Natural antioxidants in cancer prevention

Zorica Arsova-Sarafinovska¹, Aleksandar J. Dimovski²

¹Institute of Public Health of the Republic of Macedonia, Department for Quality Control of Medicine, 50 Divizija 6, 1000 Skopje, Republic of Macedonia
²Faculty of Pharmacy, Institute of Pharmaceutical Chemistry, Department of Molecular Biology and Genetics, Skopje, Vodnjanska 17, 1000 Skopje, Republic of Macedonia

Received: February 2013; Accepted: May 2013

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, atherosclerosis, 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).
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 ($O_2^-$) 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; Wilcox et al., 2004; Young and Woodside, 2001).

The non-enzymatic antioxidants are divided into metabolic and nutrient antioxidants. Metabolic antioxidants, such as lipid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc., are produced by body metabolism (Droge, 2002; Wilcox 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 (Wilcox 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>
<thead>
<tr>
<th>Type of food studied</th>
<th>Cohort Studies</th>
<th>Case-Control Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Risk*</td>
<td>Total**</td>
</tr>
<tr>
<td>Total vegetables</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Non-starchy vegetables</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Green-leafy vegetables</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Carrots</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

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

Maced. pharm. bull., 59 (1, 2) 3 - 14 (2013)
Natural antioxidants in cancer prevention


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**

<table>
<thead>
<tr>
<th>Type of food studied</th>
<th>Cohort Studies</th>
<th>Case-Control Studies</th>
<th>Ecological Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Risk*</td>
<td>Total**</td>
<td>Reduced Risk*</td>
</tr>
<tr>
<td>Fruits</td>
<td>8</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

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

**Total number of studies

Макед. фарм. билт., 59 (1, 2) 3 - 14 (2013)
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 3. Dietary quercetin, carotenoids, beta-cryptoxanthin and selenium and lung cancer

<table>
<thead>
<tr>
<th>Foods containing</th>
<th>Cohort Studies</th>
<th>Case-Control Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Risk*</td>
<td>Total**</td>
</tr>
<tr>
<td>Quercetin</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Beta-cryptoxanthin</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Selenium</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Type of food studied</th>
<th>Cohort Studies</th>
<th>Case-Control Studies</th>
<th>Ecological Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Risk*</td>
<td>Total**</td>
<td>Reduced Risk*</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Lycopene</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>1</td>
<td>7</td>
<td>n/a</td>
</tr>
<tr>
<td>Selenium</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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 vegetable 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 (Takezaki et al., 1999).

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>
<thead>
<tr>
<th>Type of food studied</th>
<th>Cohort Studies</th>
<th>Case-Control Studies</th>
<th>Ecological Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Risk*</td>
<td>Total**</td>
<td>Reduced Risk*</td>
</tr>
<tr>
<td>Vegetables</td>
<td>n/a</td>
<td>n/a</td>
<td>27</td>
</tr>
<tr>
<td>Non-starchy vegetables</td>
<td>n/a</td>
<td>n/a</td>
<td>16</td>
</tr>
<tr>
<td>Green, leafy vegetables</td>
<td>n/a</td>
<td>n/a</td>
<td>9</td>
</tr>
<tr>
<td>Letuce</td>
<td>n/a</td>
<td>n/a</td>
<td>7</td>
</tr>
<tr>
<td>Tomato</td>
<td>2</td>
<td>2</td>
<td>n/a</td>
</tr>
<tr>
<td>Allium</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Fruits</td>
<td>n/a</td>
<td>n/a</td>
<td>30</td>
</tr>
<tr>
<td>Selenium</td>
<td>n/a</td>
<td>n/a</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**Total number of studies

n/a: data not available

Таблица 6. Природные антиоксиданты и зобовая канцерогенез

Макед. фарм. билт., 59 (1, 2) 3 - 14 (2013)
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


Резиме

Природните антиоксиданси во превенција на малигни заболувања

Зорица Арсова-Сарафиновска1 и Александар Ј. Димовски2

1Институти за јавно здравје на Република Македонија, Сектор за испитување и контрола на лекови, 50 Дивизија 6, 1000 Скопје, Република Македонија
2Фармацевтски факултет, Институти за фармацевтска хемија, Катедра за биомолекуларни науки, Ворњанска 17, 1000 Скопје, Република Македонија

Ключни 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 митохондрните 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 животинот 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. Човекот 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 добени од студии изведени на клеточни култури или со експериментални животни, антиоксиданските можат да го забават, дури и спречат развојот на малигните процеси. Меѓутоа, поновите податоци добени со анализ на изведени конхортини 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.