A Review of Probable Effects of Antioxidants on DNA Damage

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ABSTRACT

Introduction: Reactive oxygen species (ROS) are normally generated from the metabolism in human body and when cellular antioxidant capacity decreased, it can cause oxidative stress and also different metabolic disorders. Based on the recent findings, antioxidants have protective role on macromolecules such as proteins, DNA and other against ROS. In this review we summarize the probable mechanisms of different antioxidants on DNA damages. Methods: Based on our search in databases, 20 eligible articles were identified. The key words used for the search were: antioxidants in combination of Reactive Oxygen Species, DNA damage and fragmentation. The amount of damage to DNA and the mechanisms by which antioxidants affect in these studies were checked out by the following methods: 8-oh-dg, comet assay, mutation analysis, micronucleus assay, and DNA base damage products. Results: Recent findings showed that antioxidants can neutralize ROS production and prevent destructive damages to DNA. Beta-carotene, selenium, vitamin E and C can prevent and improve the features of different disorders such as cardiovascular disease, diabetes, cancer and so on by activating glutathione peroxidase and superoxide dismutase enzymes. Although vitamin C, poly phenols and zinc have antioxidant properties, their appropriate dosage is not specified. So using these substances at improper dosage can elevate DNA fragmentation. Conclusion: Internal and external antioxidants have some neutralizing effects against ROS and DNA damage but some studies are controversial; so, determining the effective dosage needs further studies.

Key Words: *Reactive Oxygen Species, DNA Damage, Antioxidants, Oxidative Stress.*

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INTRODUCTION

Based on the findings of the recent years, the roles of antioxidants as health promoting factors are noticeable. Our body naturally has a powerful antioxidant system that its function is to neutralize the oxidative stress caused by oxidizing agents (ROS) following the natural metabolism of the body and preventing disturbances in the physiological systems of the body by these factors. This system requires antioxidant compounds for its activity and body access to these compounds is an important issue [1]. Although many sources are referred to as antioxidants, fruits and vegetables are known as the main sources of antioxidants that are commonly found in people's daily diet. Antioxidant compounds have a large variety, generally including some vitamins such as C and E vitamins, beta carotene, polyphenols such as coffee and catechins, zinc and selenium, peptide compounds such as glutathione, as well as nitrogenous compounds like Uric acid. Generally speaking, the antioxidant system of the body can establish the balance between antioxidants and prooxidants by enzymatic and non-enzymatic mechanisms. Antioxidants can have cofactor function for some enzymes involved in this system, which is their indirect protection against free radicals. Selenium and zinc elements can be used as cofactor for glutathione reductase and superoxide dismutase enzymes respectively. Also, in non-enzymatic methods, compounds such as vitamins A, C, E, nitrogenous compounds such as uric acid and Q10 act as internal

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antioxidants that can directly affect free radicals and reduce their damage to target cells [2-9].

However, in recent years, research on these issues indicate that the disruption of antioxidant system may interfere with the development of several diseases including atherosclerosis, neurological diseases, diabetes, kidney disease, rheumatoid arthritis, immune system disorders, Gastrointestinal tract disorders like peptic ulcer and immune system disorders such as lupus erythematosus [10-12]. One of the important roles of antioxidants in the body's biological system is to protect macromolecules from damage, including DNA, which can play a role in the pathophysiology of some diseases, such as cancer [8]. Although previous studies shows that there are several mechanisms by free radicals that cause damage to DNA, the most important reaction that has the greatest damage to DNA is the Fenton test, that the hydroxyl radicals produced in this reaction lead to destructive changes in the DNA structure caused by the reaction with its constituent parts like deoxyribose, Purine and Pyrimidine [13, 14]. Although, the results of some studies have demonstrated that DNA damage is reduced by antioxidant agents such as polyphenols, vitamin A, C, E and beta-carotene, there are also studies that express destructive effect of them [15-19]. Also, the process of DNA destruction, which is associated with an impairment in the transcriptional regulation of various genes, blocks the transcription of some genes and as a result impairs the synthesis of some proteins, which is associated with unusual changes in the biological system of the body [20-22]. Considering the protective role of antioxidants such as beta-carotene, E and C vitamins in preventing damage to DNA and also in view of the role of DNA in the pathophysiology of some diseases, such as cancer, it is necessary to investigate the role of antioxidants.

DNA damage assessment methods

These days, different methods exist to examine the extent of DNA damage by various factors. Single-cell gel electrophoresis (Comet assay) is one of the most common methods for assessing damage to DNA by various materials, as well as for assessing the strength of antioxidant compounds. In this method, the DNA, based on the ability to remove supercoils, can move in the electrophoresis gel, which is represented by special recorders and comet-shaped stars. The intensity of this comet image is interpreted as the frequency of the defects generated in the DNA [8, 23, 24]. Active ROS can produce oxidation in DNA components, such as purine and pyrimidine; since, the 8-oxo-7,8-dihydroguanine (8-OH-Gua) can also be produced by DNA repair through the cracks created in the cells. The oxidation of purine and pyrimidine can take the form of 8-OH-Gua, 8-OH-Guo or 8-OH-dGuo as oxidation factors in serum, urine or plasma [25, 26]. Also one of the most sensitive indicators for measuring DNA damage is the determination of β-H2AX, which is known as a phosphorylated form of histone H2AX. This compound, which is most commonly found in DNA-damaged sites, can be measured by chemical-related antibody techniques (ELISA) as well as flow-cytometric methods [27, 28].

Effect of vitamin C in preventing DNA damage

Vitamin C or ascorbic acid is known as one of the water-soluble vitamins that plays role in chemical reactions of the body as an electron carrier. Studies suggest that vitamin C can have an important role in preventing the destruction of DNA. In a study by Green and colleagues to investigate the mechanism of vitamin C on preventing DNA damage in human white blood cells, the results indicated that vitamin C intake significantly reduced DNA damage [29]. Also, a study by Sram et al. in 2012 showed that not only vitamin C in healthy people has a preventative effect on DNA damage, but also in people who are in poor conditions can reduce the damage to DNA. Based on this study, vitamin C and its high levels in plasma (above 50 mol / L) reduce chromosomal abnormalities, which can reduce DNA defects and decrease the amount of 8-oxodG, as one of the indicators of DNA damage.

The results of some studies indicate that the greatest effect of reducing the damage to DNA by vitamin C is observed in people exposed to inappropriate diet, environmental pollutants and ionizing radiation. In addition, vitamin C can repair gene mutations in smokers with ionizing radiation exposure [30]. In a study by Rehman et al., the effects of simultaneous supplementation of vitamin C and iron on the DNA damage were different. The result in the group with high level of vitamin C in plasma showed that not only vitamin C does not decrease the damage to DNA, but also increases the rate of destruction. Meanwhile, in the second group, with low plasma levels, vitamin C reduced the damage to the DNA [31]. In addition, Kowalik et al., in their study in 2001, investigated the prevention effect of vitamin C on the damage of anti-tumor drugs in human lymphocytic cells to the DNA. The study concluded that vitamin C in doses of 10 and 50 μm can reduce DNA damage but has no effect on DNA repair. This vitamin C can reduce the side effects of drugs that affect human genomes such as cisplatinum [32]. Table 1 presents the details of the studies.

Effect of vitamin E in preventing DNA damage

Vitamin E or tocopherols have three subtypes, the most important of which is alpha tocopherol and is known to be one of the lipid soluble antioxidant found mostly in adipose tissue. According to studies on the antioxidant properties of vitamin E, the role of this vitamin in preventing DNA damage is significant [33-35]. The result of the study conducted by Hartmann et al. showed the preventive effect of vitamin E on DNA damage of white blood cells in athletes that high level of this vitamin in the blood reduced injuries to DNA from intense exercise [36]. In the study of Jenkinson et al., which was performed on 21 healthy men, the effect of vitamin E with high chain saturated fatty acids on the DNA from lymphocytic cells was investigated. The results of this study showed that a diet rich in tocopherols and PUFA (5%) reduced the oxidative damage of cell DNA [37]. But while Konopacka et al. investigated the effect of vitamin E with vitamin C and beta-carotene on the damage of DNA in human lymphocytes, the results showed that the overall effect of these compounds on DNA damage could be influenced by the dose of antioxidant compounds. In this study, the culture of lymphocytic cells was exposed to a high dose of these compounds and the results indicated that the compounds mentioned, including vitamin E, had no effect on the damage of DNA [16]. Also in Huang et al. study on 184 non-smoker adults, the effect of vitamin E with vitamin C on DNA damage was measured by measuring one of the important markers of DNA damage (8-OH-dG). There is no evident relationship between the effect of these compounds, including vitamin E, in preventing DNA damage [38]. Table 1 illustrates the details of the studies.

Effect of beta-carotene on prevention of DNA damage

Carotenoids are a bunch of various organic compounds with antioxidant properties [39]. Beta-carotene is one of the most commonly found in fruits and plants with red and yellow colors [40-43]. This compound is one of the organic compounds with the terpene group, a precursor of vitamin A, which itself is known as fat soluble vitamin. According to studies conducted in recent years, carotenoids have a variety of properties, including the protective effect against DNA damage, which can play a role in the pathophysiology of some diseases, such as cardiovascular disease and cancer. Also, the results of various studies indicate that increased levels of carotenoids, especially beta carotene, can reduce the amount of damage to DNA [44]. A study in 2016 by Al-Shaban et al., evaluated the protective effect of β-carotene on DNA damage from hydrogen peroxide in human lymphocyte cells. The results of this study depicts that beta-carotene has the potential to reduce DNA damage. But the preventive effect of DNA by this compound was different at various doses [45]. Konopacka et al. conducted a study to investigate the antioxidant effects of beta-carotene with vitamins C and E on mice. The results of this study indicated that taking beta-carotene together with vitamins E and C has a protective effect against the creation of micronucleus and damage to DNA which was produced by gamma rays [46]. Also, the results of previous studies explain the effect of smoking cigarettes on the body's antioxidant capacity and can cause damage to the human genome. Lee et al., in their study, also evaluated the antioxidant effect of beta-carotene with vitamins C, E and red ginseng on the oxidative damage of DNA by measuring the amount (8-OH-dG) in blood samples of smokers. The results of this study showed that the level of beta-carotene in smokers is low and thus the amount of oxidative damage in these individuals is high compared to non-smokers. Overall, the results of this study indicate that supplementation with beta-carotene reduced the DNA oxidation in smokers [47].

Effect of Selenium and Zinc on prevention of DNA damage

Selenium and zinc are two rare elements with remarkable antioxidant properties in various body reactions [48]. One of the most important functions of selenium and zinc as antioxidant compounds is their role as cofactors for the activity of glutathione peroxidase and superoxide dismutase, which plays a significant role in the body's antioxidant-peroxidant system [49, 50]. A review of studies indicate the role of selenium as a preventative factor in DNA damage, while some studies have shown the contradictory role of Zinc as an antioxidant. In 2015, Shi et al. conducted a study about function of selenium in the form of sodium selenite on the side effects of aflatoxin on the mitochondrial DNA. The results of this study showed that selenium has a strong protective effect against damage to DNA, which may itself be due to its antioxidant properties [51]. Ellwanger et al., in their study in 2015, investigated the effect of selenium on the damage of DNA from paraquat in brain and leukocyte cells of Parkinson's Rats. The results of this study showed that selenium consumption could not significantly affect the DNA damage of the brain cells but reduced the DNA fragmentation of leukocytes compared to the control group [52]. In addition, a study conducted by Karunasinghe et al. in 2016 evaluated the effect of selenium on the damage to DNA in leukocyte cells. The results of this study showed that the level of DNA damage in adolescents is associated with lower selenium intake [53]. Following a study on the effect of zinc on DNA damage, Yegin et al., in 2016, showed the effect of zinc supplementation in mice with kidney disease by measuring the amount of 8-OH-dG as a marker for DNA damage. The results of this study showed that the amount of 8-OH-dG in mice group with intake of zinc was more than control group, which expresses a higher degree of damage to DNA [54]. However, the results of the Joray et al. study in 2015 was in contrast with the results of the study by Yegin et al. They showed the effect of zinc supplementation on the degree of DNA fragmentation in female blood cells. The results showed that supplements, although not altering the plasma level of this element, lead to reduction of fractures in the DNA sequence. [55].

The effect of polyphenols on the prevention of DNA damage

Polyphenols are some chemical compounds with phenolic group and antioxidant properties, are widely found in plant compounds especially in fruits and vegetables [56]. Recent studies indicate the potential impact of these compounds on the prevention of certain diseases, such as cancer. Due to their antioxidant effect, these compounds can prevent oxidative damage to DNA and other biomolecules [8]. A study by Rangel-Huerta et al. in 2015 found that the use of orange juice polyphenols in obese subjects led to a decrease in urinary 8-OH-G as one of the markers of DNA damage [57]. Also, the results of the study by Spadafranca et al. in 2010 indicated that the consumption of polyphenols in the form of dark chocolate reduced the damage to DNA from mononuclear cells in healthy people [58]. In addition, Ko et al., in their study in 2014, evaluated the property of spinach powder in the diet of hyperlipidemic rats to evaluate its effect on preventing the rate of failure in the DNA sequence. The results of this study showed that spinach as a source of polyphenols can reduce DNA damage [59]. In addition, a 2012 study by Qian et al. was designed to investigate the protective effect of polyphenols in the form of green tea on DNA damage in postmenopausal women. The results of this study indicated that green tea consumption significantly reduced the amount of urine 8-OH-G [60]. However, the study of Krajka et al. (2005) showed that apple juice consumption as a source of polyphenols in mice not only does not reduce DNA damage, but also increases the fragmentation of the DNA strand [61].

Table 1: Characteristics of Clinical trial studies related to Antioxidants as DNA protective compounds

References	Material Tested	Assays	samples	Duration	Dose	Result
Green et al 1994 [29]	Vitamin C	Comet assay	white blood cells (human)	1 hour	500 mg	Reduction in overall comet length
Rehman et al 1998 [31]	Vitamin C, Fe	DNA base damage product	white blood cells (human)	6 weeks	Ascorbic acid: 60 and 260 mg/day Ferrous Sulfate: 14 mg/day	Reduction in Total base damage
Kowalik et al 2001 [32]	Vitamin C	Comet assay	lymphocyte cells (human)	2 hours	Sodium ascorbate: 10 and 50 mmol	Reduction in DNA damage
Hartmann et al 1995 [36]	Vitamin E	Comet assay	white blood cells (human)	14 days	1200 mg/day	Reduction in DNA damage
Jenkinson et al 1999 [37]	Vitamin E, PUFA	Comet assay	lymphocyte cells (human)	4 weeks	Alpha-tocopherol acetate: 80 mg/day PUFA: 5 or 15 % in diet	Reduction in DNA damage in PUFA (5 %)
Konopacka et al 2001 [16]	Vitamins C, E and Beta-carotene	micronucleus assay	lymphocyte cells (human)	2 hours	Vit C: 1 μg/ml Vit E: 5 μg/ml Beta carotene: 5 μg/ml	No effect on DNA damage *
Huang et al 2000 [38]	Vitamin E , C	8-OH–dG	Nonsmoking adults (24-h urine sample)	2 weeks	Alpha-tocopheryl acetate: 400 IU/day Vit C: 500 mg/day	No effect on DNA damage
Al-Shaban et al 2016 [45]	Beta-carotene	Comet assay	lymphocyte cells (human)	13 months	100 and 10000 μg/ml	Reduction in DNA damage
Konopacka et al 1998 [46]	Beta-carotene, vitamins C and E	micronucleus assay	bone marrow polychromatic erythrocytes and exfoliated bladder cells (mouse)	5 days	Beta carotene: 3-12 mg/kg/day Vit C: 50-100 mg/kg/day Vit E: 100-200 mg/kg/day	Having a protective effect against micronucleus
Lee et al 1998 [47]	Beta-carotene, vitamins C, E and red Ginseng	8-OH–dG	blood samples of smokers (white blood cells)	4 weeks	Beta carotene: 9 mg/ day Vit C: 500 mg/ day Vit E: 200 IU/day Red Ginseng: 1.8 g/day	Reduction in DNA Damage
Shi et al 2015 [51]	Sodium Selenite	Mutation Analysis for D-loop Region of mtDNA	Duckling liver cell mitochondria	21 days	1 mg/kg BW/day	protective effect for DNA damage
Ellwanger et al 2015 [52]	Sodium Selenite	Comet assay	Leukocytes and brain cells (Wistar rats)	58 days	11.18 μg/ml/day	Reduction in DNA damage in Leukocytes
Karunasinghe et al 2016 [53]	Selenium	Comet assay	Leukocytes (human)	6 months	200 μg/day	Reduction in DNA Damage
Yegin et al 2016 [54]	Zinc sulfate	8-OH–dG	Serum of Wistar-Albino rats with	4 weeks	227 mg/L/day	Increases in 8-OH–dG levels

			acute and chronic kidney deficiency			
Joray et al 2015 [55]	zinc sulfate	Comet assay	Cells from whole blood (human)	17 days	20 mg/ day	Reduction in DNA strand breaks
Rangel et al 2015 [57]	Polyphenols (Orange juice)	8-OH–G	Urine sample of overweight humans	12 weeks	300 and 745 mg/day)	Reduction in 8-OH–G levels
Spadafranca et al 2010 [58]	Polyphenols (Dark chocolate)	Comet assay	PBMN cells (human)	2 weeks	860 mg/day	Reduction in DNA strand breaks in short term
Ko et al 2014 [59]	Polyphenols (Spinach)	Comet assay	Leukocytes (Hyperlipidemic rats)	6 weeks	5% (powder) in diet	Reduction in DNA strand breaks
Qian et al 2012 [60]	Polyphenols (Green tea)	8-OH–G	Urine sample of Postmenopausal women with osteoporosis	6 months	500 mg/day	Reduction in 8-OH–G levels
Krajka et al 2015 [61]	Polyphenols (apple Juice)	Comet assay	liver cells (rat)	28 days	10 mL/kg/day	Increases in DNA strand breaks

Abreviation: PBMN cells; Peripheral blood mononuclear cells.

* Reduction in DNA damage for all supplements in the fifth minute and beta carotene and vitamin E in Sixtieth minute only.

CONCLUSION

Antioxidant compounds include internal antioxidants (enzymes and cofactors such as selenium) and external antioxidants (polyphenols and some vitamins such as vitamins E and C) that can be fed through a diet for the natural needs of the human body. These compounds can neutralize free radicals and prevent damage to macromolecules, such as DNA and proteins. However, according to available evidences and a review of numerous studies in this paper, the effects of some antioxidant compounds on the prevention of DNA damage are controversial. Some of these antioxidants are dose dependent and using these substances at inappropriate doses not only does not prevent DNA damage, but also it can increase DNA fragmentation.

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