ascertained then functional foods may also be made into nutraceuticals for easing the availability and distribution. Further, one can be very sure about the dosage or achievable concentration of nutraceuticals to be delivered for accomplishing anticancer activity.

CONFLICT OF INTEREST STATEMENT

No conflict of interest

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