Available online at www.worldscientificnews.com

World Scientific News

WSN 64 (2017) 18-33 EISSN 2392-2192

Functional foods and nutraceuticals, wonders in cancer risks - a review

Prince Chikwere

Department of Nursing, All Nations University College, P.O. Box KF 1908 Koforidua, Ghana

E-mail address: uc.princechik@gmail.com

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. This led to acclamation and acceptance of certain foods as providing health benefits – functional foods. Functional foods and nutraceuticals are chemopreventive to cancers as evidenced by different researches conducted over the years. This does not conclude that functional foods and nutraceuticals have an all-preventive effect because some research findings implicate them in cancer risks and progression. This review aims to discuss some of these foods and the chemoprotective compounds therein to aid further clinical studies. Foods investigated for their role in cancer risks and included in this review are: grapes, tomatoes, red peppers, berries, chestnut, ginseng, *Rhodiola*, green tea, soy, garlic, and cruciferous vegetables. This review also considered the so-called antioxidant nutrients – selenium, vitamins A, B, C, D and E. Others include glucosamine, chondroitin, melatonin, MSM, which were taken as supplements. Anyway researches are still on-going relating cancers and foods as this list is supposedly not exhaustive.

***Keywords*:** nutraceuticals: functional foods; cancer; prevention; risks

1. INTRODUCTION

Cancer leads in mortality cause in developed countries and places second in developing countries [1]. The words 'developing and developed' being used in this review describes economic status. GLOBOCAN 2008 estimates 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008; of which 56% of new cancer cases and 63% of deaths occurred in developing countries [2]. Lifestyle changes including physical inactivity, and westernized diet are suggested to play leading role in the rising cases of cancer in developing countries. Dietary patterns have been demonstrated to exhibit positive correlation with mortality risk from cardiovascular diseases and cancer [3]. Various remedies including surgery and chemotherapy have been deployed over the years in the management and cure of cancers. These treatments are rather costly to a financially average person especially in the developing population like Ghana and Africa as a whole. At least one-third of all cancer cases are preventable; prevention offers the most cost-effective long-term strategy for the control of cancers [4]. This review seeks to focus on the use of functional foods and nutraceuticals in the primary prevention of cancers generally and specifically. Chemoprevention of cancer has gained popularity over the past decades; compounds in plant extracts have been investigated and suggested to be chemopreventive [5].

2. FUNCTIONAL FOODS AND NEUTRACEUTICALS, AND ANTIOXIDANTS

Some plant foods reduce the risk of certain cancers [6]. "Nutraceutical" was devised by Stephen De Felice in 1989 from the combination of two terms, "nutrition" and "pharmaceutical" [7]. 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 [8]. Plant foods and health-based researches have really proven plant bioactive compounds to contain antioxidants and other healthy properties [9]. For positive results large doses of some antioxidant must be taken, and this might present an undesirable condition [10]. Nutraceuticals have been deployed in many conditions requiring therapeutic needs, cancers prevention inclusive [11]. This was demonstrated by a study to investigate the role of nutraceuticals in prostate cancer prevention [8]. Antioxidants are so-called because they prevent oxidations that occur in living tissues of the body. The oxidations are caused by a group of substances referred to as reactive oxygen species. Reactive oxygen species (also known as free radicals) include superoxide radicals, hydroxyl radicals and hydrogen peroxide and are involved in oxidative damage to DNA, cells and proteins alike [12]. Evidence is available that oxidative stress is involved in the pathogenesis of many chronic diseases, and cancer is not an exception [13]. The attention that has been given functional foods and nutraceuticals is due to their acclaimed antioxidant properties.

3. NUTRIGENOMICS

Nutrients are important in the proper functioning of the body (cells, tissues, organs, and systems). Activities in cells are under the direction of the nucleus with genetic structures, genes and DNA. DNA can direct the functionality of nutrients and nutrients can as well influence gene expression but to a large extent the exact mechanisms is not precise [14].

Nonetheless, enzymes are key in metabolic pathways and any modulation affects their function in for instance disease development and/or progression [14,15].

4. FUNCTIONAL FOODS AND BIOACTIVE COMPOUNDS

4. 1. Chestnut

Chestnut extract possesses antioxidant activity and is protective against gastric cancer, and mild protective effect against prostate cancer and breast cancer [16]. Chestnut extract made with ethanol has a significant negative effect on the growth of gastric cancer cells, as compared to raw chestnut extract which had no effect and or even the water extract of chestnut which exhibited a rather growth promoting effect on cancer cells. The flesh and inner shell of chestnuts (including the leaves, and flowers), and uncooked chestnuts and processed chestnut confer antioxidant effects [16-18]. The potency of the extracts in chemoprevention is dependent on their extraction medium and dose applied [16].

4. 2. Berries

Blueberries, blackberries and strawberries are good sources of antioxidants and phenolic compounds [19]. This indicates that berries may be effective in the prevention of development of cancer cells. Strawberries as a repository of bioactive phenolic compounds [20, 21, 22], have been investigated for the contribution of their antioxidant activity to the prevention of chronic diseases [23]. Blue berries have been found to be chemopreventive to breast cancer *in vitro* and *in vivo*. The *in vitro* experiment was done with breast cancer cell lines whilst the *in vivo* was conducted with mouse model which has similar physiology (including development and progression of diseases) as compared to humans [15]. Thus the results of such study can be extrapolated to humans. However, use of whole berry as reported by this study has proven to be more efficient than isolates of each of the compounds therein [15]. This is an indication that the chemopreventive effect of blue berry is derived when the plant food is consumed in whole as a fruit and not as some extract. Blue berry exhibited this property by inhibiting growth of cancer cells [24] in which the activities of proteins involved in the oncogenesis were interrupted in their pathway [15] and rather promoting normal gene expression and healthy cell growth [25].

4. 3. 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 [26,27], especially among postmenopausal women [26,28] who are on drug therapy, tamoxifen as soy did not interfere with the efficacy of the drug [26]. However it is suggested that soy produces no significant effect for immediate consumers [29], but more beneficial to early consumers, as far as cancer chemoprevention is concerned [30]. This indicates why soy intake in adolescents is associated with reduced risk of breast cancer in premenopausal women particularly [31] but interestingly another study found this inverse association among postmenopausal women and none in the premenopausal [32]. Thus these findings are still not correlated and have not established one common conclusion as one study contradicts the other.

Soy intake especially in high amounts reduced the risk of colorectal cancer [33,34] since the effect of soy treatment depends really on the quantity (dose) administered or consumed [34]. This study was conducted *in vitro* with cultured human cancer cells that were treated with different concentrations (0 ppm, 150 ppm, 300 ppm, 600 ppm, 1200 ppm, and 2400 ppm) of soy saponins. The inhibitory effect of the different concentrations of the soy was assessed by cell count. By the first day only 2400 ppm demonstrated an effect by 40.7%. The different concentrations demonstrated an incremental inhibitory effect which was time-dependent; by the fifth day 300 ppm, 600 ppm, 1200 ppm, and 2400 ppm inhibited cancer progression by 36.0%, 57.9%, 59.7%, and 92.2% respectively. But a prospective cohort study has limited this inverse association between soy intake and risk of colorectal cancer to postmenopausal women suggesting that soy which has oestrogen-like properties [35] acts effectively in oestrogen-low environment [36]. And this is further elucidated as soy (and other isoflavone-containing foods) intake has been linked to a reduced risk of endometrial cancer in postmenopausal women, in another cohort study [37].

4. 4. 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 [38-40]. Diallyl trisulphide prevented the development of prostate cancer [38,39] and the spread of cancer to the lung in a transgenic mouse model of prostate cancer [38]. This effect was dose-dependent in that the experimental subjects who received the higher amounts of the treatment derived significantly greater benefit.

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 [38]. The organosulphur compound acts by inhibiting the expression of the androgen receptor [39] which is actively involved in the development of prostate cancers. Garlic in different forms including garlic oil has specifically been protective against liver cancer [40].

In this experiment, liver cancer was induced in rats with N-nitrosodiethylamine (10 mg/kg body weight) and these rats were administered with garlic oil (20 or 40 mg/kg body weight) one week before the inducement and throughout the experiment. The garlic oil significantly inhibited the incidence of nodules and the biochemical parameters associated with N-nitrosodiethylamine-induced 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 [41] was prevented in a rat model; rats are similar to humans in pathophysiology of prostate cancer.

This thus indicates a chemopreventive 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 [42]. 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 haematologic malignancy. However, another cohort study (10-year) depicted an increased risk of colorectal cancer with garlic supplement use [43].

4. 5. Green Tea

Green tea polyphenols have been shown to prevent the advancement of tumour cells in transgenic adenocarcinoma of the mouse prostate (TRAMP) model [44]. Green tea has been shown to protect the bladder against cell death [14]. 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 [14]. In a case-control study with Chinese women, consumption of not less than 10 g of fresh mushrooms or not less than 4 g of dried mushrooms per day was inversely associated with breast cancer risk. This inverse association was found to be greater among women who consumed ≥7 g of fresh mushrooms or ≥2 g of dried mushrooms plus ≥1.05 g of dried green tea leaves per day [45]. 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 [46]. 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 [47]. 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 [48].

4. 6. Grape Seed

Grape seed has been demonstrated as being effective in the prevention of UV-light induced cancer [49]. 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 [6]. As polyphenols, grape seed proanthocyanidins have been acknowledged in the inhibition of lung cancer [50]. The efficiency of grape seed is not limited to its extract; in cohort studies grape seed has proven to inhibit blood cancer [42], and prostate cancer [51] 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 [52].

4. 7. 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 chemopreventive in the development of colon cancer *in vitro* [53,54], and in a mouse model [55]. Notoginseng root extract demonstrated an inhibitory effect on SW480 colorectal cancers [53,56] thereby being preventive in the proliferation of cancer cells. American ginseng extract had a suppressive effect on ulcerative colitis [57], 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 chemopreventive to the cancer cells [57]. 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 [56,58], and in some cases specific metabolites are involved [59]. In a study, *P. notoginseng* saponin extract has been confirmed to have a scavenging effect

[58]. Ginseng has also been shown to protect against breast cancer [60-62] as a ginsenoside from *Panax notoginseng* significantly reduced oncogene (MDM2) expression, and the protective effect of ginsenoside diminished when the oncogene was allowed to overexpress [60]. However heat-treated *Panax quinquefolius* root has been of a greater chemoprevention against breast cancer as compared to unheated ginseng [62]. 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 [63] as liver cancer cells growth was inhibited and mice induced with liver cancer followed by treatment with ginsenoside Rg3 had a greater survival period [64]. Chen *et al* have also indicated that in children, a ginsenoside metabolite, so-called compound k have anti-cancer effects on blood cancer cells [65]. 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" [53-65]. However, a cohort study with ginseng supplement showed no effect on risk of blood cancer incidence [42]. 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.

4. 8. Rhodiola rosea

Only a few researches have involved *R. rosea* in cancer studies, so information regarding its involvement in the prevention of cancer is really limited. Nonetheless, in an *in vitro* study *Rhodiola rosea* extracts prevented the growth and/or the proliferation of cancer cells of the urinary bladder [66]. Another species *R. crenulata* also had an inhibitory effect on the growth of breast cancer cells in an experiment conducted *in vitro* [67].

4. 9. Tomato and Red pepper

Tomato contains lycopene, which has been acknowledged as being potent [68], and other antioxidants. Studies suggest lycopene is chemopreventive against cancers including prostate cancer [69], gastric cancer, breast cancer and lung cancer [70]. Tomato has been shown to be effective against liver cancer induced by some environmental carcinogens in a rat model. Diethylnitrosamine-initiated and nonalcoholic steatohepatitis-promoted early liver cancer was inhibited in rats by lycopene-containing tomato extract [71].

Similarly, mortality risk from prostate cancer was reported in a research with rats, to have been reduced with tomato powder [72]. Capsaicin (active component in pepper) in an experiment conducted *in vitro* acted as an anticancer agent by inhibiting the migration of skin cancer cells to other body parts demonstrating its chemopreventive effect [73].

This effect was dependent on the concentration of the capsaicin applied; in that, 50 μM, 100 μM, 150 μM, and 200 μM elicited 10%, 31%, 47%, and 58% of inhibitory effect respectively. In a case-control study, gall bladder cancer patients were ascertained to have consumed more red pepper than the controls. Suggestively, capsaicin was not associated with the cancer but another component, aflatoxin [74].

4. 10. Dietary fibre and Cruciferous vegetables

Dietary fibre is known to prevent constipation by increasing bulk of stool, drawing water into stool [75]. 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 [76]. 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 [77].

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 [78]. 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) [79]. Raw cruciferous vegetables have been found to be more efficient than cooked ones [79,80]. A reduced risk of bladder cancer was demonstrated in subjects who took raw cruciferous vegetables [80]. 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 [79], and >4 servings compared to <1 serving per week [81]. Carpenter *et al.* in their 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 [81].

5. ANTIOXIDANT NUTRIENTS

5. 1. Vitamins and Minerals

Male smokers with low serum levels of vitamin D have increased risk of developing bladder cancer as found by a prospective case-control study [82]. In other case-control studies, low serum 25(OH)D levels were linked to high risk of breast cancer while high levels of serum 25(OH)D were rather protective against breast cancer in post-menopausal women [83], and premenopausal women [84]. The association between vitamin D and certain cancers has mainly relied on serum vitamin D, and this does not really differentiate between dietary vitamin D and skin-metabolised vitamin D. The risk of breast cancer may be reduced with supplements of beta-carotene, vitamin C, vitamin E and zinc [85], as calcium-and-vitamin D supplementation reduced melanoma skin cancer risk in women at high risk such as those with non-melanoma skin cancer [86]. But a large prospective cohort study did not indicate any association between multivitamin use (vitamin C, E and zinc), or use of β-carotene (3000-6000 μg/day, 7days/week in 5 years) supplement with skin cancer [87]. In a case-control study, multivitamin use was associated with a reduced risk of skin cancer and interestingly, individual vitamins (A, B C, D, or E) tended not to show any association whatsoever with the cancer risk [6]. The effect of a vitamin may not be profound but when taken together with other vitamins, they produce an effect obvious enough for an association; this effect may not be immediate. Multivitamins tend to produce reasonable associations and effect after a really long term use [85,42] as this was demonstrated between multivitamins and cancer arising

from the bone marrow [42]. Paradoxically, supplements of minerals (selenium inclusive), vitamins (vitamin C and vitamin E inclusive) and anti-inflammatives like garlic were not chemopreventive against bladder cancer [88]. A Caucasian case control study associated vitamin E intake with reduced risk of prostate cancer but this was genetic-based as it was limited to subjects who were homozygous for a variant allele [89]. Supplements have thus shown to be specific in reducing the risk of cancer incidence.

In a stratified case-control study with American veterans, high intakes of folate (>700μg/day) and vitamin B-6 (>4.5mg/day) were associated with high grade prostate cancer and high intake of vitamin B-12 had no association with prostate cancer at all. On the other hand, high methionine intake (>2.6g/day) had a significant association with prostate cancer risk especially the low grade [90].

Selenium is chemoprotective against prostate cancer. Prostate cancer was inversely associated with serum selenium concentration in individuals with high vitamin E intake especially smokers in a case-control study [91]. However, in a rat prostate cancer model, neither selenium alone or vitamin E alone nor their combination had a chemopreventive effect on prostate cancer. Rats received either selenomethionine (1.5 or 3.0 mg/kg diet), vitamin E (2000 or 4000 mg/kg diet), selenised yeast (3 or 9 mg/kg), or selenomethionine + vitamin E (500 or 2000 mg/kg diet), and these doses, especially the high, increased plasma levels of selenium and vitamin E but did not influence the incidence of prostate cancer [78].Selenium in another case-control study reduced the risk of colorectal cancer mildly in African Americans [92]. In whites, selenium and vitamins C and E, β-carotene, and folate, vitamins B-6 and B-12 significantly reduced colorectal cancer risk [92]. Selenium consumption has also shown an inverse association with ovarian cancer risk [93]. Also low selenium levels have been associated with increased risk of papillary thyroid cancers in a case-control study [94]. Use of selenium supplement (50-100 μg/day, 7days/week in 5 years) demonstrated no association with skin cancer in a prospective cohort study [87]. A case-control study which recruited women (21 years and above) recorded a significant reduced risk of ovarian cancer for highest intake of selenium from food as compared to the lowest intake, but found no association between selenium intake from supplement, and the cancer. Neither the intake of vitamin C, E, or β-carotene from foods nor from supplements showed any association with prostate cancer.

6. OTHERS

A cohort study that considered specialty supplements suggested that glucosamine and chondroitin supplements intake led to a reduced incidence of lung and colorectal cancers as reduced cancer risk was observed in subjects who utilized fish oil, St. John's Wort, melatonin, and MSM supplements [43]. These active substances have commonly been investigated for their effects in conditions other than cancers.

7. CONCLUSION

Plant foods and the nutrients therein have really, as reviewed in this paper demonstrated to be effective in the primary prevention of cancer. Chest nuts, berries, dietary fibre, cruciferous vegetables, green tea, grape seed, ginseng, *Rhodiola rosea*, tomato extracts, have proven to be chemopreventive against one cancer or the other. Selenium and other antioxidant

family of nutrients also demonstrated same. Even glucosamine and chondroitin supplements and others whose known conventional functions are not cancer prevention have been demonstrated to prevent certain cancers. This is not to say that once a food or nutrient is chemopreventive, it will mask the deleterious effects of potential carcinogens. A research acknowledges plant foods as important in the prevention of cancers but claims that Finnish male smokers who consumed excess acrylamide (produced when carbohydrate is heated) are at risk of developing lung cancer [96]. Similarly the effectiveness of the supplements of the micronutrients is not guaranteed, supplements may be harmful and rather increase disease; carotene and retinol supplements increased risk of prostate cancer unlike the dietary sources [97]. Another research did not find folic acid supplementation to reduce the risk of colorectal adenoma [98]. It should not be utterly assumed and accepted that foods and/or their components, and nutraceuticals are inherently chemopreventive. This paradoxicalness of neutraceuticals indicates they should be used with caution. This review thus provides a basis for more clinical trials using these plant foods and supplements on the other hand, in the quest to fight the non-communicable disease.

References

[1] World Health Organization (2008). The Global Burden of Disease: 2004 Update. World Health Organization, Geneva. www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf (Accessed April 12, 2013)

[2] Ferlay J, Shin H.R, Bray F, Forman D, Mathers C.D, Parkin D. GLOBOCAN 2008, Cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; Year. Available at: http://globocan.iarc.fr. (Accessed April 12, 2013)

[3] Heidemann C., Schulze M.B., Franco O.H., van Dam R.M., Mantzoros C.S., Hu F.B. (2008). Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. Circulation 118:230–237

[4] World Health Organization (2008). 2008-2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases. www.who.int/nmh/publications/ncd_action_plan_en.pdf (Accessed April 12, 2013)

[5] Ruhul Amin, A.R.M., Kucuk O., Khuri F.R, Shin D.M. (2009) Perspectives for cancer prevention with natural compounds. J Clin Oncol, 27:2712-2725

[6] Asgari M.M., Chren M., Warton E.M., Friedman G.D., White E. (2011). supplement use and risk of cutaneous squamous cell carcinoma. J Am Acad Dermatol, 65(6): 1145-1151

[7] Maddi V.S., Aragade P.D., Digge V.G., Nitaliker M.N. (2007). Importance of Nutraceuticals in Health Management. Phcog Rev, 1: 377-379

[8] Trottier G., Bostrom P.J., Lawrentschuk N., Fleshner N.E. (2010). Nutraceuticals and prostate cancer prevention: a current review. Nat Rev Uro, 7: 21-30

[9] Balsano C., Alisi A. (2009). Antioxidant effects of natural bioactive compounds. Curr. Pharm, 15: 3063-3073

[10] Özten-Kandaş N., Bosland M.C. (2011). Chemoprevention of prostate cancer: natural compounds, antiandrogens, and antioxidants – in vivo evidence. J Carcinog, 10: 27.

[11] Pandey M., Verma R.K., Saraf S.A. (2010). Nutraceuticals: new era of medicine and health. Asian J Pharm Clin Res, 3: 11-15

[12] Finkel T., Holbrook N.J. (2000). Oxidants, oxidative stress and the biology of ageing. Nature, 408(6809): 239-247

[13] Halliwell B. (1994). Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet, 344(8924): 721-724

[14] Coyle C.H., Philips B.J., Morrisroe S.N., Chancellor M.B., Yoshimura N. (2008). Antioxidant effects of green tea and its polyphenols on bladder cells. Life Sci, 83(1-2): 12-18

[15] Adams L.S., Phung S., Yee N., Seeram N.P., Li L., Chen S. (2010). Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. Cancer Res, 70(9): 3594-3605

[16] Lee S.H., Kim E.J., Kim S.H. (2011). Chestnut extract induces apoptosis in AGS human gastric cancer cells. Nutr Res Pract, 5(3): 185-191

[17] Vekiari S.A., Gordon M.H., García-Macías P., Labrinea H. (2008). Extraction and determination of ellagic acid content in chestnut bark and fruit. Food Chem, 110: 1007-1011

[18] Barreira J.C.M., Ferreira I.C.F.R., Oliveira M.B.P.P., Pereira J.A. (2008). Antioxidant activities of the extracts from chestnut flower, leaf, skins and fruit. Food Chem, 107: 1106-1113

[19] Huang W., Zhang H, Liu W, Li C. (2012). Survey of antioxidant capacity and phenolic composition of blueberry, blackberry, and strawberry in Nanjing. J Zhejiang Univ-Sci B (Biomed & Biotechnol), 13(2): 94-102

[20] Oszmiański J., Wojdyło A. (2009). Comparative study of phenolic content and antioxidant activity of strawberry puree, clear, and cloudy juices. Eur Food Res Technol, 228(4): 623-631.

[21] Tulipani S., Mezzetti B., Capocasa F., Bompadre S., Beekwilder J., de Vos C.H.R., Capanoglu E., Bovy A., Battino M. (2008). Antioxidants, phenolic compounds, and nutritional quality of different strawberry genotypes. J Agric Food Chem, 56(3): 696-704

[22] Wang S.W., Millner P. (2009). Effect of different cultural systems on antioxidant capacity, phenolic content, and fruit quality of strawberries (Fragaria x aranassa Duch.). J Agric Food Chem, 57(20): 9651-9657

[23] Hannum S.M. (2004). Potential impact of strawberries on human health: a review of the science. Crit Rev Food Sci Nutr, 44(1): 1-17

[24] Seeram N.P. (2008). Berry fruits: compositional elements, biochemical activities, and the impact of their intake on human health, performance, and disease. J Agric Food Chem, 56: 627-9

[25] Li J., Zhang D., Stoner G.D., Huang C. (2008). Differential effects of black raspberry and strawberry extracts on BaPDE-induced activation of transcription factors and their target genes. Mol Carcinogenesis, 47: 286-294

[26] Guha N., Kwan M.L., Quesenberry Jr C.P., Weltzien E.K., Castillo A.L., Caan B.J. (2009). Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: Life After Cancer Epidemiology (LACE) Study. Breast Cancer Res Treat, 118(2): 395-405

[27] Shu X.O., Zheng Y., Cai H., Gu K., Chen Z., Zheng W., *et al*. (2009). Soy food intake and breast cancer survival. JAMA. 302(22): 2437-2443

[28] Wu A.H., Koh W.P., Wang R., Lee H.P., Yu M.C. (2008). Soy intake and breast cancer risk in singapore chinese health study. Br J Cancer, 99: 196-200

[29] Khan S.A., Chatterton R.T., Michel N., Bryk M., Lee O., Ivancic D. *et al*. (2012). Soy isoflavone supplementation for breast cancer risk reduction: A Randomized Phase II Trial. Cancer Prev Res (Phila), 5(2): 309-319

[30] Messina M., Hilakivi-Clarke L. (2009). Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. Nutr Cancer, 61(6):792-798

[31] Lee S., Shu X., Li H., Yang G., Cai H., Wen W., Ji B., Gao J., Gao Y., Zheng W. (2009). Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. Am J Clin Nutr, 89: 1920-6

[32] Wu A.H., Koh W., Wang R., Lee H., Yu M.C. (2008). Soy Intake and Breast Cancer Risk in Singapore Chinese Health Study. British Journal of Cancer, 99: 196-200

[33] Yang G., Shu X.O., Li H., Chow W.H., Cai H., Zhang X., Gao Y.T., Zheng W. (2009). Prospective cohort study of soy food intake and colorectal cancer risk in women. Am J Clin Nutr, 89: 577-583

[34] Tsai C., Chen Y., Chien Y., Huang W., Lin S. (2010). Effect of soy saponin on the growth of human colon cancer cells. World J Gastroenterol, 16(27): 3371-3376

[35] Yang G., Shu X., Li H., Chow W., Cai H., Zhang X., Gao Y., Zheng W. (2009). Prospective Cohort Study of Soy Food Intake and Colorectal Cancer Risk in Women. Am J Clin Nutr, 89: 577-83

[36] Hwang C.S., Kwak H.S., Lim H.J., *et al*. (2006). Isoflavone metabolites and their in vitro dual functions: they can act as an estrogenic agonist or antagonist depending on the estrogen concentration. J Steroid BiochemMol Biol, 101: 246-253

[37] Ollberding N.J., Lim U., Wilkens L.R., Wendy Setiawan V., Shvetsov Y.B., Henderson B.E., Kolonel L.N., Goodman M.T. (2012). Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the Multiethnic Cohort Study. J Natl Cancer Inst, 104: 67-76

[38] Singh S.V., Powolny A.A., Stan S.D., Xiao D., Arlotti J.A., Warin R., Hahm E., Marynowski S.W., Bommareddy A., Potter D.M., Dhir R. (2008). Garlic constituent diallyl trisulfide prevents development of poorly-differentiated prostate cancer and pulmonary metastasis multiplicity in TRAMP mice. Cancer Res, 68(22): 9503-9511

[39] Stan S.D., Singh S.V. (2009). Transcriptional Repression and Inhibition of Nuclear Translocation of Androgen Receptor by Diallyl Trisulfide in Human Prostate Cancer Cells. Clin Cancer Res, 15(15): 4895-4903

[40] Zhang C., Zeng T., Zhao X., Yu L., Zhu Z., Xie K. (2012). Protective effects of garlic oil on hepatocarcinoma induced by N-Nitrosodiethylamine in rats. Int J Biol Sci, 8(3): 363-374

[41] Park D.H., Shin J.W., Park S.K., *et al*. (2009). Diethylnitrosamine (DEN) induces irreversible hepatocellular carcinogenesis through overexpression of G1/S-phase regulatory proteins in rat. Toxi-col Lett, 191: 321-326

[42] Walter R.B., Brasky T.M., Milano F., White E. (2011). Vitamin, mineral, and specialty supplements and risk of hematologic malignancies in the prospective VITamins And Lifestyle (VITAL) study. Cancer Epidemiol Biomarkers Prev, 20(10): 2298-2308

[43] Satia J.A., Littman A., Slatore C.G., Galanko J.A., White E. (2009). Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins And Lifestyle (VITAL) Study. Cancer Epidemiol Biomarkers Prev, 18(5): 1419-1428

[44] Gupta S., Hastak K., Ahmad N., Lewin J.S., Mukhtar H. (2008). Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proc Natl Acad Sci, 98: 10350-10355

[45] Zhang M., Huang J., Xing X., Holman C.D. (2009). Dietary intake of mushrooms and green tea combine to reduce the risk of breast cancer in chinese women. Int J Cancer, 124: 1404-1408

[46] Shrubsole M. J., Lu W., Chen Z. *et al*. (2009). Drinking green tea modestly reduces breast cancer risk. J Nutr, 139(2): 310-316

[47] Iwasaki M., Inoue M., Sasazuki S., Miura T. *et al*. (2010). Plasma tea polyphenol levels and subsequent risk of breast cancer among Japanese women: A Nested Case-Control Study. Breast Cancer Res Treat, 124(3): 827-34

[48] Sasazuki S., Inoue M., Miura T., Iwasaki M., Tsugane S. (2008). Plasma tea polyphenols and gastric cancer risk: a case-control study nested in a large population-based prospective study in Japan. Cancer Epidemiol Biomarkers Prev, 17: 343

[49] Katiyar S.K. (2008). Grape seed proanthocyanidines and skin cancer prevention: inhibition of oxidative stress and protection of immune system. Mol Nutr Food Res, 52(1): S71-S76

[50] Akhtar,S., Meeran, S.M., Katiyar, N., and Katiyar, S.K. (2009). Grape seed proanthocyanidins inhibit the growth of human non-small cell lung cancer xenografts by targeting insulin-like growth factor binding protein-3, tumor cell proliferation, and angiogenic factors. Clin Cancer Res, 15(3): 821

[51] Brasky T.M., Kristal A.R., Navarro S.L., Lampe J.W., Patterson R.E., Peters U., White E. (2011). Specialty supplements and prostate cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Nutr Cancer, 63(4): 573-582

[52] Satia J.A., Littman A., Slatore C.G., Galanko J.A., White E. (2009). Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. Cancer Epidemiol Biomarker Prev, 18: 1419-1428

[53] Wang C.Z., Xie J.T., Zhang B., Ni M., Fishbein A., Aung H.H., Mehendale S.R., Du W., He T.C., Yuan C.S. (2007). Chemopreventive effects of *Panax notoginseng* and its major constituents on SW480 human colorectal cancer cells. Int J Oncol, 31: 1149-1156

[54] King M.L., Murphy L.L. (2010). Role of cyclin inhibitor protein p21 in the inhibition of HCT116 human colon cancer cell proliferation by American Ginseng (*Panax quinquefolius*) and its Constituents. Phytomedicine, 17(3-4): 261

[55] Jin Y., Kotakadi V.S., Ying L., Hofseth A.B., Cui S., Wood P.A., Windust A., Matesic L.E., Pena E.A., Chiuzan C., Singh N.P., Nagarkatti M., Nagarkatti P.S., Wargovich M.J., Hofseth L.J. (2008). American ginseng suppresses inflammation and DNA damage associated with mouse colitis. Carcinogenesis, 29: 2351-2359

[56] Xie J., Du G., McEntee E., Aung H.H., He H., Mehendale S.R., Wang C., Yuan C. (2011). Effects of triterpenoid glycosides from fresh ginseng berry on SW480 human colorectal cancer cell line. Cancer Res Treat, 43(1): 49-55

[57] Poudyal D., Le P.M., Davis T., Hofseth A.B., Chumanevich A., Chumanevich A.A., Wargovich M.J., Nagarkatti M., Nagarkatti P.S., Windust A., and Hofseth L.J. (2012). A hexane fraction of american ginseng suppresses mouse colitis and associated colon cancer: anti-inflammatory and proapoptotic mechanisms. Cancer Prev Res, 5(4): 685-696

[58] He N.W., Zhao Y., Guo L., Shang J., Yang X.B. (2012). Antioxidant, antiproliferative, and pro-apoptotic activities of a saponin extract derived from the roots of *Panax notoginseng* (Burk.) F.H. Chen. J Med Food, 15 (4): 350-359

[59] Wang C., Du G., Zhang Z., Wen X., Calway T., Zhen Z., Musch M.W., Bissonnette M., Chang E.B., Yuan C. (2012). Ginsenoside compound K, not Rb1, possesses potential chemopreventive activities in human colorectal cancer. Int J Oncol, 40(6): 1970-1976

[60] Wang W., Zhang X., Qin J., Voruganti S., Nag S.A., Wang M., Wang H., Zhang R. (2012). Natural product ginsenoside 25-OCH3-PPD inhibits breast cancer growth and metastasis through down-regulating MDM2. PLoS ONE, 7(7): e41586

[61] Aung H.H., Mehendale S.R., Wang C.Z., Xie J., McEntee E. (2007). Cisplatin's tumoricidal effect on human breast carcinoma MCF-7 cells was not attenuated by American ginseng. Cancer Chemother Pharmacol, 59(3): 369-374

[62] Wang C., Aung H.H., Zhang B., Sun S., Li X., He H., Xie J., He T., Du W., Yuan C. (2008). chemopreventive effects of heat-processed *Panax quinquefolius* root on human breast cancer cells. Anticancer Res, 28(5A): 2545-2551

[63] Thoppil R.J., Bishayee A. (2011). Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. World J Hepatol, 3(9): 228-249

[64] Jiang J, Chen X, Chen X, Zheng S. (2011). Ginsenoside Rg3 inhibit hepatocellular carcinoma growth via intrinsic apoptotic pathway. World J Gastroenterol, 17(31): 3605-3613

[65] Chen Y., Xu Y., Zhu Y., Li X. (2013). Anti-Cancer Effects of ginsenoside compound k on pediatric acute myeloid leukemia cells. Cancer Cell Int, 13: 24

[66] Liu Z., Li X., Simoneau A.R., Jafari M., Zi X. (2012). *Rhodiola rosea* extracts and salidroside decrease the growth of bladder cancer cell lines via inhibition of the mTOR pathway and induction of autophagy. Mol Carcinog, 51(3): 257-267

[67] Tu Y., Roberts L., Shetty K., Schneider S.S. (2008). *Rhodiola crenulata* induces death and inhibits growth of breast cancer cell lines. J Med Food, 11: 413-23

[68] Moselhy S.S., Al Mslmani M.A. (2008). Chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by 7,12 dimethyl(a)benzanthracene in Sprague Dawely female rats. Mol Cell Biochem, 319: 175-180

[69] Atawodi S.E. (2011). Nigerian foodstuffs with prostate cancer chemopreventive polyphenols. Infect agent cancer, 6(2): S9

[70] Mein J.R., Lian F., Wang X.D. (2008). Biological activity of lycopene metabolites: implication for cancer prevention. Nutr Rev, 66: 667-683

[71] Wang Y., Ausman L.M., Greenberg A.S., Russell R.M., Wang X. (2010). Dietary lycopene and tomato extract supplementations inhibit Nonalcoholic Steatohepatitis-promoted Hepatocarcinogenesis in rats. Int J Cancer, 126(8): 1788–1796

[72] Boileau T.W., Liao Z., Kim S., Lemeshow S., Erdman J.W. Jr., Clinton S.K. (2003). Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy restricted diets. J Natl Cancer Inst, 95: 1578-1586

[73] Shin D., Kim O., Jun H., Kang M. (2008). Inhibitory effect of capsaicin on B16-F10 melanoma cell migration via the Phosphatidylinositol 3-kinase/Akt/Rac1 signal pathway. Experimental and mol Med, 40(5): 486-494

[74] Báez S., Tsuchiya Y., Calvo A., Pruyas M., Nakamura K., Kiyohara C., Oyama M., Yamamoto M. (2010). Genetic variants involved in gallstone formation and capsaicin metabolism, and the risk of gallbladder cancer in Chilean women. World J Gastroenterol, 16(3): 372-378

[75] Sarriá B., Martínez-López S., Fernández-Espinosa A., Gómez-Juaristi M., Goya L., Mateos R., Bravo L. (2012). Effects of regularly consuming dietary fibre rich soluble cocoa products on bowel habits in healthy subjects: a free-living, two-stage, randomized, crossover, single-blind intervention. Nutrition & Metabolism, 9: 33

[76] Andersen V., Egeberg R., Tjønneland A., Vogel U. (2012). Interaction between interleukin-10 (IL-10) polymorphisms and dietary fibre in relation to risk of colorectal cancer in a Danish case-cohort study. BMC Cancer, 12: 183

[77] Mattisson I., Wirfa E., Johansson U., Gullberg B., Olsson H., Berglund G. (2004). Intakes of plant foods, fibre and fat and risk of breast cancer – a prospective study in the Malmo¨ Diet and Cancer cohort. British Journal of Cancer, 90: 122-127

[78] McCormick D.L., Rao K.V.N., Johnson W.D., Bosland M.C., Lubet R.A., Steele V.E. (2010). Null activity of selenium and vitamin E as cancer chemopreventive agents in the rat prostate. Cancer Prev Res (Phila), 3(3): 381-392

[79] Tang L., Zirpoli G.R., Jayaprakash V. *et al*. (2010). Cruciferous vegetable intake is inversely associated with lung cancer risk among smokers: a case-control study. BMC Cancer, 10: 162

[80] Tang L., Zirpoli G.R., Guru K., Moysich K.B., Zhang Y., Ambrosone C.B., McCann S.E. (2008). Consumption of raw cruciferous vegetables is inversely associated with bladder cancer risk. Cancer Epidemiol Biomarkers Prev, 17(4): 938-944

[81] Carpentera C.L., Yu M.C., London S.J. (2009). Dietary isothiocyanates, Glutathione S-Transferase M1 (GSTM1), and lung cancer risk in African Americans and Caucasians from Los Angeles County, California. Nutr Cancer, 61(4): 492-499

[82] Mondu A.M., Weinstein S.J., Männistö S., Snyder K., *et al*. (2010). Serum Vitamin D and Risk of Bladder Cancer. Cancer Res, 70(22): 9218-9223

[83] Abbas S., Linseisen J., Slanger T., Kropp S., Mutschelknauss E.J., Flesch-Janys D., Chang-Claude J. (2008). Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer-results of a large case-control study. Carcinogenesis, 29: 93-9

[84] Abbas S., Chang-Claude J., Linseisen J. (2009). Plasma 25-hydroxyvitamin D and Premenopausal Breast Cancer risk in a German case-control study. Int J Cancer, 124(1): 250-5

[85] Pan S.Y., Zhou J., Gibbons L., Morrison H., and Wen S.W. (2011). Antioxidants and breast cancer risk- a population based case-control study in Canada. BMC Cancer, 11: 372

[86] Tang J.Y, Fu T., LeBlanc E., Manson J.E., Feldman D., Linos E., Vitolin M.Z., Zeitouni N.C., Larson J., Stefanick M.L. (2011). Calcium Plus Vitamin D Supplementation and the Risk of Nonmelanoma and Melanoma Skin Cancer: Post Hoc Analyses of the Women's Health Initiative Randomized Controlled Trial. J Clin Oncol, 29: 3078-3084

[87] Asgari M.M., Maruti S.S., Kushi L.H., White E. (2009). Antioxidant supplementation and risk of incident melanomas: results from a large prospective cohort study. Arch Dermatol, 145(8): 879-882

[88] Hotaling J.M., Wright J.L., Pocobelli G., Bhatti P., Porter M.P., White E. (2011). Long-term use of supplemental vitamins and minerals does not reduce the risk of urothelial cell carcinoma of the bladder in the VITamins And Lifestyle Study. J Urol, 185(4): 1210-1215

[89] Wright M.E., Peters U., Gunter M.J., *et al*. (2009). Association of variants in two vitamin E transport genes with circulating vitamin E concentrations and prostate cancer risk. Cancer Res, 69(4): 1429-1438

[90] Vidal A.C., Grant D.J., Williams C.D., *et al*. (2012). Associations between Intake of Folate, Methionine, and Vitamins B-12, B-6 and Prostate Cancer Risk in American Veterans. J Cancer Epidemiol. doi:10.1155/2012/957467

[91] Peters U., Foster C.B., Chatterjee N., Schatzkin A., *et al*. (2007). Serum selenium and risk of prostate cancer—a nested case control study. Am J Clin Nutr, 85(1): 209-217

[92] Williams C.D., Satia J.A., Adair L.S., Stevens J. *et al*. (2010). Antioxidant and DNA methylation-related nutrients and risk of distal colorectal cancer. Cancer Causes Control, 21(8): 1171-1181

[93] Gifkins D., Olson S.H., Paddock L., King M., Demissie K., Lu S., Kong A.T., Rodriguez-Rodriguez L., Bandera E.V. (2012). Total and individual antioxidant intake and risk of epithelial ovarian cancer. BMC Cancer, 12: 211

[94] Moncayo R., Kroiss A., Oberwinkler M., Karakolcu F., Starzinger M., Kapelari K., Talasz H., Moncayo H. (2008). The role of selenium, vitamin C, and zinc in benign thyroid diseases and of selenium in malignant thyroid diseases: Low selenium levels are found in subacute and silent thyroiditis and in papillary and follicular carcinoma. BMC Endocrine Disorders 8: 2

[95] Hirvonen T., Kontto J., Jestoi M., Valsta L., Peltonen K., Pietinen P., Virtanen S.M., Sinkko H., Kronberg-Kippilä C., Albanes D., Virtamo J. (2010). Dietary acrylamide intake and the risk of cancer among Finnish male smokers. Cancer Causes Control, 21(12): 2223-2229

[96] Hirvonen T., Kontto J., Jestoi M., Valsta, L., Peltonen, K., Pietinen, P., Virtanen, S.M., Sinkko, H., Kronberg-Kippilä, C., Albanes, D., Virtamo, J. (2010). Dietary Acrylamide Intake and the Risk of Cancer Among Finnish Male Smokers. Cancer Causes Control, 21(12): 2223-2229

[97] Neuhouser M.L., Barnett M.J., Kristal A.R, Ambrosone C.B., King I.B., Thornquist M., Goodman G.G. (2009). Dietary supplement use and prostate cancer risk in the carotene and retinol efficacy trial. Cancer Epidemiol Biomarkers Prev, 18(8): 2202-2206

[98] Cole B.F., Baron J.A., Sandler R.S., Haile R.W., Ahnen D.J., Bresalier R.S. *et al*., (2007). Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA, 297(21): 2351-2359

(Received 16 December 2016; accepted 02 January 2017)