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Mindfulness of Functional Foods in Cancer Prevention and Health Promotion: A Comprehensive Review

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Abstract
Cancer is a major cause of death in the world. Common cancers include prostate cancer, breast cancer, bladder cancer, colorectal cancer, and skin cancers. Treatment of cancer is very expensive hence the need to prevent the condition primarily, or even secondarily. Foods, like chemicals, have cumulative effects and contain substances both essential and non-essential which have been shown to be healthy. Functional foods with intrinsic mixture of bioactive anti-cancer compounds could be very effective medium to contain menace caused by cancer. The health promoting effect of fruits and vegetable is indisputable. The primary role of diet is to provide sufficient nutrients to meet the nutritional requirements of an individual. There is now increasing scientific evidence to support the hypothesis that some foods and food components have beneficial physiological and psychological effects over and above the provision of the basic nutrients. Functional foods can be considered to be those whole, fortified, enriched or enhanced foods that provide health benefits beyond the provision of essential nutrients (e.g., vitamins and minerals), when they are consumed at efficacious levels as part of a varied diet on a regular basis. Linking the consumption of functional foods or food ingredients with health claims should be based on sound scientific evidence, with the "gold standard". However, not all foods on the market today that are claimed to be functional foods are supported by enough solid data to merit such claims. This review categorizes a variety of functional foods according to the type of evidence supporting their functionality, the strength of that evidence, the recommended intakes and their role in cancer prevention.

Keywords- Cancer, Functional foods, Vitamins, Antioxidants

Introduction

The global burden of cancer is projected to more than double over the next two decades **(**Vineis, P. and Wild, C. P, 2014) raising the prospect of an enormous public-health and, therefore, medical-care problem. Following cardiovascular disease, cancer is the second leading cause of death in most affluent countries. The 13.3 million new cases of cancer in 2010 were predicted to cost US$ 290 billion. The steady increase in the number of people diagnosed with cancer highlights the urgent need for expansion of cancer prevention efforts. Population-based interventions, such as those aimed at tobacco control, reducing excess alcohol consumption, vaccination against human papillomavirus (HPV) infection, and decreasing ultraviolet radiation exposures associated with indoor and outdoor tanning, are obvious strategies to help reduce the incidence rates of various cancers.

Specific diet-related factors with 'convincing' evidence of an association with increased cancer risk, as appraised by the World Cancer Research Fund (WCRF), include, for example, aflatoxins with liver cancer, red meat and/or processed meat with colorectal cancer, alcohol with cancers of the gastrointestinal tract and, for smokers, β-carotene supplementation with lung cancer **(World Cancer Research Fund/American Institute for Cancer Research, 2007; Albanes *et al*. 1995).** Many studies show the factors that contribute to the onset of cancer has determined that genetic factors account only for 5% of tumors, while 95% is due to environmental factors, encompassing as pivotal pillars lifestyle (tobacco, alcohol, physical activity), external stimuli (radiation, pollution, infections, etc.) and diet. Diet represents 30–35% of risk factors, warranting the efforts made by different international organizations and institutions like World Cancer Research Fund (WCRF) or American Institute for Cancer Research (AICR).

Cancer is a leading cause of death among adults. Cancer is one of major health problems and it is causing 1/8 deaths worldwide (Vel Szic KS, Palagani A, Hassannia -2011; Bragg FL, Smith M, Guo Y *et al*., 2014). It is estimated that about

25% of Americans will have cancer in their lifetimes. Treatment usually involves the expensive and often traumatic use of drugs, surgery, and irradiation.
Classifications of dietary patterns could present little variations between studies but globally they agree on the following features: (i) Healthy pattern: diet with a high content of fruits, vegetables, poultry, fish, whole grain cereals and a low daily intake of fats. (ii) Unhealthy pattern: diet with high content of red meat and/or processed meat, refined sugars, potatoes, sweet foods and a high daily intake of fats. (iii) Drinker pattern: diet with a high content of wines, beers and liquors. Research in these dietary patterns has also shown associations between diet and other (chronic) pathologies, including cardiovascular, endocrine or inflammatory diseases. The namely Mediterranean diet is identified by a characteristic pattern consisting mostly of fruits and vegetables, cereals, legumes, olive oil, fish, white meat and dairy products, and a moderate consumption of wine and red meats. Evidence from studies conducted during several decades (in diverse countries with a strong adherence to this dietary pattern) highlights the positive effect of health pattern on decreasing cardiovascular diseases and certain types of cancer.

Functional foods are foods and food components that supply health benefits beyond basic nutrition. These foods are similar in appearance to conventional foods; functional foods consumed as part of the normal diet. Functional food supplies the body with the needed amounts of vitamins, fats, proteins, carbohydrates, *etc.*, required for its healthy survival (Food and Agriculture Organization of the United Nations (FAO) 2007; Chiller JT, Lowy DR 2014). Collectively, functional foods represent a continuum of items that include ingredients or natural constituents in conventional, fortified, enriched, and enhanced foods. The aim of this article was to summarize the evidence concerning the association between functional foods with cancer risk in comprehensive review.

Functional foods
Some plant foods reduce the risk of certain cancers (Asgari M. M., Chren *et al*., 2011) "Nutraceutical" was devised by Stephen De Felice in 1989 from the combination of two terms, "nutrition" and "pharmaceutical". He defined nutraceutical as, "a food (or a part of food) that provides medical or health benefits, including the prevention and or treatment of a disease". Thus, functional foods can be regarded as nutraceuticals if they function as such. The International Life Sciences Institute defines them as "foods that, by virtue of the presence of physiologically-active components, provide a health benefit beyond basic nutrition". In a 1999 position paper, the American Dietetic Association defined functional foods as foods that are "whole, fortified, enriched, or enhanced," but more importantly, states that such foods must be consumed as part of a varied diet on a regular basis, at effective levels" for consumers to reap their potential health benefits. The attention that has been given functional foods and nutraceuticals is due to their acclaimed antioxidant properties. Evidence is available that oxidative stress is involved in the pathogenesis of many chronic diseases, and cancer is not an exception.

Functional Foods and Bioactive Compounds
Soy
In the research of soy and the risk of cancer much attention and interest has been given to breast cancer. Studies focused on secondary prevention demonstrate that soy (isoflavones) reduce the risk of breast cancer **(Guha N., Kwa *et al* 2009; Shu X.O., Zheng-2009)**, especially among postmenopausal women who are on drug therapy, tamoxifen as soy did not interfere with the efficacy of the drug. However, it is suggested that soy produces no significant effect for immediate consumers, but more beneficial to early consumers, as far as cancer chemoprevention is concerned This indicates why soy intake in adolescents is associated with reduced risk of breast cancer in premenopausal women particularly **(Lee S., Shu *et al*., 2009)** but interestingly another study found this inverse association among postmenopausal women and none in the premenopausal. Thus, these findings are still not correlated and have not established one common conclusion as one study contradicts the other.

Beef
An anti-carcinogenic fatty acid known as conjugated linoleic acid was first isolated from grilled beef in 1987. Nine different isomers of conjugated linoleic acid have been reported as occurring naturally in food. Conjugated linoleic acid is unique in that it is found in highest concentrations in fat from ruminant animals (e.g. beef, dairy, lamb). In recent years, conjugated linoleic acid has been shown to be effective in suppressing for stomach tumours in mice, aberrant colonic crypt foci in rats and mammary tumours in rats.

Garlic
Garlic, which belongs to the Allium genus of vegetables, and its sulphur-containing active compounds are protective against the onset and/or progression of several cancers. Diallyl trisulphide prevented the development of prostate cancer **(Singh S.V., Powolny *et al*., 2008; Stan S.D., Singh-2009)** and the spread of cancer to the lung in a transgenic mouse model of prostate cancer. The diallyl prevented progression of prostate cancer in doses of 1 mg and 2 mg given to the mice three times a week compared to placebo. The organo sulphur compound acts by inhibiting the expression of the androgen receptor which is actively involved in the development of prostate cancers. Garlic in different forms including

garlic oil has specifically been protective against liver cancer. Even nodules produced by inducement in some subjects were more significantly reduced by 40 mg/kg body weight garlic oil and this demonstrates a dose-dependent effect. Thus liver cancer induced by an environmental carcinogen, N-nitrosodiethylamine, which is not uncommonly found in some foods and tobacco products **(Park D.H., Shin *et al*., 2009)** was prevented in a rat model; rats are similar to humans in pathophysiology of prostate cancer. This thus indicates a chemo preventive property for the (garlic) oil against the deadly cancer suggestively. Even garlic supplement use was found to be associated with a reduced risk of incidence of blood cancer in a cohort study. This prospective study assessed intake of vitamins and minerals, and specialty supplements during the "10-year period prior to baseline". It was then estimated that intake of garlic supplements at least 4 days a week for not less than 3 years significantly conferred chemoprevention against hematologic malignancy. However, another cohort study (10-year) depicted an increased risk of colorectal cancer with garlic supplement use **(Satia J.A., Littman *et al*., 2009)**.

Cranberries

It has been recognized since the 1920s for their efficacy in treating urinary tract infections. A landmark clinical trial **(Avorn, J., Monane, M. *et al*., 1994)** confirmed this therapeutic effect in a well-controlled study involving 153 elderly women. More recent research has confirmed that condensed tannins (proanthocyanidins) in cranberry are the biologically active component and prevent *E. coli* from adhering to the epithelial cells lining the urinary tract. New preliminary research suggests that the anti-adhesion properties of the cranberry may also provide other health benefits, including in the oral cavity.

Green Tea

Green tea polyphenols have been shown to prevent the advancement of tumour cells in transgenic adenocarcinoma of the mouse prostate (TRAMP) model **(Gupta S., Hastak *et al*., 2008)** Green tea has been shown to protect the bladder against the process of apoptosis. The antioxidant potency of green tea extract, was examined as green tea reduced the oxidative stress induced by H_2O_2 (oxidative agent) in normal or malignant human bladder cells. In another study, the reduced risk (weak) of breast cancer among pre-menopausal women was dependent on many years of consuming green tea drinks, but in the post-menopausal women, <6years of green tea consumption was enough for a decreased breast cancer risk. However, a case-control study that investigated the effect of plasma levels of tea polyphenols on breast cancer risk among Japanese women reported no statistically significant association **(Iwasaki M., Inoue *et al*., 2010)**. In another case control study with Japanese population, high plasma levels of green tea polyphenols, was associated with a reduced risk of gastric cancer in women, and positively associated with gastric cancer in men. The study also found that men who recorded higher serum green tea polyphenol levels were cigarette smokers

Grape Seed

Grape seed has been demonstrated as being effective in the prevention of UV-light induced cancer **(Katiyar 2008)**. And in a case-control study, grape seed extract has been associated with decreased risk of cutaneous squamous cell carcinoma as research suggests that grape seed extract greatly reduced the risk of cutaneous squamous cell carcinoma when the extract was compared with a multivitamin. As polyphenols, grape seed proanthocyanidins have been acknowledged in the inhibition of lung cancer. The efficiency of grape seed is not limited to its extract; in cohort studies grape seed has proven to inhibit blood cancer, and prostate cancer **(Brasky T.M., Kristal *et al*., 2011)** incidence when taken as supplements. However, in another cohort study the effect of grape seed supplement on colorectal cancer and lung cancer risk was unclear.

Tomatoes

Tomatoes have received much attention in recent years because of interest in lycopene, the primary carotenoid in this fruit, and its potential role in cancer risk reduction. In a prospective cohort study of more than 47 000 men, those who consumed tomato products ten or more times per week had less than one half the risk of developing advanced prostate cancer. Interestingly, lycopene is the most abundant carotenoid in the prostate gland. Other cancers whose risk has been inversely associated with serum or tissue levels of lycopene include breast, digestive tract, cervix, bladder and skin. Proposed mechanisms by which lycopene could influence cancer risk are related to its antioxidant function. Lycopene is the most efficient quencher of singlet oxygen in biological systems **(Di Mascio *et al*., 1989)**.

Ginseng

Ginseng over the years has been used as medicinal plant. Ginseng belongs to the genus Panax and inclusive of Chinese ginseng, American ginseng and notoginseng. It has received extensive attention in cancer research involving various cancer types as cancer of the blood, liver, colon, breast and lung. Ginseng extract has been suggested to be chemo-preventive in the development of colon cancer in vitro, and in a mouse model. Notoginseng root extract demonstrated an inhibitory effect on SW480 colorectal cancers thereby being preventive in the proliferation of cancer cells. American ginseng extract had a suppressive effect on ulcerative colitis, an inflammation of the large intestine and a risk factor for

colon cancer, when administered to mice, and in vitro. It is thus anti-inflammatory to colitis and chemo-preventive to the cancer cells. The colon cancer prevention effect of ginseng has been attributed to its antioxidant property and ginsenosides have been suggested to be responsible for this property, and in some cases specific metabolites are involved.

However heat-treated Panax quinquefolius root has been of a greater chemoprevention against breast cancer as compared to unheated ginseng. This suggests that heating ginseng before consumption might probably confer to a larger extent more beneficial effect as compared to eating it raw. Terpenoids including ginsenosides have been suggested to have potential chemoprotective effect on liver cancer **(Thoppil R.J., Bishayee A. 2011)** as liver cancer cells growth was inhibited and mice induced with liver cancer followed by treatment with ginsenoside Rg3 had a greater survival period. It's also indicated that in children, a ginsenoside metabolite, so-called compound k has anti-cancer effects on blood cancer cells. The compound was used in vitro at concentrations 5 μM, 10 μM, or 20 μM and the highest dose (20μM) produced the greatest effect. Most researches have really made ginseng 'super' in cancer prevention. But very important and notable is the fact that the chemopreventive effects displayed by ginseng were all "dose-dependent" and "time- dependent". However, a cohort study with ginseng supplement showed no effect on risk of blood cancer incidence **(Walter R.B., Brasky T.M. *et al*., 2011)**. This is an indication that though ginseng may be effective as a natural product, its supplement may have no association with at least certain cancers.

Flaxseed
There has been an increasing interest in fibre-associated compounds known as lignans. The two primary mammalian lignans, enterodiol and its oxidation product, enterolactone, are formed in the intestinal tract by bacterial action on plant lignan precursors. Flaxseed is one of the richest sources of mammalian lignan precursors. Because enterodiol and enterolactone are structurally similar to both naturally occurring and synthetic oestrogens, and have been shown to possess weakly oestrogenic and anti-oestrogenic activities, they may also play a role in the prevention of oestrogen-dependent cancers. In rodents, flaxseed has been shown to decrease tumours of the colon, mammary gland and lung. **(Phipps WR, Martini MC *et al*., 1993)** demonstrated that the ingestion of 10 g of flaxseed per day elicited several hormonal changes associated with reduced breast cancer risk. However, as is the case with soya, epidemiological data are required to support the hypothesis that enterodiol and enterolactone have anti carcinogenic properties in man.

Citrus fruits
Several epidemiological studies have shown that citrus fruits are protective against a variety of human cancers. Although oranges, lemons, limes and grapefruits are a principal source of such important nutrients as vitamin C, folate and fibre **(Elegbede *et al*., 1993)** have suggested that another component is responsible for the anticancer activity. Citrus fruits are particularly high in a class of phytochemicals known as the limonoids. In recent years, evidence has been accumulating in support of the cancer-preventative effect of limonene. It shows that this compound to be effective against a variety of both spontaneous and chemically induced rodent tumours. However, mindful of the importance of the overall dietary pattern in cancer risk reduction, one must question the clinical implications of a single phytochemical in isolation.

Dietary fibre
Dietary fibre is known to prevent constipation by increasing bulk of stool, drawing water into stool **(Sarriá B., Martínez-López *et al*., 2012)**. It has been shown to have significant effect on the risk of colorectal cancer. In a cohort study, dietary fibre was effective in the prevention of colorectal cancer among individuals who were genotypically at risk of the chronic disease. In the colon, the dietary fibre has direct contact with the walls of the intestine which in itself reduces the pressure exerted on the walls of the canal. Also, dietary fibre-rich diet intake has been found to be associated with a reduced risk of breast cancer in a cohort study with postmenopausal women.

Cruciferous vegetables
These include broccoli, cabbage, cauliflower, Brussels sprouts, and greens (kale, turnip, collard, mustard). In a study conducted in vitro phenethyl isothiocyanate (3 μM) from cruciferous vegetables was postulated to be a chemopreventive agent as it had an inhibitory effect on human breast cancer cell lines **(McCormick D.L., Rao K.V.N. *et al*., 2010)**. A case-control study that compared fruits and other vegetables to cruciferous vegetables showed cruciferous vegetables to be significantly associated with a reduced risk of lung cancer among smokers. This association was even stronger in heavy smokers (those who took more than 20 cigarettes daily) and short-term smokers (those with less than 30 years of smoking. Raw cruciferous vegetables have been found to be more efficient than cooked ones. A reduced risk of bladder cancer was demonstrated in subjects who took raw cruciferous vegetables. And higher servings were also found to have a greater effect on lung cancer risk reduction; 4.5 servings compared with 2.5 servings per month, and >4 servings compared to <1 serving per week. In population-based case-control study that involved African Americans and their Caucasian counterparts did not record any racial difference in the chemopreventive effect of cruciferous vegetables against lung cancer **(Carpentera C.L., Yu M.C. *et al*., 2009)**.

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Fatty fish

The 2000 American Heart Association Dietary Guidelines recommend two servings of fatty fish per week for a healthy heart, and the FDA authorized a qualified health claim on dietary supplements linking the consumption of EPA and DHA (n-3) fatty acids to a reduction of coronary heart disease risk. The FDA concluded that use of (n-3) fatty acid supplements is safe, provided daily intakes of EPA and DHA from supplements do not exceed 2 g/d **(U.S. Food and Drug Administration, 2004)**.

Others

A cohort study that considered specialty supplements suggested that Saffron, Prune, oats, Avocado, Brazil nut, Apricot kernel oil, essential oils, apple, and tamarind intake led to a reduced incidence of cancers of the mouth, pharynx, oesophagus, stomach, colon, larynx, lung and ovary.

TABLE 1: Strength of evidence for functional foods currently on the U.S. market

Functional food	Bioactive component	Health benefit	Strength of evidence	Recommended amount / Frequency
Fortified margarines	Plant sterol and stanol esters	Reduce total and LDL cholesterol	Very strong	1.3 g/d for sterols
Psyllium	Soluble fibre	Reduce total and LDL cholesterol	Very strong	1 g/d
Soy	Protein	Reduce total and LDL cholesterol	Very strong	25 g/d
Whole oat products	β-Glucan	Reduce total and LDL cholesterol	Very strong	3 g/d
Cranberry juice	Proanthocyanidins	Reduce urinary tract infections	Moderate	300 mL/d
Fatty fish	(n-3) Fatty acids	Reduce TG, reduce heart disease cardiac deaths and fatal and non-fatal myocardial infarction	Strong	2/g/d
Garlic	Organosulfur compounds	Reduce total and LDL cholesterol	Moderate	600–900 mg/d
Green tea	Catechins	Reduce risk of certain types of cancer	Weak to moderate	Unknown
Spinach, kale, collard greens	Lutein/zeaxanthin	Reduce risk of age-related macular degeneration	Weak to moderate	6 mg/d
Tomatoes and processed tomato products	Lycopene	Reduce risk prostate cancer	Weak to moderate	Daily
Lamb, turkey, beef, dairy	CLA	Reduce breast cancer	Weak	Unknown
Cruciferous, vegetables	Glucosinolates, indoles	Reduce risk of certain types of cancer	Weak	3 or more servings/week
Fermented dairy products	Probiotics	Support GI health, boost immunity	Weak	Daily

Conclusion

In general, this paper discusses nutraceuticals /functional foods, especially the need for consuming appropriate diets, health issues development of new nutraceuticals /functional foods/food supplements with novel health benefits. Any health benefits attributed to functional foods should be based on sound and accurate scientific criteria, including rigorous studies of safety and efficacy. Consumers must realize that functional foods are not a “magic bullet” or a panacea for poor health habits. There are not good and bad “foods,” only good and bad dietary patterns. Thus, they should be wary of many of the promoted or implied benefits of these foods, and must realize that there is no consistent regulation or enforcement of existing regulations in the functional foods area. Diet is only one aspect of a comprehensive lifestyle approach to good health, which should include regular exercise, tobacco avoidance, stress reduction, maintenance of healthy body weight and other positive health practices. Only when all of these issues are addressed, functional foods become a part of an effective strategy to maximize health and reduce the risk of cancer.

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