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Use of Flavonoids and Green Tea Extracts as Antioxidants Induced by Oxidative Stress: A Review Article

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ABSTRACT

The aim of this work is to shed light on the importance of medicinal plants, especially those that have extracts that have a direct effect on human health. The study and identification of botany is necessary because human life has become closely linked to the life of plants as food .In addition to using plants as food, primitive man did not stop at this point, but rather developed their use to hunt prey and also used toxic plant materials in wars. With the passage of time, the ancient man was able to link the wild plants that cover the surface of the earth and the diseases that afflict him, so he used these plants or Parts of it are for treatment. A medicinal plant is defined as one or more of its parts that contain one or more chemicals in a small or large concentration and can treat one or more specific diseases or reduce the symptoms of infection if they depend on this plant part in its natural form or through chemicals effective extracted from it. green tea (Camellia Sinensis) is one of the most important natural herbs used in this field, because its chemical compounds contain beneficial effects for the body, such as its anti-inflammatory, anti-decay, anti-bacterial, and antioxidant effects. Flavonoids play a very important role in many extracts and medical preparations and their wide use in pharmacology. They are among the high-voltage compounds that can stimulate the activities of some enzymes and can change the behavior and function of a wide range of cellular systems due to their characteristics an antioxidant; it has the action of capturing free radicals, especially hydroxyl radical. It has a high ability against free radicals that cause many diseases, as it has a protective effect on blood vessels, arteriosclerosis and hepatocytes. It also shows anti-inflammatory, allergic, gastric ulcer activity and burning fat as it has significant anti-tumor activity. We conclude from this study that green tea and some plants that contain in their extracts phenolic compounds (flavonoids) play a major role in reducing the severity of common diseases, in addition to being a good antioxidant.

Key words: Green tea, Flavonoids, Antioxidants, Free Radicals

INTRODUCTION

The tea plant - a perennial yield or shrub that lives up to (70 years). Its trunk is massive and short. Rise to about 2 m. Its leaves are dark green in color, oval in shape, elongated (5-10) cm, with a short neck. Its edges are serrated, its number increases at the top of the branches, and decreases at the bottom, its texture is loose and rough to the touch, and it becomes very smooth and shiny after drying. Its size varies according to the species. Tea flowers are small, clustered (2-3 flowers), fragrant, and the fruit is three-lobed. Its three seeds ripen about 4 months after flowering. The tea tree begins with economic leaf production at the age between 3 and 7 years, according to the varieties and agricultural services. It begins with the first picking of the leaves after 3 years from the date of its cultivation(1).

The Chinese discovered it about five thousand years ago. Moreover, its leaves are from the same leaves of the black tea plant,

a shrub native to Asia**.** In addition, green tea leaves because they have not fermented, so their materials remain as they are**.** Therefore, it is beneficial a little black tea and less harmful than it. However, some Chinese use green tea as a treatment for migraines because they believe that it has an effect on it. There is a belief that tea has some benefits for the teeth due to the presence of fluoride in it, and tea helps in burning fats in the body and regulates blood sugar and insulin levels(2). Green tea can raise blood pressure due to caffeine. There are compounds in it such as Polyphenol Epigallocatechin Gallate and Bioflavonoid. It contains tatin, essential oil and theophylline. Drinking large amounts of it causes nervous tension and insomnia and is useful in preventing cardiovascular diseases, strokes, and even some types of cancer. Green tea is consumed more than black tea in Japan, China and some other Asian countries and has become more popular than black tea in Western countries(3).

Green tea ingredients - benefits and harms: The components of green tea by the wet weight of the leaves shown in table (1).

Table 1: Active ingredients in green tea

Ingredients	Percentage%
Water	75-77.5
Tannins Material	2-4
Caffeine	1-4.8
Essential Oils	0.02
Protein	12-20
Carbohydrates	3-4
Metal Elements	4-5
Vitamins	600 mg

The tea of all kinds is useful and diuretic. It was used in the past in the treatment of asthma and colds, to facilitate digestion, and to stimulate the nervous system and the heart. Recent studies show that it contains multiple phenolic salts that directly affect protection against oral cancer, and other substances that prevent lung and colon cancer. Tea, especially green tea, protects against heart attacks caused by fat deposits in the veins. It also prevents premature aging(4).

Flavonoid:

Being the most important polyphenol compounds, and in light of the expanding research area in the field of natural products, flavonoids have taken a very important part of the researchers' attention. It was extracted naturally from plants, especially the green tea plant. The interest in flavonoids is due to being compounds with biological and pharmaceutical activity, as it is anti-bacterial, anti-viral, anti-oxidant and anti-cancer. This activity is due to its chemical composition. More than 4000 flavonoid compounds have been identified and this difference is due to the diversity of vegetation and climatic regions, but on the other hand, a few types of classified plants were examined in terms of their content of flavonoids(5). Flavonoids (Latin: Flavus = yellow) are yellow pigments that are abundant in plants, and are responsible for on the coloring of flowers, fruits and sometimes leaves, along with the compounds of Anthocyanides with which it is almost in chemical structure(6).Flavonoids are pigments that were discovered in 1936 by HongroisSzent-Gyogy in lemon peels. They are natural polyphenolic compounds that contain 15 carbon atoms in their basic structure distributed over three rings A, B, C, as shown in the figure [1], have a low molecular weight(7).

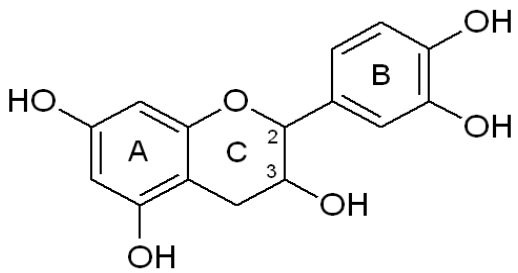


Fig. 1: Structure of Flavonoids

Flavonoids are widely spread on the level of high-end plants, especially on the level of some families such as the cucurbit and the tentacle, and to a limited extent in inferior plants, and it is more distributed in the aerial parts of plants(8). It can also be

found in the rest of the other parts of the plant such as roots, seeds, pollen. As for the cell level, it is found in vacuoles in the form of sugar-based compounds where the presence of sugar in the molecule gives it the strong ability to dissolve in water, while concentrated in the cytoplasm in the form of polymethoxy flavonoids, it dissolves in non-polar solvents(9).

Since some flavonoids are hydroxyl compounds, they have the properties of phenols, with an acidic character. Weak, soluble in strong bases (sodium hydroxide). Flavonoids that carry a greater number are also characterized of the free hydroxyl groups or containing the rest of the sugar with a polar character and therefore it is soluble in polar solvents (methanol, ethanol, acetone and water)(10). As for the less polar flavonoids, such as Flavonones, Flavones, Isoflavones, which carry a greater number of the methoxyl groups, are soluble in chloroform or ether.

The basic structure of flavonoids

Flavonoids have a common structure consisting of 15 carbon atoms distributed in the form C6-C3-C6 it is known 1,3 diphenyl propane composed of two benzene rings (A and B) linked by a heterocyclic oxygen, meaning that it contains the element oxygen or what is known as the ring (C) as shown in figure [2](11,12).

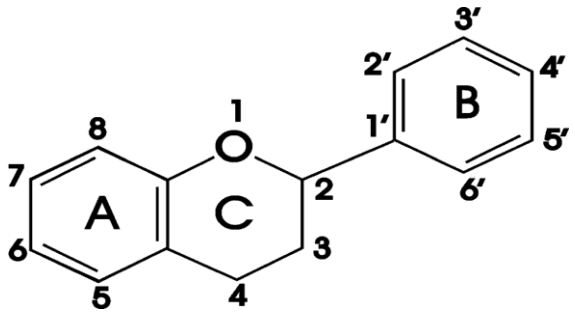


Fig.2.The basic structure of flavonoids

The compositions of flavonoids are distributed according to the nature of the oxygen heterogeneous ring, and this ring is derived either from: Pyrane or Pyrylium or Pyrone(13).

The composition of flavonoids

Flavonoids are composed at the level of chloroplasts, starting with cinnamoyl Coa, which is released from the reticulum endoplasmic malonates are formed under the form of heterosides, some of which leave the chloroplasts and accumulate in the vacuoles; these compounds are secondary metabolites, belonging to the so-called micro molecules due to its small molecular weight and its accumulation in small quantities that do not exceed its concentration in the plant cell 1millimol(14-16).

Protective properties of flavonoids

The effect of flavonoids varies according to their chemical structure, and this has different roles**.** So flavonoids anti-bacterial, anti-allergic, anti-inflammatory, anti-mutagenic, antiviral, anticancer, anticoagulant has a role in vasodilatation, and antioxidant activity, it is able to remove hydroxyl radicals superoxide anion and lipid peroxidation radicals(17). it is also playing anti-inflammatory and anti-allergic activity ,liver protector, anti-spasmodic, lowers cholesterol, it is a diuretic, and more than that, it resists the damage of collagen fibers and reduces the speed of aging(18).

Oxidative stress and free radicals

A free radical is defined as an atom or molecule that contains an unpaired electron in its outer orbit, which gives it reactivity interacting with other, more stable biological molecules; free radicals are involved in many biological functions like cell division, the process of programmed cell death(19**).** In all Healthy tissue antioxidant defense mechanisms are able to counteract and destroy excess free radicals, in this case we say that the balance Oxidation/Antioxidants in balance, but in some cases, this is due to the overproduction of free radicals or a lack of capacity Antioxidants or both lead to an imbalance between the production of free radicals and the oxidative defense system. This condition is called stress or oxidative stress. Therefore, the oxidative stress is known as

an imbalance between the oxidation systems (prooxidants). The antioxidant capacity (antioxidants) in a cell or organism. This imbalance leads to the accumulation of free radicals, which have a high ability to damage membrane phospholipids. It also causes damage at the level of large biological molecules such as proteins, fats, sugars, and nucleic acids **.**Oxidative stress is involved in the mechanisms of cell death in systemic diseases Neurological disease such as Parkinson's disease and Alzheimer's disease(20).

Types of free radicals:

1. **Superoxide Anion ($O°_2^-$):** It is a single negatively charged radical formed because of the reduction of molecular oxygen that receives an electron during a reaction that requires energy.
2. **Hydrogen peroxide(H_2O_2):** H_2O_2 is formed starting from the($O°_2^-$) radical in the presence of enzyme superoxide dismutase(SOD), and it can also be produced by other methods by enzymes.H_2O_2 is not considered a free radical, but it is very active and has a great ability to oxidize
3. **Hydroxyl radicals (OH°):** It can be formed from H_2O_2 in a non-enzymatic reaction that is catalyzed by ferrous ions (Fe^{+2}), and this is called Fenton reaction. The hydroxyl radical OH° is a very reactive molecule and can react with proteins nucleic acids, lipids and other molecules to change their structure and cause tissue damage(21).The three free radicals above are formed as in the chemical equations shown in the figure [3].

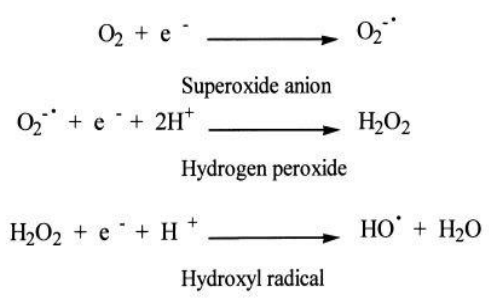


Fig.3. Formation of and superoxide anion, hydrogen peroxide and hydroxyl radical.

Nitrogen monoxide radical(NO°): This radical is derived mainly from nitrogen, which is produced by the endothelial cells, plays a key physiological role in regulating blood pressure, and with increased oxidative stress, it can lead to a dysfunction of the endothelial cells. Thus, increasing radical (NO°) production.

Antioxidants

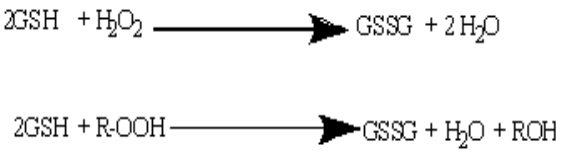
It is a group of elements and compounds that have the ability to prevent or slow down the oxidation process, in order to protect other compounds of oxygen. Antioxidants are found in the body of an organism in the form of enzymes or Co-enzymes or compounds containing reduced sulfur such as glutathione. Antioxidants are also found naturally in vegetables, fruits, grains, and most medicinal herbs(22). The interest in antioxidants has increased in recent years due to their ability to immunize the body against the invasion of germs. Eliminating it, it also protects the body from common diseases of the age. Antioxidants have multiple functions to cover most the human body needs of prevention, healing and restoration of its tissues and cells. It also protects and inhibits ADN from damage free radical action(23). Although the mechanism action of antioxidants is not precisely clear, scientific research and studies the statistics confirmed its effectiveness in the prevention and resistance of diseases. Antioxidants are classified into two groups(24):

Enzymatic antioxidants: We will briefly discuss some enzymatic antioxidants.

1. **Superoxide Dismutase (SOD):** This enzyme is considered one of the most important enzymes active as an antioxidant. It removes superoxide radicals by accelerating its removal rate by about four times with the help of some minerals such as selenium, copper and zinc (25).
2. **Catalase (CAT):** It is found in most living organisms and in all organs of the body. It is concentrated especially in the

liver and red blood cells and kidneys and in small quantities in the brain, heart and muscles and works on the elimination of H_2O_2 by turning it into H_2O and O_2, so it prevents the accumulation of hydrogen peroxide produced, one of the processes of respiration in the tissues, which causes the accumulation of cell poisoning and then death(26).

3. **Glutathione Peroxidase (GPX):** This enzyme is found in red blood cells and other tissues. This enzyme stimulates the breakdown of H_2O_2. and hydro peroxides of lipids by reduced glutathione(GSH) and H_2O_2 to give oxidized glutathione(GSSG) and water, as shown in the following equation(27):



Glutathione peroxidase protects the lipids of vital membranes and hemoglobin against oxidation by Peroxides that can be used as other substrates. The presence of selenium in composition of glutathione peroxidase protects components of the cell and biological membranes from oxidative damage, so the exposure of the body to oxidative damage leads to the significant decrease in the level of glutathione peroxidase.

Non-enzymatic antioxidants: We will briefly discuss some non-enzymatic antioxidants**.**

1-**Vitamin C:** It is an antioxidant that dissolves in water and works inside cells, can it work to support the body's defense system. It used within the body's mechanisms to remove free radicals and toxicity of some chemicals. It has an important role in the process of oxidation and reduction in the body. In addition, this vitamin plays a role Anti-programmed cell death and affects some anti-proliferative substances(28).

2- **Vitamin-E:** Vitamin E is one of the most fat-soluble antioxidants and its compounds are known as tocopherols. Tocotrienols the most important of which is the α-tocopherol compound, which plays a vital role in protecting cell membranes from oxidative damage and thus prevent cholesterol from sticking to the walls of the arteries, as this vitamin takes up peroxide radicals in the cell membranes, and therefore it is called the term "radical scavenger".

3- **Glutathione:** It is a peptide made up of three amino acids, cysteine, glutamine and glycine. Glutathione (GSH) is a non-protein nitrogenous substance. It contains a large amount of sulfur, is characterized by its low molecular weight, and has structure ($C_{10}H_{17}N_3O_6S$). Glutathione is found in various living organisms such as humans, animals, plants and microorganisms. It is one of the most abundant cellular non-protein thiol compounds, and it is one of the non- enzymatic anti-oxidants (endogenous) (29).

The relationship between oxidative stress and diseases

An increase in free radicals or a decrease in the antioxidant systems leads to oxidative stress, which can cause damage in cells as loss of their integrity or cell death. Disruption of the antioxidant system especially active detoxification accompanied by oxidative stress contributes to nervous death, and free radicals are involved in carcinogenesis. Its Play a role a mediator in its early stages (Initiation and Promotion), as these substances that help in the formation of free radicals are carcinogens(30,31).

Effect of flavonoids extract on diseases

Flavonoids have become a wide range of therapeutic use to combat diseases caused by free radicals among the diseases associated with its overproduction: infections and Ischemia/Reperfusion. Clinical and therapeutic effects were also shown in the treatment of viral infection, diabetes mellitus and headache. Several studies also confirmed the importance of flavonoids for their anti-free radical activity(32). Thus, they act as effective inhibitors of lipid peroxidation and the overproduction of oxygen radicals caused by inflammatory cells, cytotoxicity, and chromosomal damage. These phenolic compounds (flavonoids) may be able to activate the natural defense mechanism anti-cancer, as the first phases of the primary stage of cancer can be stopped, with the ability target tissues to intercept and destroy carcinogens.20 Flavonoids inhibit lipid peroxidation in the initiation stage by trapping the superoxide anion and Hydroxyl, which terminates the reaction of the radical chain by giving a hydrogen atom to the peroxyl radical(33). Thus, the flavonoxy radical according to the following reaction:

As for diabetes, Flavonoids can stimulate insulin secretion and protect pancreatic cells from the damaging action of free radicals. Where Plant extracts, especially phenolic, showed their hypoglycemic action in infected animals. With experimental diabetes, in addition to its antioxidant properties, all of which were observed in association studies decreased blood sugar level by decreasing lipid super-oxidation and increasing the activity of antioxidant enzymes like SOD and catalase(34). On the hand , Flavonoids have the ability to influence the enzymes involved in the production of Inflammatory substances, as proven effective in the treatment of asthma and allergies, where Quercetin plays an anti-inflammatory action by maintaining the stability of the membrane of histamine-secreting cells, it also affects the structure of Leukotrien(35). Flavonoids also play a major role in inhibiting LDL oxidation caused by free radicals that lead to arteriosclerosis, as it was proven that the phenolic compounds isolated from red wine have a greater capacity than α-tocopherol on inhibiting the oxidation of LDL catalyzed by copper ions, as flavonoids reduce the formation of free radicals.

The effect of green tea extract on diseases

The substances contained in green tea may help prevent some common eye diseases Such as "glaucoma" known as "blue water." Moreover, it was found in research conducted by the "Chinese University of Hong Kong" that the lens, retina and other parts of the eye absorb the substance in green tea known as Catechins(36). Experts believe that Catechins have counter effects Antioxidant, protective properties that protect the body from the damage that may be caused by oxygen. Green tea extract has many uses for the treatment of diseases. As drinking, a cup of green tea protects the gums and teeth, resists decay, and resists the harmful bacteria that cause bad breath. A study published by the French newspaper “Le Journal Santé” also indicated that the decrease in the rate of the incidence of oral cancer in China is due to the high consumption of green tea(37). A new study revealed that the antioxidants in green tea could prevent or reduce the severity of symptoms Associated with arthritis, and the antioxidants in green tea can inactivate the Cox-Z gene, which triggers inflammation in the same way that ant rheumatic drugs do. The cause of high blood pressure is an enzyme secreted by the kidneys. Antihypertensive drugs act on blocking enzyme secretion, so blood pressure can be lowered by inactivating the enzyme(38). As for a green tea is a natural in activator of the enzyme, and many studies have shown that blood pressure decreased in animals and

humans after giving them green tea preparations. Green tea extract also protects against Alzheimer's and Parkinson's disease, helps fight allergies, burn fat and strengthens the body's immunity. In an exclusive study on the spread and development of cancer, it was found that the rate of cancer diseases decreases in areas where its population eats high levels of green tea, such as Japan, China and Korea(39). Where a study on the feeding pattern was conducted in areas of Japan, green tea is considered a popular drink that causes cancer of the stomach, liver, pancreas, kidneys, the lungs and skin spread slightly in people who drink this drink, and the study showed that the rate of infection Lung cancer is 45 % lower in smokers who drink large amounts of tea(40).

CONCLUSION

This study concluded that extracts of phenolic compounds (flavonoids) in addition to green tea extract (Camellia Sinensis) have an antioxidant action. It reduces the effectiveness of free radicals and works to sweep them, thus eliminating the disease generated because of these free radicals. These extracts work to prevent the oxidation of many biomolecules such as fats and proteins, which leads to curbing diseases related to the formation of free radicals, thus activating and revitalizing the therapeutic role of many diseases as highly efficient natural antioxidants.

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