Chapter 3

REVIEW OF LITERATURE

Food additives are natural or synthetic substances added to foods which improve flavour, texture, colour, taste, appearance and also function as processing aid. Additives provide protection against food spoilage during storage, transportation, distribution or processing. Flavouring additives are the ingredients, which occurs both naturally and in derived form, that give the characteristic flavour to almost all the foods in our diet. A wide variety of compounds may be responsible for flavouring food products such as alcohols, aldehydes, esters, dicarbonyls, short to medium-chain free fatty acids, methyl ketones, lactones, phenolic compounds and sulphur compounds (Urbach, 1997).

Some of the components in food additives are associated with varying levels of negative health implications. Sorbitol is a sugar alcohol that is used in diet drinks, candy and chewing gum. The reported side effects of sorbitol in young infants include diarrhea, colic and nutrient malabsorption (Duro et al., 2002). Long term consumption of artificial sweetener aspartame increases the risk of leukemia, lymphoma and mammary cancer in rats (Soffritti et al., 2007). McCann et al (2007) conducted a randomized double-blinded, placebo-controlled crossover trial to test whether the intake of synthetic food colours and additives affects child behavior and the results indicated that the mixture of additives commonly found in children’s food increased hyperactivity in children. Sasaki et al (2002) studied the genotoxicity of 39 commonly used food additives. Dyes, colour fixatives, preservatives, antioxidants and sweeteners were tested on male mice. Dyes
were the most toxic compared with other additives and all the additives induced dose dependent DNA damage in the glandular stomach, colon and urinary bladder. The study conducted by Amin et al (2010) evaluated the toxic effect of the azo dyes tatrazine and carmoisine on renal and hepatic function, lipid profile, blood glucose, body weight gain and biomarkers of oxidative stress in young male rats. The conclusion of this study was that these food dyes alter biochemical markers in liver and kidney. The in vitro studies have been conducted to assess the neurotoxic effects of four common artificial food additives in combinations of two (brilliant blue and L-glutamic acid, quinoline yellow and aspartame). Study showed synergistic effects to inhibit neuronal cell differentiation and showed that both combinations are potentially more toxic than their individual compounds (Lau et al., 2006).

3.1. MSG as a flavour enhancer

Monosodium glutamate (MSG), a stable salt of glutamic acid is used in restaurants, cafeterias and found in a wide variety of packaged foods. In 1908, Dr. Kikunae Ikeda at Tokyo Imperial University discovered the taste active components of the konbu stock (extract of seaweed) and named this putative taste “umami” (Ikeda, 1908). He isolated, purified and identified the umami taste component as L-glutamate and he began the industrial production of MSG in 1909. Only the free form of glutamate, in its L-configuration elicits flavor enhancing properties, thus it is widely used as a flavor enhancer in the food industry (Populin et al., 2007). It is used to enhance the natural flavors of meats, poultry, seafood, snacks, soups and stews (Fuke and Shimizu, 1993). Commonly used additives that contain MSG includes malt extract, malt flavourant, bouillon, broth, stock, flavourant, natural flavourant, natural beef, chicken flavourant, seasoning, carrageenan, soy protein concentrate and soy protein isolate.
Yamaguchi (1998) reported that when MSG is added to foods in small quantities, the palatability of those foods is increased by stimulating the sense of taste. Ohguro et al. (2002) have noticed the taste quality provided by MSG and related substances such as inositol monophosphate are unique. These taste and palatability are mediated through glutamate receptors located on the taste buds (Nelson et al., 2002). Ionotropic glutamate receptors, especially NR1, NR2D, KA2 and GluR delta-1 subunits are expressed in lingual epithelium obtained from rat foliate and vallate papillae, in addition to mGluR4a. These GluRs may be responsible for sensory transduction of “umami” taste in addition to the taste specific receptor, T1R1/T1R3 dimer, which is coupled to G-protein for activation by dietary Glutamate (Chaudhari et al., 1996; Li et al., 2002). The optimal palatability concentration for MSG is between 0.2 and 0.8%, but the good taste of food added with MSG has often caused people to consume higher dosage of this compound (Isa and Ghani, 2009).

Worldwide demand for MSG is estimated at 625000 to 700000 metric tons per year. Chinese consumption estimates range from 500000 to 1 million metric tons per year. MSG consumption is flat in Europe, while Latin America shows encouraging growth rates between 5 and 8 percent. China’s MSG consumption is estimated to be rising by 10% or more per year and overall world growth rate is between 5 to 7% (Matthew, 1997). In Western societies, there is a general trend to an increased consumption of flavored food. This change in behavior might lead to an increased glutamate intake, which is used in these products as flavor enhancer. Based on the survey on added glutamate content in food items obtained from the grocery, the daily dose of glutamate in UK was about 12 mg/kg (Rhodes et al., 1991). This is comparable to U.S which estimates of roughly 0.55 g/day
of the average consumer (NAS, 1979). In Asia, especially in Japan and Korea, glutamate and other glutamate salts are used more intensively than in Europe. In these countries the intake of added glutamate is estimated to 1.2-1.7 g/day (Biesalski et al., 1997). Malaysia showed 0.24-8.16 mg/g use of free glutamic acid in local processed foods and prepared dishes. However, the content of free glutamic acid was found to be higher in condiments at 0.28 mg/g in mayonnaise to 170.90 mg/g in chicken stock powder (Khairunnisak et al., 2009). In a highly seasoned restaurant meal, intake may reach to as high as 5000 mg or more (Yang et al., 1997). In Taiwan, consumption figures are to an average of 3 g/day (Giacometti, 1979). In 2003, a joint inquiry by the governments of Australia and New Zealand reviewed previous research exploring the glutamate content of common foods. According to this research, a typical Chinese restaurant meal contains 10 to 1500mg of MSG per 100 g food. A condensed soup typically contains 0 to 480mg, Parmesan cheese contains 1200mg and packaged sauces or seasonings contain 20 to 1900 mg. Thus the average daily intake of MSG in industrialized countries is 0.3 to 1g and in a highly seasoned restaurant meal as much as 5g may be ingested but it can be higher depending on the MSG content of individual food items and an individual’s taste preferences (FSANZ, 2003).

3.2. Health implications of MSG

3.2.1. MSG symptom complex

In the late 1960s a complex of symptoms were reported after the ingestion of a Chinese meal and it was known as Chinese restaurant syndrome (CRS). Kwok (1968) reported the first case on MSG as the causative agent in CRS. Most frequently reported symptoms were headache, numbness/tingling, flushing, muscle tightness and generalized
weakness. Later, the term ‘MSG symptom complex’ has been used instead of CRS. In 1995, the Federation of American Societies for Experimental Biology (FASEB), who had been commissioned by United States Food and Drug Administration (FDA) to undertake a review of reported adverse reactions to MSG and reported that the following symptoms are considered as a representative of the acute, temporary and self-limited reactions to oral ingestion of MSG: burning sensations at the back of the neck, forearms, chest, facial pressure/tightness, chest pain, headache, nausea, palpitation, numbness in the back of the neck, radiating to arms and back, tingling, warmth, weakness in face, temples, upper back, neck and arms, drowsiness and weakness.

Schaumburg et al (1969) administered MSG at different doses ranged from 1-12g in a variety of vehicles such as soup, water and chicken broth. This study found that oral administration of MSG could cause dose dependent symptoms such as burning sensation, facial pressure and chest pain in subjects. A study of double-blind, placebo-controlled challenges by Kenney and Tidball (1972) identified a number of individuals who experienced symptoms of the ‘MSG symptom complex’ only after ingesting 3-5 g of MSG. Yang et al (1997) conducted a double-blind, placebo-controlled study in 61 self-identified MSG-sensitive subjects. Subjects were given placebo or 5 g MSG on an empty stomach and a significant increase in the frequency of MSG-attributed symptoms were observed.
Earlier these symptoms have been suggested as the cause of acetylcholenosis (Ghadimi et al., 1971), vitamin B6 deficiency (Folkers et al., 1984), reflux oesophagitis (Kenney, 1986) and histamine toxicity (Chin et al., 1989). Geha et al (2000b) also noticed the symptoms such as numbness, weakness, flushing, sweating, dizziness and headaches that commenced between 10 min and 2 hr after the intake of MSG containing meal and lasted 4 hr or less. MSG consumption has been linked to headaches both as a component of the ‘MSG symptom complex’ and as a potential trigger for migraines (Raiten et al., 1995). MSG induced headaches in cases with and without double-blind challenge testing revealed that MSG avoidance improved symptom frequency (Scopp, 1991). Yang et al (1997) identified a higher rate of headache following ingestion of high dose MSG than placebo in self identified MSG sensitive subjects. High concentrations of MSG caused arteriospasm in rabbit model due to the vasoactive effect of glutamate. This vascular response might account for MSG induced headache (Merritt and Williams, 1990).
In addition to the MSG symptom complex, ingestion of MSG has been alleged to cause or exacerbate numerous conditions, including asthma, urticaria, atopic dermatitis, ventricular arrhythmia, neuropathy and abdominal discomfort. The reports of MSG-triggered CRS were followed in the early 1980s by reports of a possible association between MSG and the triggering of bronchospasm/bronchoconstriction in small numbers of asthmatics. Single blind oral challenges with 2.5 g capsules containing MSG was associated with the development of severe asthma 12 h after the intake (Allen and Baker, 1981). Allen et al (1987) conducted single-blind, placebo-controlled MSG challenges with increasing doses of MSG (0.5-2.5 g) in 32 asthmatic subjects in which, 14 self identified MSG-reactors and 18 unstable asthmatics with a history of bronchospasm. The authors identified 13 subjects who had a decrease in peak expiratory flow rate within 1-12 hr after ingesting MSG and suggested that ‘MSG is not safe for some individuals with asthma’. Moneret-Vautrin (1987) observed decline from baseline in peak expiratory flow rate, occurred in two subjects with MSG exposure. A study published by Germano et al (1991) identified one of 30 asthmatics showed greater than 20% decline in forced expiratory volume after ingesting 7.6 g of MSG in single-blind challenge. The report by FASEB (1995), mentions that the oral ingestion of MSG to be a possible asthma trigger in a subset of patients. Asthmatics who are sensitive to MSG perceive bronchospasm. Woods et al (1998) conducted double-blind, placebo-controlled challenges with 1 and 5 g of MSG in 12 asthmatics who perceived that MSG might be responsible for worsening of their asthma symptoms. A study by Woessner et al (1999) identified 30 asthmatics who believed that MSG ingestion exacerbated their asthma.
An association between MSG ingestion and asthmatic bronchospasm might also trigger cutaneous reactions in the form of urticaria and angio-oedema. Genton et al (1985) conducted food additive challenge study in 19 adult subjects. Fourteen days before the challenges, all patients were asked to discontinue antihistamine medications and begin a food additive free diet. Challenges were then performed to placebo and five food additives including MSG. The authors concluded that four of 19 subjects were noted to have urticaria within 6 hr of receiving a dose of MSG. Subramaniam and Warner (1986) examined the possible role of MSG in 36 children with urticaria with or without angio-oedema. Double blind challenges with capsules containing placebo and MSG 100mg were conducted at 4 hr intervals. Three of the 36 children had a positive reaction, which was defined as the appearance of urticaria or angio-oedema within the 4 hr interval between challenges. A case study by Botey et al (1988) described four children with a history of urticaria who developed urticaria or pruritic cutaneous erythema 1-12 hr after an uncontrolled oral challenge with 50mg of MSG. A single case of angio-oedema without urticaria induced by MSG has also been reported by Squire (1987).

There is a possibility that MSG may induce acute rhinitis symptoms and contribute to chronic rhinitis. In two separate reports, Asero has described three patients with chronic rhinitis symptoms attributed to dietary MSG ingestion, two patients with perennial rhinorrhoea, nasal itching, and episodes of sneezing paroxysms and one patient with chronic rhinosinusitis with nasal polyposis, anosmia and obstructive nasal symptom (Asero, 2002; Asero and Bottazzi, 2007).

3.2.2. MSG and neurotoxicity

The neurotoxicity of MSG has been much studied. The development of the brain is a very complex process that occurs in a spatial and temporal
sequence that is controlled by biochemical, structural and neurophysiologic events. Any changes in these parameters can produce ultimate changes in brain function such as alteration in behavior, learning and attention (Suzuki and Martin, 1994). Animal studies showed a clear relationship between MSG and spatial learning and memory. Experiments in which newborn animals were exposed to monosodium glutamate have demonstrated significant neurobehavioral alterations (Wong et al., 1997). Other studies have shown that when pregnant female animals were fed MSG, their offspring demonstrated normal simple learning but showed significant deficits in complex learning (Freider and Grimm, 1984). Collison et al (2010) conducted a study on dietary trans fat combined with MSG and reported increased central adiposity promoted dyslipidemia and impaired spatial learning. Park et al (2000) reported that MSG could impair memory retention and induce damages in the hypothalamic neurons in mice. Histology of rat cerebellum showed disruption of the Purkinje and granular layers, sparse granular cell distribution and cellular degenerative changes in the granular layer; this may lead to defects in the functions of cerebellum, tremor, unstable and uncoordinated movement and ataxia (Eweka and OmIniabohs, 2007). Single systemic administration of MSG showed significantly reduced locomotor and rearing activities as horizontal locomotion (James and Yetunde, 2011). Systemic study also revealed behavioral alterations characterized by screeching, tail stiffness, head nodding, emprosthotonic flexion episodes and generalized tonic-clonic convulsions which were associated with electroencephalographic pattern alterations (Lopez-Perez et al., 2010).

Neuronal degeneration and brain lesions were involved in MSG treatment. Neurodegenerative changes in the form of vacuolization, pyknosis, satellitosis and choroid plexus congestion were observed in the
histology of cerebral cortex (Abass and El-Haleem, 2011). The treatment of neonatal rats with MSG induced a substantial reduction in the volume of the subfornical organs accompanied by the degeneration of 35% of the nitricergic neurons within the circumventricular organ. These findings suggest that the subfornical organs could be implicated in some of the cardiovascular alterations observed in MSG treated rats (Pesini et al., 2004).

In 1969, Olney was first reported that MSG could cause brain lesions leading to acute neuronal necrosis in several regions of the developing brain of the neonatal mice and acute lesions in the brain of adult mice. Such brain lesions were reported to cause alterations in the levels of hormones. Administration of MSG to immature animals causes destruction of specific regions of brain that lack blood-brain barrier such as arcuate nucleus (ARC) of the hypothalamus. Neonatal MSG exposure caused arcuate nucleus damage, which is associated with impaired secretion of growth hormone and luteinizing hormones (Sasaki et al., 1994). Bloch et al (1984) reported that MSG caused complete loss of growth hormone releasing factor (GRF) and disappearance of GRF-immunoreactive fibers in the median eminence of rats.

Oral administration of glutamate caused an increase in maternal plasma glutamate level (Walker and Lupien, 2000) and cerebral changes were also observed in pregnant rat by glutamate oral consumption (Navarro et al., 2005). Therefore particular attention should be paid to glutamate consumption during pregnancy. MSG was shown to penetrate placental barrier and distribute to embryonic tissue (Yu et al., 1997). MSG feeding at a dose of 5g/day to pregnant rats showed a severe birth weight reduction of the offspring and continuous suppression of growth hormone in serum (Hermanussen et al., 2006). Neuropeptide Y (NPY) in the arcuate nucleus are particularly sensitive to MSG treatment and altered regulation of feeding
in MSG treated rats may be due to the decrease in the NPY contents in the different parts of the hypothalamus. Thus MSG was removed from baby food, because the child’s brain is 4 times more sensitive to MSG than adult brain.

Dietary MSG administration in mice increased total brain weight with simultaneous increase in lipid peroxidation and reduction in catalase activity (Adebayo et al., 2011). Oxidative stress was produced by MSG in different regions or rat brain such as cerebral hemisphere, cerebellum, brain stem and diencephalon with the impairment in mitochondrial function (Singh et al., 2003). A direct correlation between the neurotoxicity and the neurotoxic properties of glutamate has been linked to activation of excitatory amino acid receptors. This stimulation leads to an enzymatic cascade of events ultimately resulting in cell death (Maragakis and Rothestein, 2001).

3.2.3. MSG and cardiotoxicity

Cardiovascular diseases (CVD) remained as one of the main causes of death all over the world and several developing countries like India. Oxidative stress is reported to be responsible for the pathophysiology of many diseases like coronary heart disease, diabetes, cancer etc (Dhalla et al., 2000). Subcutaneous treatment of MSG at dose of 4mg/g body weight and above induced oxidative stress in the cardiac tissue and thereby being responsible for the initiation of coronary heart disease (Singh and Ahluwalia, 2007). Oral ingestion of MSG at same doses to chronic alcoholic adult mice acts as an additional factor for the initiation of atherosclerosis (Singh et al., 2012). Oral exposure of MSG at gestational period caused severe atrophy and destruction of cardiac muscle fibers in the myocardium of its fetal mice (Sakr, 2004). Obesity is an important risk factor for the development of cardiovascular diseases and MSG is used to develop obesity in rats.
Intradermal injection of MSG on neonatal rats causes hypertension with the elevation of prostaglandins and lipoperoxidation in plasma and cyclooxygenase-2 in cardiac tissue (Cunha et al., 2010). Subcutaneous injection of MSG caused hyperglycemia and hyperinsulinaemia with significant decrease of GLUT 4 content in skeletal and cardiac muscles (Papa et al., 1997). MSG injection (4g/kg) to neonatal rats displayed vascular dysfunction (Lobato et al., 2011). Gross weight of rat heart was also increased with continuous and increased use of MSG indicating cardiac muscle hypertrophy (Kingsley et al., 2013). Tokarev and Jezova (2000) suggested that cardiovascular and endocrine alterations in rats treated with MSG may be due to abnormal function of nitric oxide system.

3.2.4. MSG and hepatotoxicity

Liver is the main organ involved in detoxification reactions including the action of a variety of antioxidants, free radical scavenging molecules and enzymes like SOD, catalase, GPx etc. This helps the hepatic cells to maintain a reducing environment and prevent the deleterious effects of ROS on cell membranes and organelles. The continuous ROS production may affect the energetic, respiratory and regenerative pathway in hepatocytes. The subcutaneous ingestion of MSG at a dose of 4g/kg body weight and above increased free radical initiating enzyme, xanthine oxidase, where as the activities of free radical scavenging enzymes like catalase and SOD was decreased in hepatic tissue (Singh and Ahluwalia, 2002). Diniz et al (2004) indicated increased lipid hydroperoxide and decreased SOD in hepatic tissue of MSG treated rats. Mitochondrial dysfunction in the liver also leads to enhanced production of reactive oxygen species (Kowaltowski et al., 2001). Lazarin Mde et al (2011) identified liver mitochondrial dysfunction and oxidative stress in rats treated with MSG at neonatal period.
Oxidative stress is involved in functional disorder, degenerative changes and damages in liver. MSG administration indicated oxidative stress and liver function disorder (Soliman, 2011). Histopathological analysis in liver tissue of neonatal rats ingested with MSG showed non-alcoholic steatosis (Cunha et al., 2010). Steatosis and necrosis in hepatic tissue were observed in rats treated with MSG (Ortiz et al., 2006). Subcutaneous ingestion causes lobular and portal inflammation with lymphocyte infiltration and this resembles human non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) (Nakanishi et al., 2008). The long term effect of MSG after neonatal administration even at a low dose showed hepatocellular damage in mice. Liver of experimental animal showed alterations in histological pattern like disruption of hepatic cords, presence of inflammatory cells around central vein with uneven sizes of nucleus in hepatocytes (Bhattacharya et al., 2011). Vacuolar degeneration of hepatocytes cords, nuclei pyknosis and congestion of blood vessels were observed by intraperitoneal ingestion of MSG (AL-Mosaibih, 2013). Chronic oral intake of low doses of MSG on liver histology resulted in a loss of normal liver architecture with varying degrees of disorganization and apoptotic cell death compared to controls (Onaolapo et al., 2013). Eweka et al (2011) reported dilation of central vein, atrophic and degenerative changes on the liver of rats that received feed incorporated with MSG. Oral treatment also increased liver weight, liver function markers and rate of lipid peroxidation with central venous congestion, degeneration and necrosis in liver (Thomas et al., 2009).

3.2.5. MSG and renal toxicity

The kidney is among the major organs of the body and the consumption of MSG may affect its vital functions and resulting in severe
pathologies. Oral exposure of MSG significantly altered renal functions in rats by compromised urea and creatinine metabolism (Cemaluk et al., 2010). Marked increase in serum creatinine and blood urea nitrogen accompanied by variable histopathological changes in renal tissues like glomerular atrophy, swelling in the endothelium of glomeruli, hydropic degeneration of tubules congestion and hemorrhages between tubules were noticed (Abass and El-Haleem, 2011). MSG causes an adverse effect on the renal function and tissue damage which might be due to oxidative stress induced by MSG. Oxidative stress is recognized as a key role in the pathophysiologic pathways of a wide variety of progressive clinical and experimental renal diseases (Haugen and Nath, 1999). Increase in serum urea, creatinine and lipid peroxidation markers and decreased GSH was induced by MSG. Cloudy swelling in convoluted tubules and congestion and oedema in both cortex and medulla were also observed (Attia et al., 2008). MSG injection in rats causes increase in lipid peroxidation products and degenerative changes like cloudy swelling and hydropic degeneration in convoluted tubules, glomeruli were denser and glomerular cells exhibited hyper-chromatic nuclei (Ortiz et al., 2006). Distortion of the renal cortical structure and cellular necrosis were also associated with kidney in MSG treated rats (Eweka, 2007).

### 3.2.6. MSG and obesity

Monosodium glutamate is widely used to create obese test experimental subjects in laboratory. Oral administration of MSG during pregnancy and development in neonatal rats significantly affects hypothalamic control of various hormones and increases appetite (Fernandez-Tresguerres, 2005). In a study with 36 young men and women weekly test of free intake of experimental foods with 0.6% MSG showed that subjects ate progressively more and faster (Bellisle et al., 1991). A cross
sectional study involving 752 people randomly sampled from three rural villages in China was conducted by He et al (2011). This research data showed that prevalence of overweight was significantly higher in MSG users than in nonusers. The study showed that MSG intake may be associated with increased risk of becoming overweight independent of physical activity and total energy intake in humans. But not all rodent species become obese with MSG ingestion, some just get diabetes. Komeda et al (1980) showed no sign of obesity, but developed a diabetic syndrome in Chinese hamsters. Nagata et al (2006) created obese type 2 (non-insulin dependent) diabetes mellitus mice who were useful as experimental animals for examining diabetes. Diniz et al (2004) showed that MSG added to a standard diet increased food intake and this overfeeding induced metabolic disorder associated with oxidative stress in the absence of obesity.

MSG has been shown in rats to over stimulate the pancreas resulting in hyperinsulinemia. Macho et al (2000) found an increase of plasma insulin in 3 month old rats treated with MSG during the postnatal period and Niijima et al (1990) recognized that even just adding MSG to the mouth of a rat, after 3 minutes can trigger an increase in insulin release. The excess insulin in the blood increases the conversion of glucose into fat. In a double-blind, placebo-controlled crossover study with 18 healthy volunteers (19-28 years old), 10 g MSG was given orally. The MSG enhanced glucose induced insulin secretion in healthy volunteers in a concentration dependent manner (Chevassus et al., 2002)

3.2.7. MSG toxicity related to other tissues

Sakr et al (2004) conducted a study on mice fetus maternally treated with MSG reported that MSG caused narrowing of the lung airways, thickening of the alveolar walls, collapsing of the alveoli, remarkable
damage of type I and type II pneumocytes as well as endothelial cells. Subchronic oral exposure of high dose of MSG leads to the cause of male infertility (Ismail, 2012). MSG may reflect impairment of visual organs. Neonatal treatment of MSG resulted in the dose dependent deficit in brightness discrimination, pattern (shape and texture) discrimination and visual acuity (Praputpittaya and Wililak, 2003). In 2002, Ohguro et al (2002) found that rats fed with 10g of sodium glutamate added to a 100g daily diet for 3 months, showed a significant increase in the amount of glutamic acid in vitreous, lead to the damage of retina which affects retinal function.

The bone length, diameters of femur diaphysis and bone mineral density especially metaphysic region were decreased by MSG treatment and histology revealed the decrease of trabecular bone in the epiphysis and metaphysic regions together with an increase of adipose tissue in the bone marrow (Teranishi et al., 1998). Thus the studies on experimental animals have confirmed toxic effects of MSG in different organs and mainly manifested by increased oxidative stress and cytotoxicity.

3.2.8. MSG and oxidative damage

Excessive formation of free radicals or reactive oxygen species (ROS) produces detrimental effects, including lipid peroxidation of cellular membranes, alteration of lipid-protein interactions, enzyme inactivation and DNA breakage, and it eventually causes cell injury, necrosis or apoptosis (Agarwal et al., 2003). Body has multiple antioxidant systems to protect cellular molecules against oxygen radical-induced damage. Antioxidant defense system protects the tissues from the deleterious effects of reactive oxygen metabolites. These defense mechanisms include antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione transferase (GST) and glutathione peroxidase (GPx) (Lassen et
al., 2008). GPx, GST and catalase act as preventive antioxidants and SOD, a chain-breaking antioxidant, play an important role in protection against the deleterious effect of lipid peroxidation (Ray and Husain, 2002). Reduced glutathione (GSH), a tripeptide thiol is an important non-enzymatic antioxidant as well as a co-factor for various antioxidant enzymes (Kidd, 1997).

Oxidative stress is a consequence of imbalance between ROS production and antioxidant action. Dietary MSG consumption in cerebrum caused elevation in the end product of lipid peroxidation and reduction in the activity of catalase and in cerebellum indicated decreased levels of SOD and GSH (Adebayo, 2011). Increased lipid hydroperoxide and decreased SOD activity were observed in hepatic tissue of rats treated subcutaneously with MSG (Diniz et al., 2004). Significant increase in lipid peroxidation and decrease in the activity of SOD and catalase was noticed in cardiac tissue of MSG treated mice subcutaneously (Singh and Pushpa, 2005). Vinodini et al (2010) noticed an increase in renal tissue lipid peroxidation and decrease in SOD and catalase activities in rats injected MSG intraperitoneally.

Oxidative stress causes cellular deterioration readily in the tissues due to the presence of polyunsaturated highly oxidizable fatty acids in membrane (Cini et al., 1994) which leads to tissue damage and dysfunction. Intraperitoneal treatment of MSG in rats increased degeneration of neurons associated with significantly increased lipid peroxidation and decreased glutathione, catalase and SOD (Ramanathan et al., 2007). Ortiz et al (2006) noticed increments in the concentration of ALT, AST and degenerative changes in liver and kidney with increased lipid peroxidation products by intraperitoneal treatment. Necrotic focal lesions were also showed in cardiac muscle with oxidative stress and increase in CPK and AST (Baky et al.,
2009). MSG administered intraperitoneally induced significant increase of MDA and xanthine oxidase with decreased activity of catalase which leads to thymocyte apoptosis (Pavlovic et al., 2007). These studies indicated that oxidative stress contributed to MSG associated impairment in physiological functions and tissue injury in the liver, heart and other organs.

3.3. Functions of \(\alpha\)-tocopherol

3.3.1. Antioxidant therapy of \(\alpha\)-tocopherol

It is believed that reduction in antioxidant capacity is one of the major factors in several chronic diseases (Lefer and Granger, 2000; Tak et al., 2000). In recent years, antioxidant treatment has attained lot of importance because of their potential as prophylactic and therapeutic agents in many diseases. Importance of antioxidant treatment in the protection of organisms or tissues or non-living systems against oxidative stress has become evident. Antioxidants have been reported to play a significant role in protection against free radicals induced lipid peroxidation (Steenvoorden and Henegouwen, 1999). It scavenges ROS and may prevent oxidative damage to important biological macromolecules such as DNA, proteins and lipids.

Antioxidant vitamins play an important role in the regulation of physiological and pathological processes by enhancing the immune system, modifying carcinogen metabolism, altering cell proliferation, stimulating the repair of carcinogen induced DNA damage and elicit free radical scavenging properties (Chaudiere and Ferrar-Iiou, 1999). Vitamin E is the most important lipophilic antioxidant that resides mainly in the cell membranes and thus helps to maintain membrane stability (Altuntas and Delibas, 2002). The most important antioxidant of this group is \(\alpha\)-tocopherol. \(\alpha\)-Tocopherol is the primary membrane bound lipid-soluble, chain-breaking antioxidant
that protects cell membranes against lipid peroxidation (Gulec et al., 2006). Studies carried out with α-tocopherol have shown that it may effectively minimize lipid peroxidation in biological systems by preventing the propagation of free radical reaction in the lipid components of membranes, vacuoles and plasma lipoproteins (Kalender et al., 2004). During the antioxidant reaction, oxidation of the chromanol moiety of α-tocopherol occurs. The main oxidation product was described as α-tocopheryl quinone resulting from the reaction of tocopheroxyl radical with a peroxyl radical (Liebler, 1993).

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\begin{align*}
\text{α-Tocopherol} & \xrightarrow{\text{LOO}'} \text{Tocopherol peroxide} \\
& \xrightarrow{\text{LOOH}} \text{α-Tocopherol quinone}
\end{align*}
\]

α-Tocopheryl quinone can be reduced to α-tocopheryl hydroquinone to α-tocopheronic acid and its lactone by NADPH-dependent microsomal and mitochondrial enzymes and excreted through urine (Hayashi et al., 1992).
3.3.2. Non-antioxidant property of \( \alpha \)-tocopherol

Apart from the protective effect against low density lipoprotein (LDL) oxidation and other free radical induced oxidative damage, the nonantioxidant action of \( \alpha \)-tocopherol appears to be particular relevance at cellular level. Inhibition of smooth muscle proliferation, preservation of endothelial function, inhibition of monocyte endothelial adhesion, inhibition of monocyte reactive oxygen species and cytokine release, and inhibition of platelet adhesion and aggregation are some examples of the cellular events that are regulated by \( \alpha \)-tocopherol.

Antiproliferative effect of \( \alpha \)-tocopherol was established in rat smooth muscle cells and human aorta smooth muscle cells by inhibiting protein kinase C. This may act by inhibiting protein kinase C phosphorylation or by stimulating protein kinase C dephosphorylation (Azzi et al., 1995). Dephosphorylation of protein kinase C occurs via protein phosphatase PP\(_2\)A,
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which is activated by the treatment with α-tocopherol (Ricciarelli et al., 1998). Protein kinase C is responsible for the release of reactive oxygen species and lipid peroxidation. α-Tocopherol attenuates human platelet aggregation through its incorporation into the platelet and inhibition of platelet protein kinase C stimulation. Moreover, α-tocopherol inhibits aggregation at physiologically relevant platelet levels and its effects on protein kinase C are also relevant to in vivo α-tocopherol supplementation. These properties of α-tocopherol could partially explain its beneficial effect on coronary artery disease (Freedman et al., 1996).

α-Tocopherol inhibited the production of chemokines and inflammatory cytokines, in addition to inhibition of adhesion of human aortic endothelial cells to monocytes by reducing expression of adhesion molecules when cells were activated with an inflammatory cytokine. These mediators are actively involved in the pathogenesis of atherosclerosis. Thus their inhibition by α-tocopherol may contribute to reduction in risk of CVD (Wu et al., 1999). In addition to its effects in decreasing LDL oxidation, α-tocopherol supplementation resulted in an intracellular antiatherogenic effect. α-Tocopherol decreases the ability of the monocytes to release ROS and significantly reduces lipid oxidation by inhibition of protein kinase C activity. Its supplementation also causes suppression of a potentially atherogenic cytokine, interleukin-1β and inhibition of monocyte endothelial cell adhesion (Devaraj et al., 1996).

3.3.3. Role of α-tocopherol on tissues

α-Tocopherol supplementation has shown beneficial effects for numerous diseases, particularly neurological disorders, atherosclerosis, ischemic heart disease and development of different types of cancer. Both the neurological syndromes and the adenoma were regressed after the treatment
with α-tocopherol (Benomar et al., 1999). Free radical formation and subsequent lipid peroxidation are important factors in the pathogenesis of ischemic brain injury. α-Tocopherol in the rodent diet provides substantial protection against focal cerebral ischemic damage compared with rats consumed α-tocopherol deficient food (Van der Worp et al., 1998). α-Tocopherol supplementation prevented the decrease in glucocorticosteroid receptors in the hippocampus and the increase in corticosterone secretion caused by oxidative stress induced hyperoxia (Kobayashi et al., 2009). α-Tocopherol treatments have been reported to protect the liver in several models of liver injury by inhibiting oxidative damage. α-Tocopherol therapy is associated with a significant improvement in nonalcoholic steatohepatitis (Sanyal et al., 2010). Oral administration of α-tocopherol with carbon tetrachloride caused a significant elevation of liver α-tocopherol level and ameliorated liver necrosis in rats (Iida et al., 2009).

α-Tocopherol may act as a cardioprotectant against oxidatively induced injury to heart tissue and prevent chronic diseases such as cardiovascular diseases and atherosclerosis. It significantly improved the reduction of blood viscosity, blood pressure and hypertrophy in rats (Costa et al., 2005). Marked reduction in myocardial infarction was observed in patients with coronary artery disease (Rapola et al., 1997). Dietary supplementation with α-tocopherol in hyperlipidemic rabbit reduced LDL oxidation and post mortem examination of aortic tissue revealed a significant (32%) inhibition of surface area lesion involvement in the arch region (Williams et al., 1992). It is also an effective chemopreventive agent against ferric nitritotriacetate induced renal oxidative stress (Iqbal et al., 1998). Koya et al (1997) reported that prevention of glomerular dysfunction in diabetic rats can be achieved by treatment with α-tocopherol. α-Tocopherol is effective therapy of certain
of cataract. Orally supplemented α-tocopherol protects against ultraviolet radiation induced cataract associated with protection of GSH depletion (Wang et al., 2011). It has beneficial effects on glycemic control in experimental diabetes. α-Tocopherol was reported to decrease hyperglycemia induced protein kinase C activation which is responsible for many pathological changes observed in diabetes (Bursell and King, 1999).

Many studies were continued to express its importance in maintaining health and preventing chronic disease. Argyriou et al (2006) showed that α-tocopherol acetate supplementation in chemotherapy patients protected them from paclitaxel-induced peripheral nerve damage. Supplementation with α-tocopherol in smokers was associated with a minor decrease in the incidence of angina pectoris in men without known previous coronary heart disease. α-Tocopherol has been shown to decrease C-reactive protein levels, in patients with cardiovascular disease and in those with risk factors for cardiovascular disease (Murphy et al., 2004). Thus its antioxidant and anti-inflammatory activities could have beneficial effects on several diseases.