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Review paper

Natural antioxidants in cancer prevention

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Abstract

It is well known that oxidative stress is an inevitable event in aerobic life. When our cells use oxygen to create energy, a variety of reactive oxygen (ROS) and nitrogen species (RNS) are generated. These species could attack DNA directly and form mutagenic lesions afterwards. According to the oxidative stress hypothesis of aging, the oxidative damage to critical molecules accumulates over the life period and could ultimately impair the body's function. Moreover, severe oxidative stress causes mutations of tumor suppressor genes, known as one of the initial events in carcinogenesis. Furthermore, it could also play a crucial role in the promotion of the multi-step carcinogenesis. On the other hand, the human body possesses a number of mechanisms that counteract oxidative stress by producing antioxidants *in situ*, or externally supplied them through foods and/or supplements. Indeed, a considerable amount of laboratory evidence from chemical, cell culture, and animal studies indicates that antioxidants may slow down or possibly prevent the cancer development. Yet, the information from recent cohort, case-control and/or ecological studies is less clear. Therefore, the objectives of this review are to compile a compendium of studies, and to identify effective and promising natural antioxidant interventions.

Key words: oxidative stress; reactive oxygen species; reactive nitrogen species; natural antioxidants; cancer;

Introduction

It is well known that oxidative stress is an inevitable event in aerobic life. When our cells use oxygen to create energy, a variety of reactive oxygen (ROS) and nitrogen species (RNS) are generated as a consequence of ATP (adenosine triphosphate) production by the mitochondria (Bahorun et al., 2006; Halliwell and Gutteridge, 2007). These reactive species could damage the cell structures, including lipids and membranes, proteins and nucleic acids. Their destructive effects are balanced by the antioxidant action of non-enzymatic antioxidants and antioxidant enzymes (Halliwell, 1996). Despite the presence of the cell's defense system, oxidative damage accumulates during the life period. Moreover, this radical-related damage to DNA, to proteins and to lipids could play a crucial role in the development of age-dependent diseases such as cancer, arteriosclerosis, arthritis, neurodegenerative disorders and other conditions (Halliwell and Gutteridge, 2007; Pham-Huy, 2008). According to the oxidative stress hypothesis of aging, the oxidative damage to critical molecules accumulates over the life period and could ultimately impair the body's function. Moreover, severe oxidative stress causes DNA damage and mutations of tumor suppressor genes, known as one of the initial events in carcinogenesis (Chatterjee et al., 2007; Valko et al., 2006; Valko et al., 2007).

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The human body possesses a number of mechanisms that counteract oxidative stress by producing antioxidants. They are either produced *in situ*, or externally supplied through foods and/or supplements. The roles of antioxidants are to act as "free radical scavengers" – to prevent and/or repair damages caused by ROS and RNS, and ultimately to lower the cancer risk (Chatterjee et al., 2007; Valko et al., 2006; Valko et al., 2007; Raj et al., 2011).

Endogenous compounds in cells can be classified as enzymatic and non-enzymatic antioxidants. The most important antioxidant enzymes directly involved in the scavenging of reactive species are: superoxide dismutase (CuZn-SOD, EC 1.15.1.1), catalase (CAT, EC 1.11.1.6), and glutathione peroxidase (GPX, EC 1.11.1.9) (Kenneth, 2003). CuZn-SOD is the first line of defense against free radicals, that catalyzes the dismutation of superoxide anion ($O_2^{\bullet-}$) into hydrogen peroxide (H_2O_2). The last further transforms into water and oxygen (O_2) by another enzymes such as catalase (CAT) or glutathione peroxidase (GPX). The selenoprotein GPX enzyme removes H_2O_2 and uses it to oxidize reduced form of glutathione (GSH) into oxidized glutathione (GSSG). Besides H_2O_2, GPX also reduces lipid or non-lipid hydroperoxides while oxidizing glutathione (GSH) (Bahorun et al., 2006; Droge, 2002; Genestra, 2007; Halliwell, 2007; Pacher et al., 2007; Willcox et al., 2004; Young and Woodside, 2001).

The non-enzymatic antioxidants are divided into metabolic and nutrient antioxidants. Metabolic antioxidants, such as lipoid acid, glutathione, L-ariginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc., are produced by body metabolism (Droge, 2002; Willcox et al., 2004). On the contrary, nutrient antioxidants, such as vitamin E, vitamin C, carotenoids, trace metals (selenium, manganese, zinc), flavonoids, omega-3 and omega-6 fatty acids, must be externally supplied through foods and/or supplements.

Dietary antioxidants play a key role in helping endogenous compounds to combat oxidative stress. They minimize the deleterious effects of free radicals and fight off tumors (Willcox et al., 2004; Donaldson, 2004; Hercberg et al., 2010; Riso et al., 2010; Myung et al, 2011). Vegetables, fruits, legumes, nuts, and seeds are sources of a variety of those bioactive compounds, such as carotenoids (including beta-carotene and lycopene), vitamin C, vitamin E, quercetin, and selenium. Experimental evidence indicates a strong connection between oxidative damage, cancer, and aging. Epidemiological observations suggest that a diet rich in fruits and vegetables is associated with lower incidence of some cancers and longer life expectancy; since fruits and vegetables contain natural antioxidants, a considerable effort has been dedicated to understanding their effects in experimental studies and in human trials (Dolara et al., 2012; Somannavar and Kodliwadmath, 2012).

Most cases of cancer (80–90%) are linked to environmental causes, and of these, 30–40% of cancers are linked to the diet. It is believed that most cancers could be prevented by following the recommendations of the 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Diet and Cancer Report, by not smoking, and by avoiding other types of exposure to tobacco as well as by following recommendations on the subject of diet, physical activity, and weight. (http://www.aicr.org/research/research_science_expert_report.html). Although many dietary recommendations have been proposed to lower the risk of cancer up to date, only few have significant supporting scientific evidence. Therefore, the objectives of this review are to compile a compendium of studies, and to identify effective and promising natural antioxidant interventions.

Natural antioxidants and lung cancer

Vegetables and lung cancer

According to the Second Diet and Cancer Report of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) there are 17 cohort studies of vegetables consumption and lung cancer risk published up to date. 14 cohort studies showed reduced risk associated with higher levels of vegetable consumption (World Cancer Research Fund / American Institute for Cancer Research, DC: AICR, 2007). Out of 27 case-control studies of total vegetables consumption and risk of lung cancer, 17 showed reduced risk associated with higher levels of con-

Table 1. Vegetables and lung cancer

Type of food studied	Cohort Studies		Case-Control Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**
Total vegetables	14	17	17	27
Non-starchy vegetables	3	3	*n/a*	*n/a*
Green-leafy vegetables	5	5	12	17
Carrots	6	6	20	21

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies
n/a: data not available

sumption (World Cancer Research Fund / American Institute for Cancer Research., Washington, DC: AICR, 2007).

Three cohort studies investigated the association between non-starchy vegetables consumption and lung cancer risk and reported non-significant reduced risk when comparing highest and lowest vegetable intakes (Jansen et al., 2001; Knekt et al., 1997; Kvale et al., 1983). Non-starchy vegetables are a good source of cancer-preventive substances (such as carotenoids and vitamin C, flavonoids, allylsulphides, and phytoestrogens). Few possible mechanisms of action are proposed: via their antioxidant activities, induction of detoxification enzymes, stimulation of the immunity, antiproliferative potential, and/or modulation of hormone metabolism.

Five cohort studies of green, leafy vegetables intake and risk of lung cancer reported reduced risk when comparing high to low intake groups (Stahelin et al., 1991; Steinmetz et al., 1993).

All six cohort studies of the association between carrots consumption and risk of lung cancer published up to date reported reduced risk (Speizer et al., 1999). Twenty out of the 21 case-control studies showed decreased risk when comparing high against low carrots intake groups.

Carrots contain high levels of carotenoids, mostly alpha-carotene and beta-carotene, as well as other vitamins with protective effects. Tomatoes are a source of vitamin C and carotenoids, mainly lycopene. Suggested mechanisms of action of carotenoids include the antioxidant properties and ligand-dependent signaling via retinoid receptors (Shardell et al., 2011).

Fruits and lung cancer

According to the Second Diet and Cancer Report of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) there is convincing evidence that fruits consumption protect against lung cancer. Pooled analysis from 8 cohort studies of fruits intake and lung cancer showed a statistically significant reduced risk for the highest intake group when compared to the lowest. Similar results were obtained from the 21 case-control studies published up to date. Of the seven ecological studies, four reported non-significant decreased risk in areas of higher fruit consumption, one reported no consistent association, and two reported non-significant increased risk.

A few possible mechanisms are proposed to explain the antioxidant properties of fruits. Fruits, in particular citrus fruits, are main sources of vitamin C and flavonoids. Vitamin C traps ROS and RNS, protecting against free-radical damage. It also regenerates other antioxidants such as vitamin E (Miller, 2002; Padayatty et al., 2003). Some fruits (for instance apples and grapefruit) contain high levels of beta-carotene and other carotenoids, or quercetin and other flavonoids. They can further inhibit carcinogen-activating enzymes and reduce oxidative damage generated by inflammation. Furthermore, Liu et al. (2005) reported that apples given in physiological quantities inhibited carcinogen-induced mammary cancer in rodents.

Dietary quercetin and lung cancer

According to the WCRF/AICR Diet and Cancer Report there is limited evidence suggesting that dietary quercetin protects against lung cancer. In fact, there are only two cohort studies that investigated foods containing quercetin consumption and lung cancer risk and they showed significant decreased risk for the highest intake groups when compared to the lowest (Hirvonen et al., 2001; Knekt et al., 2002). Two case-control studies showed decreased risk for the highest intake groups when compared to the lowest (statistically significant in one), while one study reported non-significant increased risk (World Cancer Research Fund / American Institute for Cancer Research. Washington, DC: AICR, 2007).

The proposed mechanism of action is that quercetin inhibits expression of cytochrome P450 enzyme CYP1A1 that consequently results in reduced formation of DNA adducts. Indeed, elevated CYP1A1 activity has been linked with increased risk of lung cancer, predominantly in smokers. The protective association of flavonoids is related with specific CYP1A1 genotypes; the fact that explains heterogeneity of the results (Kang et al., 1999; Le Marchand et al., 2000).

Dietary carotenoids and lung cancer

There is a substantial amount of evidence available from both cohort and case-control studies that food containing carotenoids probably protect against lung cancer. All 11 cohort studies showed decreased risk for the highest intake group, which was statistically significant in three. Twelve of the case-control studies showed decreased risk for the highest intake group when compared to the lowest, which was statistically significant in seven. Three stud-

Table 2. Fruits and lung cancer

Type of food studied	Cohort Studies		Case-Control Studies		Ecological Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**	Reduced Risk*	Total**
Fruits	8	8	21	21	4	7

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies

Table 3. Dietary quercetin, carotenoids, beta-cryptoxanthin and selenium and lung cancer

Foods containing	Cohort Studies		Case-Control Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**
Quercetin	2	2	2	3
Carotenoids	11	11	12	16
Beta-cryptoxanthin	7	7	0	1
Selenium	0	1	0	2

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies

ies reported increased risk, statistically significant in one, while one study reported no effect on risk (World Cancer Research Fund / American Institute for Cancer Research. DC: AICR, 2007). The similar results were obtained from the studies of serum or plasma levels of carotenoids and risk of lung cancer - four cohort studies and five case-control studies reported decreased risk for the highest serum or plasma levels when compared to the lowest.

Pooled analysis from 7 cohort studies of dietary beta-cryptoxanthin consumption and lung cancer risk showed a statistically significant decreased risk when comparing high against low intake groups (Mannisto et al., 2004). On the contrary, the single ecological study reported association between increased intake and increased risk (Le Marchand et al., 1995).

Interestingly, data on beta-carotene supplements provide considerable evidence that high-dose supplements have a contrasting effect, at least in smokers, increasing the risk of lung cancer. Data on dietary beta-carotene (15 cohort studies, a pooled analysis, 32 case-control studies, 2 ecological studies) and serum or plasma beta-carotene (13 cohort studies, 16 case-control studies, 1 ecological study) showed no consistent evidence for association (Lin et al., 2009; Druesne-Pecollo et al., 2010; Jeon et al., 2011).

Dietary selenium and lung cancer

According to the WCRF/AICR Diet and Cancer Report there is limited evidence to suggest that selenium-rich foods protect against lung cancer. One cohort study showed non-significant increased risk in non-smokers and non-significant decreased risk in smokers for the highest intake group comparing to the lowest (Schrauzer et al., 1977). Both case-control studies showed a non-significant increased risk for the highest intake group (Cheng et al., 1996; Hu et al., 1997). Similar results were obtained in the studies of plasma or serum selenium and lung cancer - seven cohort studies showed decreased risk for the highest selenium levels, but statistical significance was reached in only two of them (Knekt et al., 1998; Salonen et al., 1985). Six case-control studies showed decreased risk for the highest levels when compared to the lowest. One study investigated plasma or serum selenium demonstrated non-significant increased risk (Tominaga et al., 1992). Two cohort studies that investigated selenium levels in nails showed decreased risk for the highest selenium levels when compared to the lowest, statistically significant in one (van den Brandt et al., 1993; Fritz et al., 2011).

Natural antioxidants and colorectal cancer

Vegetables and colorectal cancer

A substantial amount of evidence is available that non-starchy vegetables protect against colorectal cancer but the findings are inconsistent (Papaioannou et al., 2011). 17 cohort studies of non-starchy vegetables consumption and risk of colorectal cancer reported comparable risk between the highest and lowest intake groups, while 11 were in the direction of reduced risk (World Cancer Research Fund / American Institute for Cancer Research. Washington, DC: AICR, 2007).

Additionally, there is consistent evidence, mostly from case-control studies, that garlic consumption protects against colorectal cancer in a dose-response manner. Indeed, all six case-control studies showed decreased risk for the highest consumers of garlic, statistically significant in three (Levi et al., 1999; Yang et al., 1994). Additionally, the data obtained from the study with model carcinogens and transplantable tumors were in favor of the anticancer effect of garlic and some of its allyl sulphur components. Furthermore, the findings from studies with animal models demonstrated that allyl sulphides effectively inhibit tumor formation in the colon (Chu et al., 2007).

Fruits and colorectal cancer

There are a number of researchers that studied the association between the fruit consumption and colorectal cancer, but the evidence obtained is inconsistent. Twenty cohort studies and 57 case-control studies investigated fruits and colorectal cancer. Thirteen cohort studies showed decreased risk with increased intake, but the statistical significance was reached only in two studies (World Cancer Research Fund / American Institute for Cancer Research. Washington, DC: AICR, 2007).

Table 4. Natural antioxidants and colorectal cancer

Foods/ Foods containing	Cohort Studies		Case-Control Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**
Non-starchy vegetables	11	17	n/a	n/a
Garlic	n/a	n/a	6	6
Fruits	13	20	30	57
Selenium	n/a	n/a	15	15

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies
n/a: data not available

Dietary selenium and colorectal cancer

A substantial amount of data on the association between dietary selenium and colorectal cancer (although from case-control studies only) suggested that selenium-rich foods protect against colorectal cancer. Fifteen case-control studies reported decreased risk, statistically significant in four (World Cancer Research Fund / American Institute for Cancer Research., Washington, DC: AICR, 2007).

The proposed mechanism of action is that selenium deficiency causes a lack of selenoprotein expression. There are twenty-five selenoproteins identified up to date; all of them having significant anti-inflammatory and antioxidant functions. For example, four selenoproteins belong to glutathione peroxidases family; they protect lipids, lipoproteins, and DNA from oxidative damage. Three selenoproteins are thioredoxin reductases which regenerate oxidized ascorbic acid to its active form. All of them are known to be rapidly degraded during selenium deficiency. Moreover, it was suggested that supraphysiological amounts of selenium could affect programmed cell death, DNA repair, carcinogen metabolism, immune system, and anti-angiogenic effects (Ganther, 1999; Higdon, et al., 2007).

Natural antioxidants and prostate cancer

Tomatoes, dietary lycopene and prostate cancer

Lycopene is the most efficient antioxidant among all carotenoids identified up to date. It is most bioavailable from cooked and pureed tomatoes. Therefore, the best way of measuring the systemic exposure is study on tomato sauce, or on serum or plasma lycopene.

There is a substantial amount of consistent evidence, from both cohort and case-control studies that lycopene-containing foods protect against prostate cancer (Seren et al., 2008; Vance et al., 2013).

Three of the cohort studies of tomatoes consumption and risk of prostate cancer showed decreased risk for the highest intake groups when compared to the lowest (Platz et al., 2004). Seven of the case-control studies reported decreased risk for the highest intake groups when compared to the lowest. Two cohort studies of dietary lycopene consumption and prostate cancer reported non-significant decreased risk for the highest intake groups when compared to the lowest, while the other study showed non-significant increased risk. Nine case-control studies showed decreased risk for the highest intake groups when compared to the lowest, which was statistically significant in one.

Five cohort studies of serum or plasma lycopene and prostate cancer risk reported a non-significant reduced risk for the highest intake groups when compared to the lowest; the other study showed an increased risk (Gann et al., 1999). Both case-control studies of serum or plasma lycopene showed a statistically significant reduced risk for the highest intake groups (Lu et al., 2001; Dahan et al., 2008).

Dietary beta-carotene and prostate cancer

In accordance with the evidence from cohort and case-control studies it could be concluded that foods containing beta-carotene does not have a substantial effect on the risk of prostate cancer.

Three cohort studies of dietary beta-carotene consumption and prostate cancer showed non-significant increased risk with increased intake, while three studies showed no effect on risk. Although fourteen case-control studies reported decreased risk with increased intake, statistical significance was reached only in two relatively low quality studies. The similar findings were obtained from the cohort and case-control studies of serum or plasma beta-carotene and prostate cancer risk (Vogt et al., 2002).

Dietary vitamin E and prostate cancer

It is well known that vitamin E slows down DNA damage, increases DNA repair, reduces lipid peroxidation, and prevents activation of some carcinogens. Additionally, it protects body's vitamin A and selenium. While acting as a free-radical scavenger, it enhances the immune response in the body, which may play a crucial role in cancer defenses (Willis and Wians, 2003). Vitamin E has also been shown to delay the growth of human prostate tumors induced in animal models (Fleshner et al., 1999).

Table 5. Natural antioxidants and prostate cancer

Type of food studied	Cohort Studies		Case-Control Studies		Ecological Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**	Reduced Risk*	Total**
Tomatoes	3	5	7	9	n/a	n/a
Lycopene	2	2	9	14	n/a	n/a
Beta-carotene	4	10	14	21	n/a	n/a
Vitamin E	1	7	n/a	n/a	n/a	n/a
Selenium	1	1	2	7	2	2

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies
n/a: data not available

However, there is limited evidence that vitamin E- rich foods protect against prostate cancer. Indeed, the evidence, obtained mostly from case-control studies, was inconsistent. For example, statistical significant decreased risk for the highest intake groups was demonstrated only in one out of seven cohort studies of serum or plasma alpha-tocopherol and prostate cancer (Goodman et al., 2003). Most studies of dietary vitamin E consumption and prostate cancer risk showed non-significant decreased risk, although there is heterogeneity in the direction of effect reported and effect estimates are usually very close to 1 (no effect). All six cohort studies that investigated serum gamma-tocopherol and prostate cancer reported inverse association (Weinstein et al., 2005; Lin et al., 2009; Klein et al., 2011).

Dietary selenium and prostate cancer

According to the 2007 WCRF/AICR Diet and Cancer Report there is a considerable amount of evidence from both cohort and case-control studies, that selenium-rich foods protect against prostate cancer. Eight cohort studies and four case-control studies reported inverse associations between serum or plasma selenium and prostate cancer (Li et al., 2004). Two cohort studies of selenium levels in nails and prostate cancer risk demonstrated non-significant decreased risk for the highest intake groups. Two cohort studies investigated selenium levels in nails for advanced or aggressive prostate cancer. Both showed statistically significant decreased risk for the highest intake groups (van den Brandt et al., 2003; Klein et al., 2011).

Natural antioxidants and breast cancer

Fruits, vegetables and breast cancer

Some epidemiologic studies suggest that fruit and vegetable consumption could reduce risk of breast cancer. However, most have been case-control studies in which selection bias may strongly influence the results. In 2000, a meta-analysis was performed, aimed to summarize existing data on the relationship between breast cancer, fruit and vegetable consumption and/or the intake of beta-carotene and vitamin C. Relative risks were extracted from 26 studies published in the period from 1982 to 1997. It confirms the association between intake of vegetables and, to a lesser extent, fruits and breast cancer risk from published sources (Gandini et al., 2000).

Smith-Warner et al. (2001) studied the relation between breast cancer and total and specific fruit and vegetable group intakes by means of standardized exposure definitions. No associations were found for green leafy vegetables, 8 botanical groups, and 17 specific fruits and vegetables. Therefore, the results suggest that fruit and vegetable consumption during adulthood is not significantly associated with reduced breast cancer risk (Smith-Warner et al., 2001).

Riboli and Norat (2003) wanted to summarize evidence from case-control and prospective studies on fruit and vegetable consumption and cancer risk with a meta-analytic approach. According to their findings, breast cancer is associated with vegetables, but not with fruits consumption (Riboli and Norat, 2003).

Furthermore, of the results from the European Prospective Investigation into Cancer and Nutrition (EPIC) study (the largest study of nutrition and health ever undertaken, with over half a million people from ten European countries enrolled) confirmed that the consumption of fruit and vegetables is not associated with breast cancer risk. This critical finding helped to narrow down the factors involved in breast cancer etiology and prevention (http://epic.iarc.fr/research/cancer.php).

Natural antioxidants and stomach cancer

Vegetables and stomach cancer

There are a number of researchers that studied the possible association between the vegetables consumption and stomach cancer. On the basis of a substantial amount of evidence available, including on specific subtypes, particu-

larly green yellow vegetables, the 2007 WCRF/AICR Diet and Cancer Report sums up that vegetables probably protect against stomach cancer in a dose-response manner. Of 45 case-control studies that studied non-starchy vegetable consumption and stomach cancer, 28 reported statistically significant decreased risk. Additionally, the majority of the 17 remaining studies that reported no significant effect on risk were in the direction of decreased risk (Gajalakshmi and Shanta, 1996).

Results from ecological studies on non-starchy vegetable consumption were inconclusive, with almost as many studies reporting increased risk as reported decreased risk (Engel et al., 2003).

Of the 21 case-control studies on green yellow vegetable consumption and stomach cancer incidence, 16 showed decreased risk. This exposure included green-yellow vegetables, green vegetables, yellow vegetables, yellow-orange vegetables, carrots and pumpkins, and high-carotenoid vegetables (Zickute et al., 2005). Nine case-control studies that investigated green, leafy vegetables consumption and stomach cancer showed decreased risk with increased intake (Zickute et al., 2005).

Significant inverse association was found in seven out of 12 case-control studies reporting decreased risk with increased intake of lettuce or salad leaves (Ito et al., 2003).

Two cohort studies on tomatoes consumption and stomach cancer demonstrated a non-significant increased risk with increased intake, while most case-control studies showed decreased risk with increased intake (Tokui et al., 2005).

One of the proposed mechanisms of action is that bioactive constituents could protect against *H.pylori*-induced damage, particularly inflammation, the crucial event in the development of stomach cancers. It is well known that allium vegetables, especially garlic, are high in flavonols and organosulphur compounds. They have antibiotic properties. Although this may act directly against *H pylori*, a study in humans has not proven this effect. The possible mechanism of action is that antibacterial effects of garlic might inhibit the colonization of the stomach after *H pylori*-induced atrophy. Indeed, a study with animals provided evidence that dietary garlic can reduce the severity of *H pylori*-associated gastritis (Iimuro et al., 2002).

According to the findings, allium vegetables-rich diet most likely protects against stomach cancer. The data from two ecological studies suggested significant decreased incidence of stomach cancer with increased consumption of allium vegetables. Similar results were obtained in case controls studies that showed reduced risk when comparing high with low intake groups (Takezaki et al., 1999).

Fruits and stomach cancer

On the basis on the substantial amount of evidence on association between fruits intake and stomach cancer risk, the 2007 WCRF/AICR Diet and Cancer Report summarized that fruits probably protect against stomach cancer in a dose-response manner. Forty case-control studies demonstrated decreased risk for the highest intake groups when compared to the lowest, being statistically significant in 25 (López-Carrillo et al., 2004).

Dietary selenium and stomach cancer

There is a substantial amount on the association between dietary selenium consumption and stomach cancer incidence, mostly from case-control studies. However there is no strong evidence that selenium-rich foods protect

Table 6. Natural antioxidants and stomach cancer

Type of food studied	Cohort Studies		Case-Control Studies		Ecological Studies	
	Reduced Risk*	Total**	Reduced Risk*	Total**	Reduced Risk*	Total**
Vegetables	*n/a*	*n/a*	27	45	*n/a*	*n/a*
Non-starchy vegaables	*n/a*	*n/a*	16	21	*n/a*	*n/a*
Green, leafy vegetables	*n/a*	*n/a*	9	12	*n/a*	*n/a*
Letuce	*n/a*	*n/a*	7	12	*n/a*	*n/a*
Tomato	2	2	*n/a*	*n/a*	*n/a*	*n/a*
Allium	*n/a*	*n/a*	*n/a*	*n/a*	2	2
Fruits	*n/a*	*n/a*	30	40	*n/a*	*n/a*
Selenium	*n/a*	*n/a*	0	1	2	2

*Number of the studies that reported reduced cancer risk with higher levels of consumption
**Total number of studies
n/a: data not available

against stomach cancer onset (Table 6).

The single case-control study that investigated dietary selenium consumption and stomach cancer reported that dietary selenium was not significantly associated with stomach cancer risk, while most ecological studies showed that low selenium levels were associated with increased stomach cancer risk (World Cancer Research Fund / American Institute for Cancer Research. Food, Washington, DC: AICR, 2007).

Conclusion

The implication of oxidative stress in the promotion of carcinogenesis suggests that antioxidant therapy represents a promising opportunity for cancer prevention. Additionally, a therapeutic strategy to increase the antioxidant capacity of cells may be used to fortify the long term effective treatment. In the past it was generally believed that high-dose dietary supplements can modify the risk of some cancers. Although some studies in specific, usually high-risk, groups have shown evidence of cancer prevention from some supplements, this finding may not apply to the general population. Their level of benefit may be different, and there may be unexpected adverse effects. Therefore it is unwise to recommend widespread supplement use as a means of cancer prevention.

The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Diet and Cancer Report strongly recommend that increasing the consumption of the relevant nutrients through the usual diet is preferred and the best source of antioxidants is foods and drinks, not dietary supplements.

References

Bahorun, T., Soobrattee, M.A., Luximon-Ramma, V. Aruoma, O.I. 2006. Free radicals and antioxidants in cardiovascular health and disease. Internet J. Med. Update 1, 1-17.

Chatterjee, M., Saluja, R., Kanneganti S. 2007. Biochemical and molecular evaluation of neutrophil NOS in spontaneously hypertensive rats. Cell. Mol. Biol. 53, 84-93.

Cheng, T.J., Christiani, D.C., Xu, X., Wain, J.C., Wiencke, J.K., Kelsey, K.T. 1996. Increased micronucleus frequency in lymphocytes from smokers with lung cancer. Mutat. Res. 17, 349(1), 43-50.

Chu, Q., Lee, D.T., Tsao, S.W., Wang, X., Wong, Y.C. 2007. S-allylcysteine, a water-soluble garlic derivative, suppresses the growth of a human androgen-independent prostate cancer xenograft, CWR22R, under in vivo conditions. BJU Int. 99(4), 925-32.

Dahan, K., Fennal, M., Kumar, N.B. 2008. Lycopene in the prevention of prostate cancer. J. Soc. Integr. Oncol. 6, 29-36.

Dolara, P., Bigagli, E., Collins, A. 2012. Antioxidant vitamins and mineral supplementation, life span expansion and cancer incidence: a critical commentary. Eur. J. Nutr. 51(7):769-81. Epub 2012 Jun 9.

Donaldson M.S. 2004. Nutrition and cancer: A review of the evidence for an anti-cancer diet. Nutr. J. 3, 19-25.

Droge W. 2002. Free radicals in the physiological control of cell function. Review. Physiol Rev. 82, 47-95.

Druesne-Pecollo, N., Latino-Martel, P., Norat, T., Barrandon, E., Bertrais, S., Galan, P., Hercberg, S. 2010. Beta-carotene supplementation and cancer risk: a systematic review and meta-analysis of randomized controlled trials. Int. J. Cancer. 127(1),172–184.

Engel, L.S., Chow, W.H., Vaughan, T.L., Gammon, M.D., Risch, H.A., Stanford, J.L., Schoenberg, J.B., Mayne, S.T., Dubrow, R., Rotterdam, H., West, A.B., Blaser, M., Blot, W.J., Gail, M.H., Fraumeni J.F. 2003. Population attributable risks of esophageal and gastric cancers. J. Natl. Cancer. Inst. 17, 95(18), 1404-13.

Fleshner, N., Fair, W.R., Huryk, R., Heston, W.D. 1999. Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice. J. Urol. 161(5), 1651-4.

Fritz, H., Kennedy, D., Fergusson, D., Fernandes, R., Cooley, K., Seely, A., Sagar, S., Wong, R., Seely, D. 2011. Selenium and lung cancer: a systematic review and meta analysis. PLoS One 6(11):e26259

Gajalakshmi, C.K., Shanta, V. 1996. Lifestyle and risk of stomach cancer: a hospital-based case-control study. Int. J. Epidemiol. 25, 1146-53.

Gandini, S., Merzenich, H., Robertson, C., Boyle, P. 2000. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. Eur.J. Cancer 36, 636-646.

Ganther, H.E. 1999. Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogenesis 20, 1657-66.

Genestra, M. 2007. Oxyl radicals, redox-sensitive signalling cascades and antioxidants. Review. Cell Signal. 19, 1807-19

Goodman, G.E., Schaffer, S., Omenn, G.S., Chen, C., King, I. 2003. The association between lung and prostate cancer risk, and serum micronutrients: results and lessons learned from beta-carotene and retinol efficacy trial. Cancer Epidemiol. Biomarkers Prev. 12(6), 518-26.

Halliwell, B. 1996. Antioxidants in human health and disease. Ann. Rev. Nutr. 16, 33–50.

Halliwell, B. 2007. Biochemistry of oxidative stress. Biochem. Soc. Trans. 35, 1147-50.

Halliwell, B., Gutteridge, J.M.C. 2007. Free radicals in biology and medicine. 4th ed. Oxford, UK: Clarendon Press.

Hercberg, S., Kesse-Guyot, E., Druesne-Pecollo, N., Touvier, M., Favier, A., Latino-Martel, P., Briançon, S., Galan, P. 2010. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a post-intervention follow-up in the SU.VI.MAX study. Int. J. Cancer. 127(8), 1875–1881.

Higdon, J., Drake, V.J., Whanger, P.D. 2007. Selenium. Linus Pauling Institute. Oregon State University. Micronutrient Information Center. http://lpi.oregonstate.edu/infocenter/minerals/selenium/

Hirvonen, T., Virtamo, J., Korhonen, P., Albanes, D., Pietinen, P. 2001. Flavonol and flavone intake and the risk of cancer in male smokers (Finland). Cancer Causes Control 12(9), 789-96.

http://epic.iarc.fr/research/cancer.php

Hu, J., Johnson, K.C., Mao, Y., Xu, T., Lin, Q, Wang, C., Zhao, F., Wang, G., Chen, Y., Yang, Y. 1997. A case-control study

of diet and lung cancer in northeast China. Int. J. Cancer. 11;71(6), 924-31.

Iimuro, M., Shibata, H., Kawamori, T., Matsumoto, T., Arakawa, T., Sugimura, T., Wakabayashi, K. 2002. Suppressive effects of garlic extract on Helicobacter pylori-induced gastritis in Mongolian gerbils. Cancer Lett. 10; 187(1-2), 61-8.

Ito, L.S., Inoue, M., Tajima, K., Yamamura, Y., Kodera, Y., Hirose, K., Takezaki, T., Hamajima, N., Kuroishi, T., Tominaga, S. 2003. Dietary factors and the risk of gastric cancer among Japanese women: a comparison between the differentiated and non-differentiated subtypes. Ann. Epidemiol. 13(1), 24-31.

Jansen, M.C., Bueno-de-Mesquita, H.B., Räsänen, L., Fidanza, F., Nissinen, A.M., Menotti, A., Kok, F.J., Kromhout, D. 2001. Cohort analysis of fruit and vegetable consumption and lung cancer mortality in European men. Int J Cancer. 15, 92(6), 913-8.

Jeon, Y.J., Myung, S.K., Lee, E.H., Kim, Y., Chang, Y.J., Ju, W., Cho, H.J., Seo, H.G., Huh, B.Y. 2011. Effects of beta-carotene supplements on cancer prevention: meta-analysis of randomized controlled trials. Nutr. Cancer. 63(8), 1196–1207.

Kang, Z.C., Tsai, S.J., Lee, H. 1999. Quercetin inhibits benzo[a] pyrene-induced DNA adducts in human Hep G2 cells by altering cytochrome P-450 1A1 gene expression. Nutr. Cancer. 35, 175-9.

Kenneth A.C. 2003. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr. Cancer 37, 1–18.

Klein, E.A., Thompson, I.M. Jr., Tangen, C.M., Crowley, J.J., Lucia, M.S., Goodman, P.J., Minasian, L.M., Ford, L.G., Parnes, H.L., Gaziano, J.M., Karp, D.D., Lieber, M.M., Walther, P.J., Klotz, L., Parsons, J.K., Chin, J.L., Darke, A.K., Lippman, S.M., Goodman, G.E., Meyskens, F.L. Jr, Baker, L.H. 2011. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 306(14), 1549–1556.

Knekt P, Marniemi J, Teppo L, Heliövaara M, Aromaa A. 1998. Is low selenium status a risk factor for lung cancer? Am J Epidemiol. 148(10), 975-82.

Knekt, P., Järvinen, R., Seppänen, R., Heliövaara, M., Teppo, L., Pukkala, E., Aromaa, A. 1997. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am. J. Epidemiol. 146, 223-30.

Knekt, P., Kumpulainen, J., Järvinen, R., Rissanen, H., Heliövaara, M., Reunanen, A., Hakulinen, T., Aromaa, A. 2002. Flavonoid intake and risk of chronic diseases. Am. J. Clin. Nutr. 76(3), 560-8.

Kvale, G., Bjelke, E., Gart, J.J. 1983. Dietary habits and lung cancer risk. Int. J. Cancer 31, 397-405.

Le Marchand, L., Hankin, J.H., Bach, F., Kolonel, L.N., Wilkens, L.R., Stacewicz-Sapuntzakis, M., Bowen, P.E., Beecher, G.R., Laudon, F., Baque, P., et al. 1995. An ecological study of diet and lung cancer in the South Pacific. Int. J. Cancer. 63(1), 18-23.

Le Marchand, L., Murphy, S.P., Hankin, J.H., Wilkens, L.R., Kolonel, L.N. 2000. Intake of flavonoids and lung cancer. J. Natl. Cancer Inst. 92(2), 154-60.

Levi, F., Pasche, C., La Vecchia, C., Lucchini, F., Franceschi, S. 1999. Food groups and colorectal cancer risk. Br. J. Cancer. 79(7-8), 1283-7.

Li, H., Stampfer, M.J., Giovannucci, E.L., Morris, J.S., Willett, W.C., Gaziano, J.M., Ma, J. 2004. A prospective study of plasma selenium levels and prostate cancer risk. J. Natl. Cancer Inst. 96(9), 696-703.

Lin, J., Cook, N.R., Albert, C., Zaharris, E., Gaziano, J.M., Van Denburgh, M., Buring, J.E., Manson, J.E. 2009. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. J. Natl. Cancer. Inst. 101(1),14–23.

Liu, R.H., Liu, J., Chen, B. 2005. Apples prevent mammary tumors in rats. J. Agric. Food Chem. 53, 2341-3.

López-Carrillo, L., Torres-Lopez, J., Galvan-Portillo, M. 2004. Helicobacter pylori-CagA seropositivity and nitrite and ascorbic acid food intake as predictors for gastric cancer. Eur. J. Cancer 40, 1752-9.

Lu, Q.Y., Hung, J.C., Heber, D., Go, V.L., Reuter, V.E., Cordon-Cardo, C., Scher, H.I., Marshall, J.R., Zhang Z.F. 2001. Inverse associations between plasma lycopene and other carotenoids and prostate cancer. Cancer Epidemiol. Biomarkers Prev. 10(7), 749-56.

Männistö, S., Smith-Warner, S.A., Spiegelman, D., Albanes, D., Anderson, K., van den Brandt, P.A., Cerhan, J.R., Colditz, et al.. 2004. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. Cancer Epidemiol. Biomarkers Prev. 13(1), 40-8.

Miller, A.B. 2002. Vegetables and fruits and lung cancer. IARC Sci Publ 156, 85-7.

Myung, S.K., Ju, W., Kim, S.C. 2011. Korean Meta-analysis (KORMA) Study Group. Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: a meta-analysis. BJOG 118(11),1285–1291.

Pacher, P., Beckman, J.S., Liaudet, L. 2007. Nitric oxide and peroxynitrite in health and disease. Physiol. Rev. 87, 315-424.

Padayatty, S.J., Katz, A., Wang, Y., Eck, P., Kwon, O., Lee, J.H., Chen, S., Corpe, C., Dutta, A., Dutta, S.K., Levine, M. 2003. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J. Am. Coll. Nutr. 22, 18-35.

Papaioannou, D., Cooper, K.L., Carroll, C., Hind, D., Squires, H., Tappenden, P., Logan, R.F. 2011. Antioxidants in the chemoprevention of colorectal cancer and colorectal adenomas in the general population: a systematic review and meta-analysis. Colorectal. Dis. 13(10), 1085–1099.

Pham-Huy, L.A., He, H., Pham-Huy, C. 2008. Free Radicals, Antioxidants in Disease and Health. Int.J.Biomed. Sci. 4(2), 89-96.

Platz E.A., De Marzo A.M., Erlinger T.P., Rifai N., Visvanathan K., Hoffman S.C., Helzlsouer K.J. 2004. No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. Prostate. 59, 393-400.

Raj, L., Ide, T., Gurkar, A.U., Foley, M., Schenone, M., Li, X., Tolliday, N.J., Golub, T.R., Carr, S.A., Shamji, A.F., Stern, A.M., Mandinova, A., Schreiber, S.L., Lee, S.W. 2011. Selective killing of cancer cells by a small molecule targeting the stress response to ROS. Nature 475(7355), 231–234.

Riboli, E., Norat, T. 2003. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am. J. Clin. Nutr. 78, 559S-569S.

Riso, P., Martini, D., Møller, P., Loft, S., Bonacina, G., Moro, M., Porrini, M. 2010. DNA damage and repair activity after broccoli intake in young healthy smokers. Mutagenesis, 25(6), 295–602.

Salonen, J.T., Salonen, R., Lappetelainen, R., et al. 1985. Risk of cancer in relation to serum concentrations of selenium

and vitamins A and E: matched case-control analysis of prospective data. BMJ 290, 417-20.

Schrauzer, G.N., White, D.A., Schneider, C.J. 1977. Cancer mortality correlation studies - III: statistical associations with dietary selenium intakes. Bioinorg. Chem. 7, 23-31.

Seren, S., Lieberman, R., Bayraktar, U.D., Heath, E., Sahin, K., Andic, F., Kucuk, O. 2008. Lycopene in cancer prevention and treatment. Am. J. Ther. 15(1), 66-81.

Shardell, M.D., Alley, D.E., Hicks, G.E., El-Kamary, S.S, Miller, R.R., Semba, R.D., Ferrucci, L. 2011. Low-serum carotenoid concentrations and carotenoid interactions predict mortality in US adults: the Third National Health and Nutrition Examination Survey. Nutr. Res. 31(3), 178–189.

Smith-Warner, S.A., Spiegelman, D., Yaun, S.S., Adami, H.O., Beeson, W.L., van den Brandt, P.A., Folsom, A.R., et al. 2001. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA. 285(6), 769-76.

Somannavar, M.S., Kodliwadmath, M.V. 2012. Correlation between oxidative stress and antioxidant defence in South Indian urban vegetarians and non-vegetarians. Eur. Rev. Med. Pharmacol. Sci. 16(3), 351–354.

Speizer, F.E., Colditz, G.A., Hunter, D.J., Rosner, B., Hennekens, C. 1999. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). Cancer Causes Control. 10(5), 475-82.

Stähelin, H.B., Gey, K.F., Eichholzer, M., Lüdin, E., Bernasconi, F., Thurneysen, J., Brubacher G. 1991. Plasma antioxidant vitamins and subsequent cancer mortality in the 12-year follow-up of the prospective Basel Study. Am. J. Epidemiol. 133, 766-75.

Steinmetz, K.A., Potter, J.D., Folsom, A.R. 1993. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. Cancer Res. 53, 536-43.

Takezaki, T., Gao, C.M., Ding, J.H., Liu, T.K., Li, M.S., Tajima, K. 1999. Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu Province, China; with special reference to allium vegetables. J Epidemiol. 9(5), 297-305.

Tokui, N., Yoshimura, T., Fujino, Y., Mizoue, T., Hoshiyama, Y., Yatsuya, H., Sakata, K., Kondo, T., Kikuchi, S., Toyoshima, H., Hayakawa, N., Kubo, T., Tamakoshi A., JACC Study Group. 2005. Dietary habits and stomach cancer risk in the JACC Study. J. Epidemiol. 15, S98-108.

Tominaga, K., Saito, Y., Mori, K., Miyazawa, N., Yokoi, K., Koyama, Y., Shimamura, K., Imura, J., Nagai, M. 1992. An evaluation of serum microelement concentrations in lung cancer and matched non-cancer patients to determine the risk of developing lung cancer: a preliminary study. Jpn. J. Clin. Oncol. 22, 96-101.

Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J. 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39, 44-84.

Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M., Mazur, M. 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 160(1), 1-40.

van den Brandt, P.A., Goldbohm, R.A., van 't Veer, P., Bode, P., Dorant, E., Hermus, R.J., Sturmans, F. 1993. A prospective cohort study on selenium status and the risk of lung cancer. Cancer Res. 53, 4860-5.

van den Brandt, P.A., Zeegers, M.P., Bode, P., Goldbohm, R.A. 2003. Toenail selenium levels and the subsequent risk of prostate cancer: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 12, 866-71.

van Gils, C.H., Peeters, P.H., Bueno-de-Mesquita, H.B., Boshuizen, H.C., Lahmann, P.H., Clavel-Chapelon, F., Thiébaut, A., et al. 2005. Consumption of vegetables and fruits and risk of breast cancer. JAMA. 293, 183-93.

Vance, T.M., Su, J., Fontham, E.T., Koo, S.I., Chun, O.K. 2013. Dietary antioxidants and prostate cancer: a review. Nutr. Cancer. 65(6), 793-801.

Vogt, T.M., Mayne, S.T., Graubard, B.I., Swanson, C.A., Sowell, A.L., Schoenberg, J.B., Swanson, G.M., Greenberg, R.S., Hoover, R.N., Hayes, R.B., Ziegler, R.G. 2002. Serum lycopene, other serum carotenoids, and risk of prostate cancer in US Blacks and Whites. Am. J. Epidemiol. 155, 1023-32.

Weinstein, S.J., Wright, M.E., Pietinen, P., King, I., Tan, C., Taylor, P.R., Virtamo, J., Albanes D. 2005 Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. J. Natl. Cancer Inst. 97, 396-9.

Willcox, J.K., Ash, S.L., Catignani, G.L. 2004. Antioxidants and prevention of chronic disease. Review. Crit. Rev. Food Sci. Nutr. 44, 275-95.

Willis, M.S., Wians, F.H. 2003. The role of nutrition in preventing prostate cancer: a review of the proposed mechanism of action of various dietary substances. Clin. Chim. Acta 330, 57-83.

World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.

Yang, G., Gao, Y., Ji, B. 1994. Dietary factors and cancer of the colon and rectum in a population based case-control study in Shanghai. Zhonghua Liu Xing Bing Xue Za Zhi 15, 299-303.

Young, I., Woodside, J. 2001. Antioxidants in health and disease. J. Clin. Pathol. 54, 176–86.

Zickute, J., Strumylaite, L., Dregval, L., Petrauskiene, J., Dudzevicius, J., Stratilatovas E. 2005. Vegetables and fruits and risk of stomach cancer. Medicina (Kaunas). 41, 733-40.

Резиме

Природните антиоксиданси во превенција на малигни заболувања

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Клучни зборови: оксидативен стрес; реактивни кислородни форми; реактивни азотни форми; природни антиоксиданси; канцер.

Оксидативниот стрес е неизбежна последица на аеробниот живот. Во тек на клеточната респирација и продукција на високоенергетски соединенија во митохондриите се создава широк спектар на реактивни кислородни (РКФ) и азотни форми (РАФ) кои можат директно да ја нападнат молекулата на ДНК. Според теоријата на оксидативен стрес, стареењето и дегенеративните болести настануваат како резултат на акумулација на оксидативно оштетување на критични молекули (ДНК, липиди, протеини) во тек на животниот век. Познато е дека тешкиот оксидативен стрес доведува мутација на тумор супресорните гени (рани настани во процесот на карциногенеза), но се поврзува и со стадиумите на промоција и прогресија. Човечкиот организам развил одбранбен механизам за заштита од оксидативниот стрес, кој го сочинуваат систем на антиоксиданси, создадени *in situ* или обезбедени преку храна или суплементи. Според податоците добиени од студии изведени на клеточни култури или со експериментални животни, антиоксидансите можат да го забават, дури и спречат развојот на малигните процеси. Меѓутоа, поновите податоци добиени со анализа на изведени кохортни студии, студии на случаи, и/или еколошки студии се контрадикторни. Заради тоа, цел на овој преглед е да се резимираат податоците од објавените студии и да се идентификуваат ефективни третмани со природни антиоксиданси.