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Original Research Article

Monosodium Glutamate as a Food Additive: Toxic Implications and the Protective Role of Quercetin

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Abstract

Food additives are used widely for various purposes like preservation, coloring and sweetening. Some food additives however, have been prohibited from use because of their toxicity. Despite the wide use of monosodium glutamate (MSG) as food additive, its toxic effects related to oxidative stress were reported in numerous animal studies. However, this mechanism is still unclear. Although the defense system of human body consisting of antioxidants eliminates the negative effects of reactive oxygen species, the accumulated free radicals over the human life weaken the efficiency of his immune system. Thus, supplementation of exogenous antioxidants through diet becomes of great concern. Flavonoids are natural antioxidants derived from plants and commonly found in fruits and vegetables with a great ability to scavenge free radicals. Quercetin is a flavonoid greatly present in food. An extensive *in vitro* and *in vivo* animal research has focused on the antioxidant potential of quercetin against ischemia-reperfusion injury, toxic compounds, and other factors that can induce oxidative stress. This review summarizes the implications of MSG, as a food additive, on animals and human and the probable protective role of Quercetin.

Keywords: Food additives, monosodium glutamate, toxicity; Quercetin.

INTRODUCTION

A food additive is any substance not commonly regarded or used as food, which is added to, or used in or on, food at any stage to affect its keeping quality, texture, consistency, taste, color, alkalinity or acidity, or to serve any other technological function in relation to food, and includes processing aids in so far as they are added to or used in or on food [1-5].

Food additives can be added directly or indirectly. Direct additives are added during processing for specific purposes like keep the product fresh or make the food more appealing. For example, the low-calorie sweetener, aspartame. While indirect food additives are substances that may be added to food during or after processing, packing and storing. They were not used or placed in the food on purpose. These additives are present in small amounts in the final product. Some colourants like cantaxanthin (orange), erythrosine (red), and annatto bixine (yellow orange) are considered indirect food additives [4, 6-8].

Classification

Food additives are divided into the following categories (Fig. 1) [4, 9]:

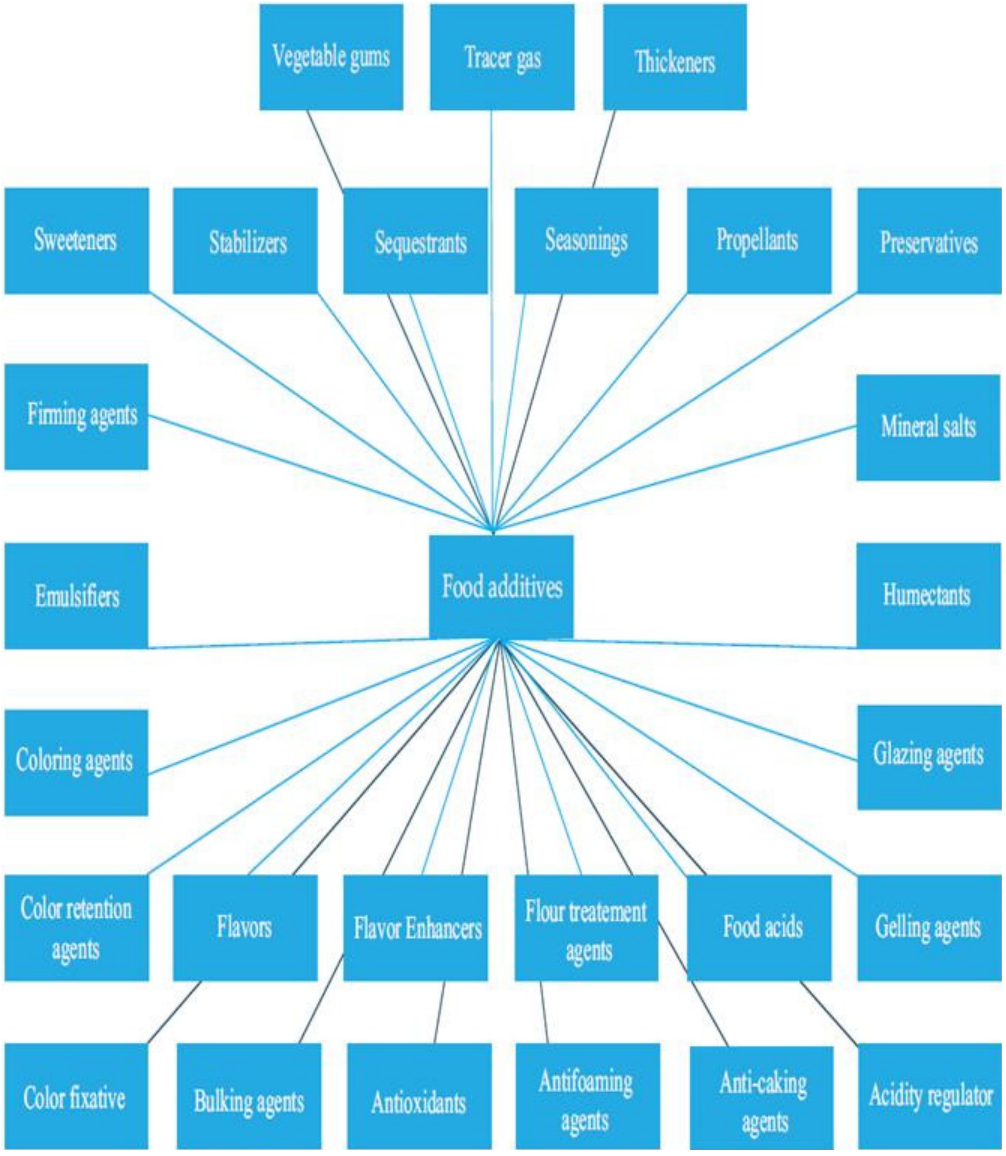

Fig. 1: The classification of food additives [9]

Advantages of food additives

Food additives may be found in varying quantities in foods, perform different functions in foods and ingredients, and function synergistically with other additives. Additives help Maintain the wholesomeness and appealing of foods while en-route to markets sometimes thousands of miles away from where it is grown or manufactured. Additives also improve the nutritional value of certain food and can make them more appealing by improving their taste, texture, consistency or color [11, 13].

Their functions can usually be one of the following [11, 13]:

- maintain or improve nutritional quality
- maintain or improve product safety or quality
- aid in processing or preparation
- Improve sensory characteristics
- Regulate acidity and alkalinity

Adverse effects of food additives

The effects of food additives may be immediate or may

be harmful in the long run if one has constant exposure or accumulations. Immediate effects may include headaches, change in energy level, and alterations in mental concentration, behavior, or immune response [9]. Long-term effects may increase one's risk of cancer, cardiovascular disease and other degenerative conditions [9].

Some food additives have been shown to have side effects in human and animal model. For example, Tartrazine which is an artificially synthesized azo pigment and its use is permitted as a colorant in food products, cosmetics and pharmaceuticals, with a recommended acceptable daily intake (ADI) of 7.5 mg/ kg b. wt. However, long-term and excessive ingestion of tartrazine may cause a variety of adverse effect [16-22].

Caramel is a famous flavoring and coloring agent that can cause vitamin B6 deficiencies [13]. It can cause certain genetic defects and even cancer. Another famous colorant and flavoring which has a deleterious effect is Caffeine. It has diuretic and stimulant properties. It can cause nervousness, heart palpitations and occasionally heart defects.

Saccharin are used as sweetening tablets and widely used by the soft drink and sweet food industry. Saccharin causes toxic reactions and allergic response, affecting skin, gastrointestinal tract and heart. It has been shown to produce cancer when tested on animals [9, 23]. Bladder cancer associated with saccharin ingestion was found to be specific to rodent physiology [13, 24].

Sodium chloride which is used as preservative can lead to high blood pressure, kidney failure, stroke and heart attack. Some modern synthetic preservatives such as (BHT) and (BHA) have become controversial because they have been shown to cause respiratory or other health problems [9-11]. Butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are commonly used in many food formulations as food preservatives for their antioxidant properties [25]. Research studies have shown that BHA and BHT can be carcinogenic for human [9]. It also has been known to induce fore-stomach squamous cell carcinomas in rodents [26], hyperplasia and cytotoxicity [27]. Butylates are also found to be responsible for high blood cholesterol levels as well as impaired liver and kidney function[13].

Monosodium glutamate

MSG is commonly marketed as a flavor enhancer and is used as a food additive particularly in West African and Asian dishes [28-30]. Its popularity originates from the tastiness of the Far East Cuisine [31].

It (MSG/E621) is added as a flavor enhancer to soups, sauces, and meat- preparation products. It produces a flavor that cannot be provided by other foods. It elicits a taste described in Japanese as umami, which is translated to "savory". Umami is considered as one of the five main tastes which enhancing food palatability [15, 32-35]. MSG consumption has increased throughout the world in recent years as flavoring in cooking [36-37].

There have been many researches on glutamate and its relation to food palatability [29, 38-40]. It is suggested that Food palatability increases with appropriate concentrations of MSG [41-42].

Glutamate has different physiological effects on the gastro- intestinal tract and on the endocrine and exocrine pancreas. Some of these effects are believed to occur through binding to receptors which are present in numerous cell types [35].

Some researchers have also attributed the taste and palatability to specific glutamate receptors located on the taste buds and in the stomach [34, 35, 43]. These receptors play physiologic actions beneficial to gut function by stimulating the gastric vagus nerve [34, 44].The effect of MSG is attributed to the presence of the sodium ion, although the glutamate ion by itself can also intensify the activity of gustatory nerves [45].

Glutamate receptors are also distributed throughout the central nervous system including amygdala, hippocampus and hypothalamus where they regulate many vital metabolic and autonomic functions [46]. In the central nervous system glutamate is acting as predominant excitatory neurotransmitter [47-49]. These receptors induce more salivation, create greater stimulation of the olfactory and limbic system of the brain and promote immune function [50].

The estimated daily intake (EDI) is calculated to protect against the most sensitive harmful effect, it also protects against other adverse effects occurring at higher exposures to the ingredient. The US Food and Drug Administration's (FDA's) and Generally Recognized as Safe (GRAS) Committee reported a mean daily intake of MSG per capita of 550 mg/d in the United States in 1979 [51]. A survey published in 1991 found an average intake of 580 mg/d for the general population and 4680mg/d for extreme users (97.5^{the} percentile consumers) in the United Kingdom[52].

Table 1. Content of glutamate in various foods expressed in mg /100g[67].

Food	Bound glutamate (mg/100g)	Free glutamate (mg/100g)
Milk/dairy products:		
Cow's milk	819	2
Human milk	229	22
Parmesan cheese	9847	1200
Poultry products:		
Eggs	1583	23
Chicken	3309	44
Duck	3636	69
Meat:		
Beef	2846	33
Pork	2325	23
Fish:		
Cod	2101	9
Mackerel	2382	36
Salmon	2216	20
Vegetables:		
Peas	5583	200
Corn	1765	130
Carrots	218	33
Spinach	289	39
Tomatoes	238	140
Potato	280	180

In Japan and Korea, the estimated average MSG intake in the 1990s was 1200– 1700 mg/d [53]. It is speculated, however, that the average daily MSG intake may be up to 1000 mg/d [53, 54].The estimated average daily MSG intake per person in industrialized countries is 300–100 mg and it depends on the MSG content in foods and an individual's taste preferences [55].

A food additive generally is considered safe for its intended use if the estimated daily intake (EDI) of the additive is less than, or approximates, the acceptable daily intake (ADI). In case of monosodium glutamate, the oral lethal in rats and mice is 15.000–18.000 mg/kg body weight [56].

Chemical and physical properties

Monosodium glutamate (MSG), a white crystalline powder, is the sodium salt of a naturally occurring non-

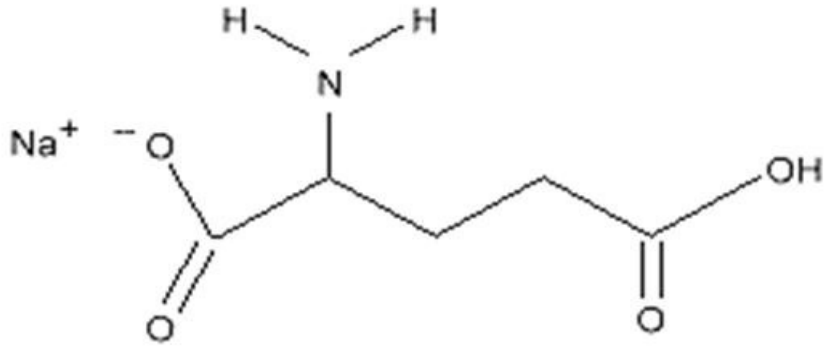

Fig. 2: Chemical structure of Monosodium Glutamate [58].

essential amino acid, glutamic acid (Fig. 2) (57)

Constituent

MSG contains 78% of glutamic acid, 22% of sodium and water [59].

Occurrence

Monosodium glutamate belongs to the larger group of chemicals that are labeled "glutamate" [60]. Glutamate is one of the most common amino acids found in nature [15] It is a major oxidative fuel and an important substrate for the synthesis of the other amino acids, glutathione, and protein in the intestine [61-63]. It is considered the main component of many proteins and peptides, present in most tissues and plays an essential role in human metabolism [61, 64-66].

Glutamate (Glu) in a free form is found at marked concentrations both in animal and plant food stuffs such as green tea, seaweed, mushrooms, potato, Chinese cabbage, soybean, sardines, shrimps, milk, tomato products and soy sauces (Table 1)[29,35, 37, 67].

When glutamate bounds to protein molecule, it is tasteless and does not provide umami taste to food [68]. When present in its “free” form, not “bound” together with other amino acids in protein, glutamate has a flavor-enhancing effect in foods [26, 35, 48, 50, 68].

Protein hydrolysis during fermentation, aging, ripening and heat cooking process liberate free glutamate [14, 68]. Modern commercial MSG is produced by fermentation of starch, sugar, beet, sugarcane or molasses [56].

Side effects

Monosodium glutamate (MSG) is one of the most abundant naturally occurring non-essential amino acids which are able to produce metabolic changes that can further result in severe body disturbances [69, 70].

Despite its taste stimulation, and improved appetite enhancement, reports indicate that monosodium glutamate is toxic to humans and experimental animals [67, 71]. Several studies in animals have shown that MSG is toxic to various organs such as the liver, brain, thymus, ovary, testis and kidneys [28, 66, 72-75].

Toxicity

Neurotoxicity

MSG is an excitotoxin, which may damage the brain especially by oral intake without food [56, 75-76].The mechanism of MSG's neurotoxic effects has been attributed to a prolonged increase in extracellular glutamate concentrations [67]. It altered the activity and sensitivity of rat hypothalamic-pituitary-adrenocortical axis which may result in neurotoxicity [77- 78].

Neurotoxic effects of MSG lead to brain cell damage [67, 76], retinal degeneration, and endocrine disorder. It also involved in some pathological conditions such as addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, depression, Parkinson’s disease, Al- zheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis [59, 79].

Hepatotoxicity

MSG induces oxidative stress and hepatotoxicity in rats [28, 80].It is reported that MSG causes changes in the liver parenchyma around central vein, with dilated sinusoids, inflammatory cells and pyknotic form [81]. Moreover, MSG administration initially attacked the peripheral hepatocytes in the central lobules of the liver tissues leading to hepatocellular degeneration[82].

Reproductive systems toxicity

The ability of monosodium glutamate to damage nerve cells of the hypothalamus is a pointer to the fact that it may alter the neural control of reproductive hormone secretion *via* the hypothalamic-pituit-gonadal regulatory reproductive capacity of the affected animals [83-84]. Fertility rate has been reported to be reduced in both sexes[85-87].

Testicular toxicity

MSG has been implicated in male rat infertility by causing testicular hemorrhage, degeneration and alteration of primary spermatocytes and sperm cell population [88-90]. Male rats treated with MSG show significant abnormalities in sperm concentration (oligozoospermia) and morphology [88,91-92].

There had been specific reports of adverse effects of MSG consumption or administration on both immature and adult male rat's reproductive system and hormones, mostly when very high doses of MSG are administered [87, 93, 94]. Administration of MSG to rats resulted in the decreased weight of pituitary glands and testes and lowered testosterone level[95].

Adverse effects may be arisen through disruption of the hypothalamic pituitary- testis axis regulation by monosodium glutamate [83, 96-97]. Hypothalamic pituitary- testis axis controls the production of testosterone of testicular Leydig cells [83, 98]. This will significantly affect testosterone levels at the serum, because Leydig cells produce 95 % of the 5 % [83, 96].

Ovarian toxicity

The effect of MSG on the female reproductive system has been studied by many researchers who found that it causes many pathologies in the ovaries that lead to an ovulatory infertility [97, 99-100]. The histopathological evaluation of the tissues of the ovary treated with MSG showed degenerated follicles with degenerated oocytes, infiltration of inflammatory cells in and around the oocyte as well as in the zonal granulosa layer, destruction of basement membrane and stroma cells within the cortex and it also lead to distortion of tissue architecture.

Researchers attributed toxic effect of MSG on the follicles and oocytes to oxidative stress induced by it [36, 94, 101-102]. Medulla also appeared degenerated, having multiple vacuoles with congested blood vessels. Moreover, few histomorphological alterations including increased numberofatretic follicles, reduced number of graffian follicles and absence of corps lutea were recorded[36, 90, 97, 101].

Effects on body weight

Weight gain

As a food additive, monosodium glutamate is described and listed on food labels as a Flavor enhancer or Hydrolyzed vegetable protein. It stimulates the orosensory receptors and improves the palatability of meals. Monosodium glutamate influences the appetite positively and induces weight gain [103]. MSG subcutaneous injections or large oral dose of MSG dietary supplementation in rodent have shown an impairment of glucose homeostasis, a dyslipidemia and weight gain[104-105].

Obesity

The prevalence of obesity is increasing worldwide, which indicates that the primary cause of obesity lies in environmental and behavioral changes rather than in genetic modifications [106-107].

It has been reported that MSG intake could induce an increase in energy intake[108] which could lead to obesity [109] or alter the levels of carbohydrates, lipids and proteins in rats [72]. The oral consumption of MSG leads to negative effects with regards to obesity and body mass in rats [110].Studies showed that animals treated with MSG developed central obesity, altered glucose tolerance and hyperinsulinaemia[111].

Prevention of MSG side effects

Oxygen is an element important for life. When cells use

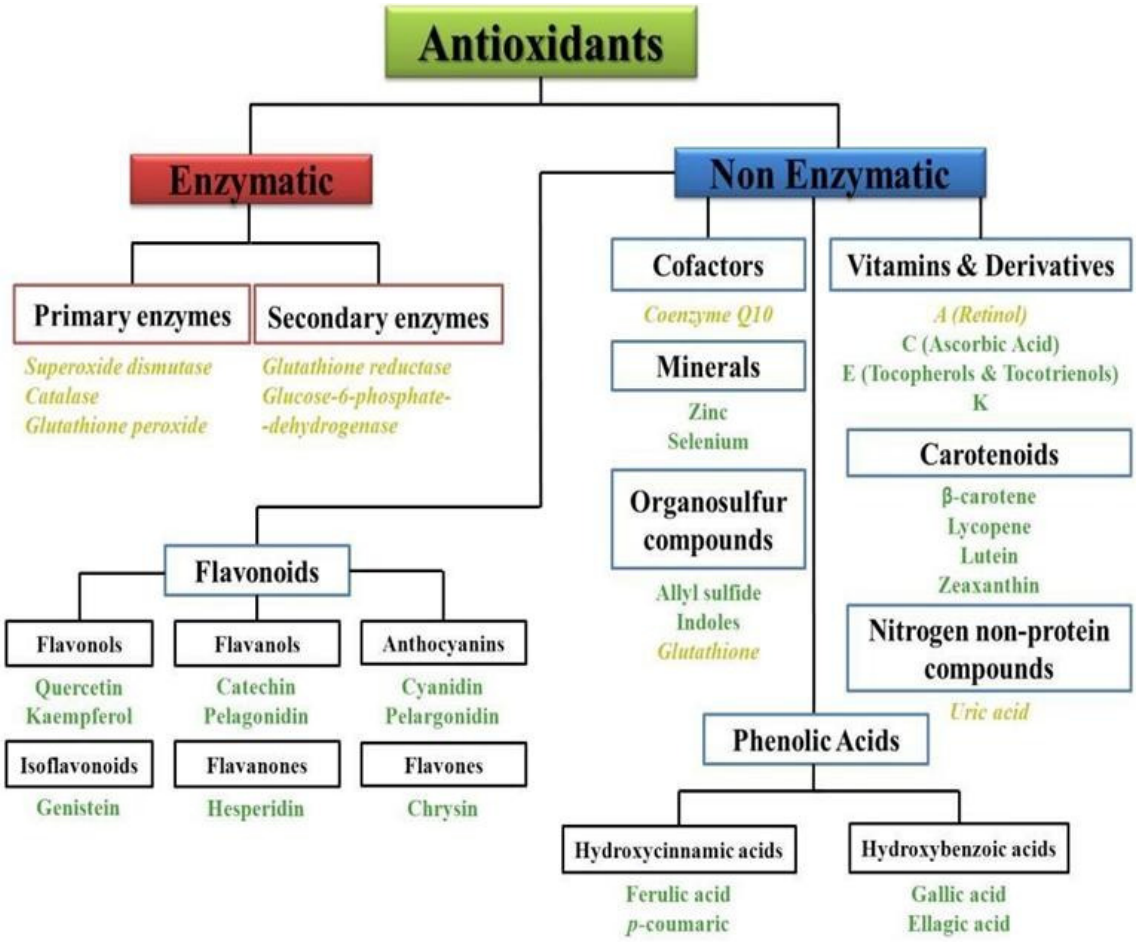

Fig. 3: Antioxidant defense system. Green words represent exogenous antioxidants, while yellow ones represent endogenous antioxidants [10, 144-146].

oxygen to produce energy, free radicals are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria [12].

Reactive oxygen species (ROS) are oxygen derived molecules, which are formed as intermediary products and are a class of powerful oxidants in the human body[12,112]. ROS include superoxide anion (O2), hydrogen peroxide (H2O2) and hydroxyl radical (OH.). A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital**.** Many radicals are unstable and highly reactive [113-114]..

Free radicals and other ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to X- rays, ozone, cigarette smoking, air pollutants, and industrial chemicals [117-119].

Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non-enzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system [120]. Free radicals can also be formed in non- enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions [18,121-122].

Free radicals can oxidize macromolecules, such as DNA, proteins, carbohydrates and lipids [123-124]. The oxidative damage created by free radicals is referred to as oxidative stress, and has been associated with several degenerative diseases, including cardiovascular and inflammatory diseases, cancer, aging, and stoke [12, 123,125].

An imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage, is termed 'oxidative stress'[110,119, 126-128]. So, oxidative

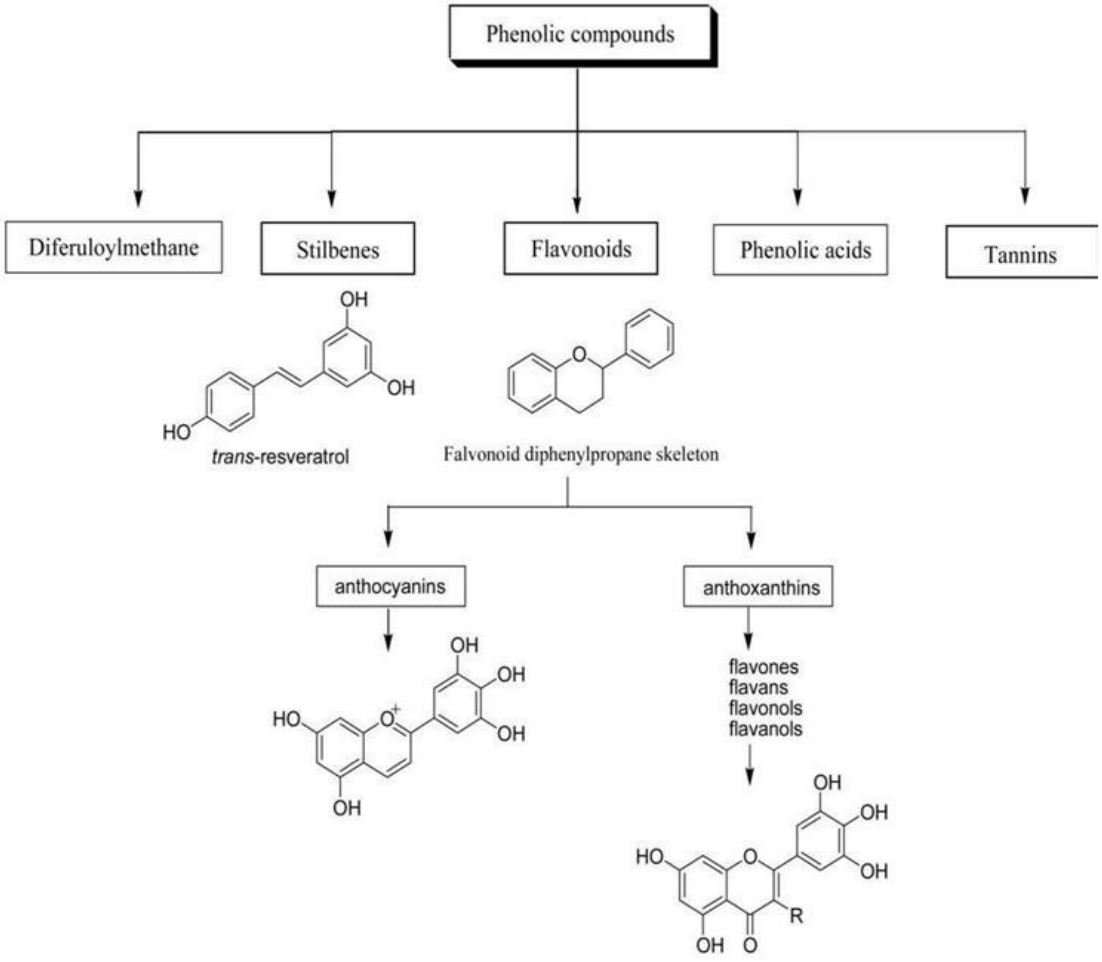

Fig. 4: The main phenolic compounds and their classification [148].

stress is considered as an indicator of the damage that results from a change in the balance between oxidants and antioxidants in favor of oxidants.

It was documented that MSG causes an imbalance between free oxygen radicals (ROS) and antioxidants. As previously shown by Singh and Ahluwalia[129], it produces oxygen derived free radicals and related reactive oxygen species (ROS) which are very dangerous for biological systems as they react with DNA, proteins and lipids, leading to cellular damage [113,124].

Administration of monosodium glutamate to rats showed prolonged and delayed effects on the mitochondrial free radical scavenger system and the consequential membrane damage which lead to cell death [130].

The studies which brought the evidence about the toxic effects of MSG administration led to further research of potential protective effects of different molecules, especially antioxidants [36, 101, 131-133].

Antioxidants

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. Precisely, they delay or prevent the oxidation process that transfers electrons from a substance to an oxidizing agent [14, 132, 134]. Oxidation reactions can generate free radicals, which start a series of reactions that results in cell damage [135]. Antioxidants end these reactions by removing free radical intermediates and suppress other oxidation reactions by being oxidized themselves [136-137].

To protect the cells and organs of the body against excessive accumulation of ROS, humans have evolved a highly sophisticated and complex antioxidant protection

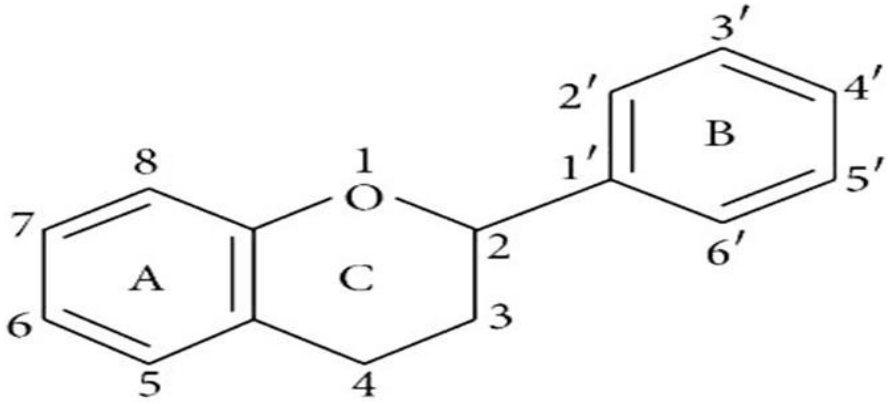

Fig. 5: Basic Flavonoid skeleton (151).

system (138) which involves a variety of components; both endogenous and exogenous in origin (Fig. 3), that function interactively and synergistically to neutralize free radicals (113,139-143).

Moreover, Endogenous compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants (12, 113,141). They can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants(115-116).

Flavonoids

Flavonoids belong to a group of non-enzymatic antioxidants with variable phenolic structure, low-molecular-mass and are widely distributed in plants (147-149). They are considered secondary metabolites of phenolic nature which are synthesized by phenylpropanoid pathway.

Classification of phenolic compounds

The main phenolic compounds and their classification are illustrated in (Fig. 4) (148).

Classification of flavonoids

Flavonoids are a group of plant compounds that share a similar flavone backbone (a three-ringed molecule with hydroxyl [OH] groups attached).They occurs as aglycones (without attached sugars), glycosides (with attached sugars) and methylated derivatives (150). The flavonoid aglycone comprises of a benzene ring (A) condensed with a six membered ring (C), which in the 2-position carries a phenyl ring (B) as a substituent (Fig. 5) (91).

The Flavonoids can be divided into various classes on the basis of their molecular structures (Fig. 6). Six-member ring condensed with the benzene ring is either a-pyrone (flavonols and flavonones) or its dihydroderivative (flavanols (catechins) and(flavanone) (152).

Sources

More than 4000 varieties of flavonoids have been identified. Flavonoids are found in the fruits, vegetables, grains, bark roots, stem, flowers, tea and wine (155-157). Many of flavonoids are responsible for the attractive colors of flowers, fruits and leaves of these plants (158-160). Therefore, it is commonly included in human diets (Table 2) (153, 161).

Therapeutic effects

These natural products were known for their beneficial effects on health long before flavonoids were isolated as the effective compounds. Flavonoids contain numerous double bonds and hydroxyl groups that can donate electrons through resonance to stabilize the free radicals (125).

The radical scavenging properties associated with the structure of flavonoids defend against oxidative stress, reduce heart disease, prevent cancer, and slow the aging processes in cells responsible for degenerative diseases

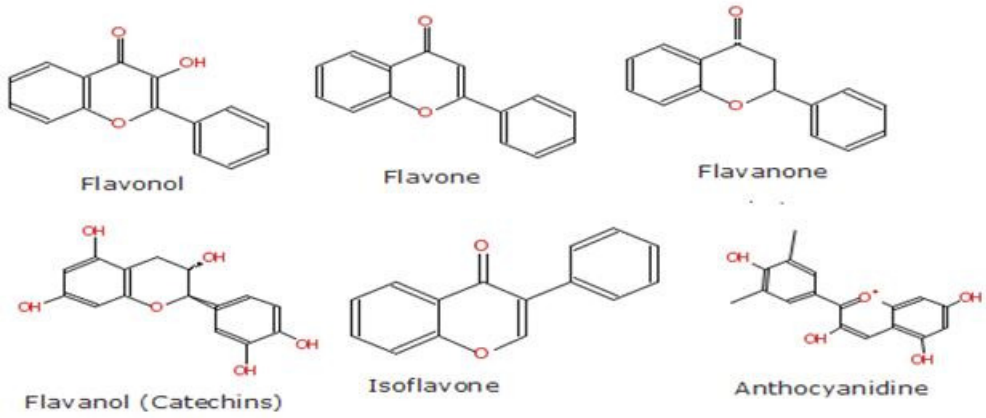

Fig. 6: Structures of major classes of flavonoids [153-154].

Table 2. Classes, compounds and food sources of some dietary flavonoids [153].

Class	Examples	Food source
Flavanone	e.g. hesperetin, tangeretin	citrus fruit, Grapefruit, orange and lemon
Flavanol	e.g. quercetin, kaempferol and myricetin	Onion, red wine, olive oil and grapefruit.
Flavanol	e.g. epicatechin, catechin	Tea
Anthocyanin	e.g. delphinidin,cyaniding	Cherry, easberry and strawberry.
Flavone	e.g. Luteolin, apigenin	Fruit skins, red wine
Isoflavone	e.g. Genistein, daidzein	soya bean

[160]. They have been recognized for having interesting clinical properties, such as anti-inflammatory, antiallergic, antiviral, antibacterial and antitumoral activities (Fig. 7) [156].

Quercetin

Among common dietary flavonols is quercetin [162]. It is widely available and is easy to extract and isolate [163]

Chemical structure

Quercetin (3, 30, 40, 5, 7- pentahydroxyflavone), is a polyphenolic flavonoid compound that occurring mainly in glycosidic forms (Fig. 8) [162, 164-166].

Sources

Quercetin is widely distributed in plants [159, 160].It occurs naturally in fruits and vegetables, including onions, apples, grapes, tea, broccoli and nuts. Therefore, it is commonly included in human diets [145, 168]. It has been reported that amount of quercetin in food might be significantly affected by growing conditions for example quercetin aglycone in naturally grown tomatoes is higher than conventionally produced ones [169].

Researchers have separated and quantified different amounts of flavonols by applying (HPLC) on different plants extract. Table (3), shows list of different contents and forms of quercetin in some selected food [170- 173]. The Estimated daily intake of quercetin has found to be 50-50 mg[174].

Bioavailability

Bioavailability is reliable on form of quercetin that is ingested. It has been reported that glycoside form of quercetin brings about better absorption than a glycone form [160, 174]. They suggest that the bond of flavonoid glycosides can be hydrolyzed by intestinal micro-flora in the colon [175-176].

In contrast, other studies had reported that glycoside

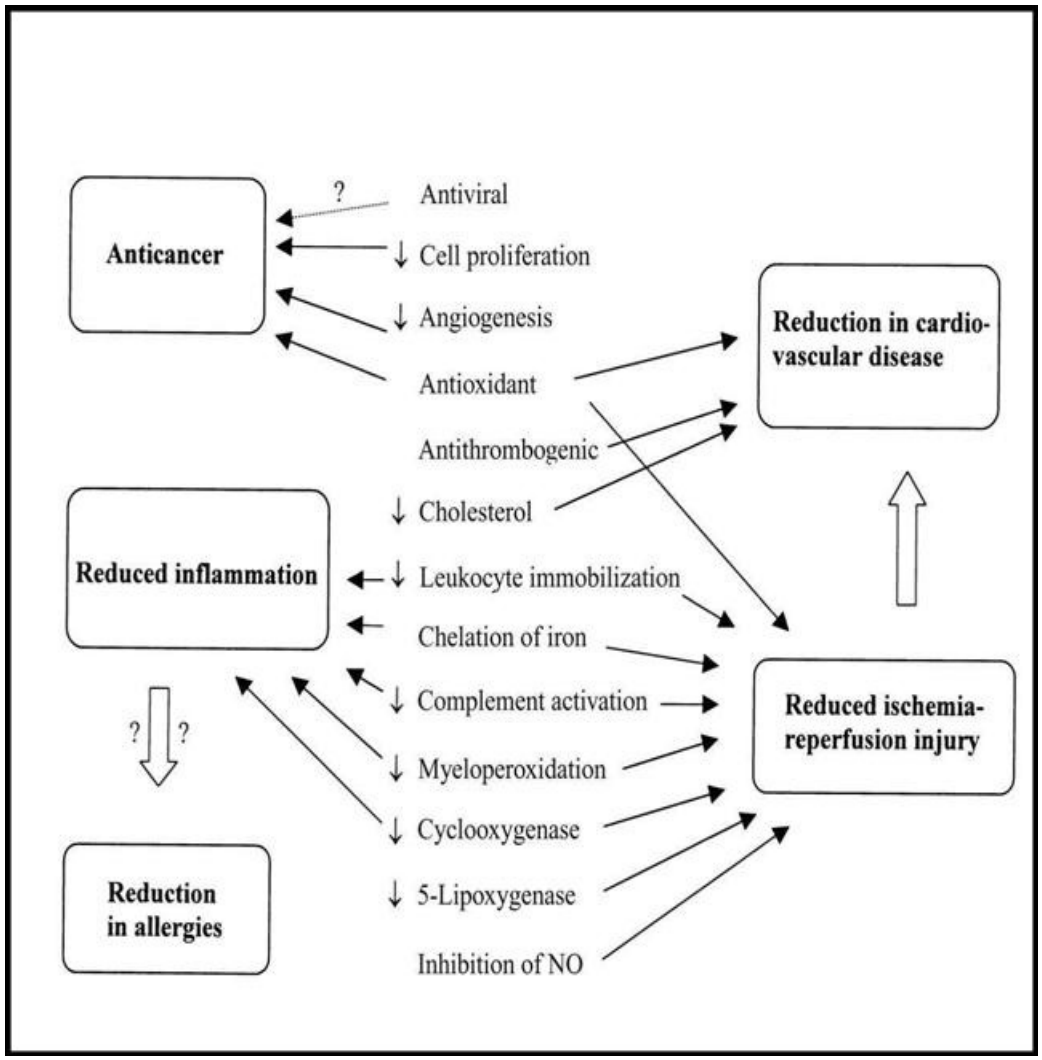

Fig. 7: Hypothesis of the links between the working mechanisms of flavonoids and their effects on disease [161].

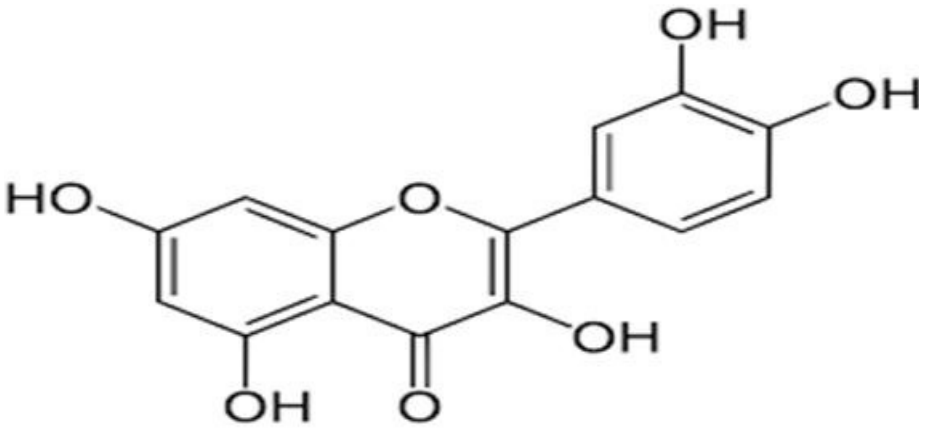

Fig. 8: Chemical structure of quercetin [167].

Table (3): Content of quercetin in some selected food [147].

Food Source	Quercetin Content (mg/100g)
Apple, with skin	4.42
Broccoli, raw	3.21
Raw Onions	13.27
Spinach, raw	4.86
Black Tea Leaves, dry	204.66
Green Tea Leaves, dry	255.55
Red Wine	0.84

form molecules are thought to be poorly absorbed because of two reasons. First, the sugar increases their hydrophilicity. Second, there is no enzyme found to split the glycosidic bond. Sugar- free flavonoids (aglycone form) can efficiently be absorbed through the gut wall [164, 168]. Researchers have found that despite of majority of quercetin glycoside in plants, it is hydrolyzed to quercetin aglycones after ingestion by enzymes in the mouth and the intestines [176-177].

Clinical significance

Quercetin has drawn attention for its remarkable scope of health benefits, which make quercetin a leading compound [178-179]. Quercetin has also been demonstrated to display the antioxidant antibacterial, anticarcinogenic, hepatoprotective and anti-inflammatory effects [180-184].

Antioxidant action

Quercetin is one of the most potent antioxidants among polyphenols. It prevents free radical induced tissue injury by various ways [153]. It contains some phenolic hydroxyl groups that functioning as a free radical scavenger [185]. It inhabits lipid peroxidation by which unsaturated fatty acids are converted to free radicals *via* the hydrogen abstraction [186-187] and promote levels of superoxide dismutase, glutathione peroxidase and reduced glutathione which convert hydrogen peroxide to oxygen and water preventing the formation of free radicals [188-190].

Another route to prevent the oxidative injury is xanthine oxidase pathway. Especially after ischemia-reperfusion, xanthine oxidase pathway is considered an important route in the oxidative injury to the tissues [191]. Xanthine dehydrogenase and xanthine take part in

metabolism of xanthine to uric acid. Under oxidative stress and ischemic conditions xanthine dehydrogenase is converted to xanthine oxidase. It was reported that quercetin have a potent Inhibitory action on xanthine oxidase activity which results in less oxidative injury[192-193].

Anti-inflammatory action

Quercetin is known for its anti-inflammatory effects [194]. It suppresses the expression and production of inflammatory mediators such as, leucotrienes and prostaglandins and their receptors [195].It also inhabits the activity of inflammatory enzymes like cyclooxygenase and lipoxygenase, down-regulate the production and activity of second messengers and inhibit the expression of transcription factors that increase the production of inflammatory molecules [196-197]. Quercetin is reported to show inhibitory action on cytokine tumor necrosis factor-α (TNF-α) which mediated the pathogenesis of chronic inflammatory disease and to modulate Th1/Th2 cytokine production which are involved in asthma pathology[198].

Quercetin also can decrease inflammation by scavenging free radicals. Free radicals can activate transcription factors that generate pro- inflammatory cytokines, which elevate in patients with chronic inflammatory diseases [199]. It is one of the flavonoid that decreases ischemia-reperfusion injury. It is attributed to its inhibitory action against inducible nitric oxide synthase activity which is known as inflammatory causing agent [194,200].

Nitric oxide acts as a messenger molecule for different pathological procedures. It is generated by endothelial cells, macrophages and other several different types of cells. Although the early release of nitric oxide through the activity of constitutive nitric-oxide synthase is important in maintaining the dilation of blood vessels [201]. When nitric oxide reacts with free radicals, it produces the highly damaging peroxynitrite which can directly oxidize LDLs, resulting in irreversible damage to the cell membrane. Quercetin scavenges free radicals and so they can no longer react with nitric oxide, decreasing damage [202]. Anti-inflammatory impacts of quercetin are resembled to that afforded by allopathic medicines [203].

Anti-Cancer effect

Quercetin has been reported as potent anticancer agent against numerous cancer cell types [190]. These cancer types are including, breast [204], leukemia [205], colon [206], ovary [207], stomach [208] and non- small cell lung [209].

The anticancer properties of quercetin are attributed to its significant impact on an increase in the apoptosis and metastasis against tumor cell line, inhibition of DNA synethsis and inhibition of cancerous cell growth, decrease and modification of cellular signal transduction pathways[210]. Moreover, it exhibits inhibitory effect on tyrosine kinase which has been suggested to have antitumor therapeutic potentials[211].

Antibacterial effects

Quercetin is considered a remarkable antimicrobial agent against different species of bacteria such as *Escherichia coli*, *Salmonellae enteric* and *Listeria monocytogenes*[186, 212]. Moreover, Quercetin was reported to inhibit D-Ala-D- Ala ligation in bacterial cells, by inhibiting D-alanine: Dalanine ligase enzyme and preventing the bacterial growth[213].

Hepatoprotective effect

It has been reported that quercetin protect against drug induced hepatotoxicity[184, 190, 214]. It has preliminary showed protection against carbon tetrachloride induced cirrhosis in rats[215]. Administration of quercetin to gerbils decreased deposition of fats in liver cells, protecting liver cells against fibrosis[216]. In another study on mice hepatoprotectivity of quercetin was observed to decrease plasma concentration of alanine aminotransferase[214] and activate of glutathione peroxidase (GPx) in hydrogen peroxide toxicity in cultured rat hepatocytes BL-9[217].

Also, hepatoprotective properties of quercetin may return to its capability of scavenging the reactive metabolites and hydroxyl radicals and preventing their interaction with hepatic macromolecules[218].

Quercetin has been stated as the most potent hepatoprotecrive agent among other flavonoids like silymarine, apigenin, and naringenin against LR- induced hepatotoxicity [219].

Cardiovascular protection

Quercetin has been reported to prevent cardiovascular diseases [220]. This property is attributed to its anti-inflammatory action [221]. It provides a significant protection against atherosclerosis. It can normalize HDL cholesterol which injures the endothelial wall and thereby promotes atherosclerotic, reduce insulin, leptin, glucose and creatinine levels [191] and inhabit LDL[222].

Other effects

Quercetin has significant impacts in treating diabetic rats. it can bring about regeneration of pancreatic islets, increase insulin level in case of streptozotocin – induced diabetes in rats. Many studies have reported that quercetin has vasodilator effects in vitro isolated rat arteries [177, 223-224]. Quercetin has been reported to have remarkable effects against Alzheimer's disease where it inhibits acetylcholinesterase[225].

CONCLUSION

Research conducted using animal models has shown promising results indicating multiple potential mechanisms of action by which quercetin, the cousin of rutin, which is widely found in apple skin, onion peels, certain berries and tea, can overcome different toxic manifestations related to dietary monosodium glutamate administration.

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