International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Review Article **CODEN: IJPNL6**

THE BENEFICIAL ROLE OF NATURAL POLYPHENOLIC COMPOUNDS AS ANTIOXIDANTS IN ALZHEIMER DISEASE: BIOLOGICAL ACTIONS AND MECHANISMS UNDERPINNING THEIR BENEFICIAL EFFECTS

Bisht Neha*, Kumar Arun, Kothiyal Preeti

Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Sciences, Dehradun, Uttarakhand, 248001

***Corresponding author e-mail:** nhbisht@gmail.com

ABSTRACT

Oxidative stress has been strongly implicated in the pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD). Mitochondrion is a key player that produces reactive oxygen species (ROS). Mitochondrial dysfunction found in AD patients may amplify the generation of ROS and oxidative stress. Increased ROS can cause damage to protein, lipid and nucleic acids. In recent years, antioxidants- especially those of dietary origin have been suggested as possible agents useful for the prevention and treatment of AD. Continuing research highlights the dynamic capacity of natural polyphenolic compounds to exhibit their antioxidant effect by a number of potential mechanisms. The free radical scavenging, in which the polyphenols can break the free radical chain reaction, as well as suppression of the free radical formation by regulation of enzyme activity or chelating metal ions involved in free radical production. Thus, the antioxidant properties certainly contribute to their neuroprotective effect. This article reviews the role of oxidative stress and the contribution of free radicals in the development of AD, and also discusses antioxidant effects of natural polyphenolic compounds such as green tea catechins, curcumin, resveratrol and their intracellular targets focusing on neuroprotective strategies for AD.

Keywords: Alzheimer disease, Oxidative stress, Mitochondria, Reactive oxygen species, Natural Polyphenolic compounds, Antioxidant, Green tea catechins, Curcumin, Resveratrol, Neuroprotection.

INTRODUCTION

Alzheimer's disease (AD) is the major dementing disorder, takes away the very essence of a person-their sense of self. Clinical manifestations of AD are severe impairments in thought, learning, memory and language abilities. The disease is pathologically characterized by two microscopic features, namely extracellular "amyloid plaques," consisting of amorphous extracellular deposits of a β –amyloid protein (known as Aβ) and intraneuronal "neurofibrillary tangles," comprising filaments of a phosphorylated form of microtubule-associated protein (Tau). AD affects approximately 10% of the population older than 65 years of age [1]. It has millions of victims worldwide and the world prevalence is assumed to increase to 1 in 85 people in 2050 [2]. Multiple factors involved in AD pathogenesis have been identified, but specific mechanisms underlying the neurodegeneration in AD still remains to be elucidated. There is overwhelming evidence that brain tissue in AD patients is exposed to oxidative stress during the course of the disease. Since oxidative stress is characterized by an imbalance in radical production of reactive oxygen species (ROS) and antioxidative defense, both are considered to have a major role in the process of age-related neurodegeneration and cognitive decline [3].

Decreased levels of plasma antioxidants and total plasma antioxidant activity were observed in AD patients [4, 5, 6]. Besides, there is rise in byproducts of lipid and protein oxidation in transgenic mouse models for AD [7, 8]. Significantly, these elevated markers for oxidative stress pave the way for amyloid deposition and neurofibrillary tangles, suggesting

oxidative stress as an early event involved in AD pathogenesis [9, 7]. Most of cellular reactive oxygen species (ROS) are produced by the mitochondria [10]. Mitochondrial dysfunction is pragmatic in AD brain, which exacerbates release of ROS [11]. Particularly, consistent deficiency in mitochondrial intermembrane-space protiens such as cytochrome c (Cyt c) oxidase was reported in AD brains [12]. Mitochondrial antioxidant coenzyme Q (CoQ) showed antioxidant and neuroprotective properties both in vitro and in vivo [13]. Another source of ROS is amyloid-beta peptide itself. The peptide generates free radicals in the presence of metal ions [14]. Thus, this situation will bring huge economic and personal burdens to current and future generations. In order to tackle the problem, effective therapeutic and preventive interventions should be developed urgently.

Natural polyphenols have pleiotropic activity including antioxidant properties. Above all, natural polyphenols appreciably attenuated cognitive impairments and amyloid-beta burden [7,15]. Epidemiological studies proposed that dietary habit and intake of antioxidant can affect the prevalence of neurodegenerative diseases such as AD [16]. Although multiple drugs for AD are now available, none of them are able to slow down, halt, or cure the neurodegeneration in AD. In relation to pharmacological therapy for AD, natural polyphenols might be a potential strategy for prevention or treatment of AD. In this review we will discuss antioxidant properties of different natural polyphenolic compounds such as green tea catechins, curcumin, resveratrol compounds and their intracellular targets focusing on neuroprotective strategies for AD.

MITOCONDRIA -Main source of free radical generation:

There is overwhelming evidence that mitochondrial dysfunction plays a crucial role in brain ageing as well as in the pathogenesis of neurodegenerative diseases, including AD [17]. Mitochondria are highly complex, dynamic, network-forming organelles, involved in different metabolic pathways, e.g. energy transformation, tricarboxylic acid cycle (TCA), amino acid metabolism and urea cycle [18]. Mitochondria consist of inner and outer membranes composed of phospholipid bilayers and proteins. The inner mitochondrial membrane harbours the proteins of the electron transfer system (ETS) that are responsible for oxidative phosphorylation. The mitochondrial oxidative phosphorylation (OXPHOS) system is the final biochemical pathway that produces energy in form of ATP by consuming oxygen. Electrons are transferred through the complexes of the mitochondrial respiratory chain and simultaneously, an electrochemical proton gradient is built across the inner mitochondrial membrane, creating the proton-motive force that drives the generation of ATP [19, 20].

The outcome of diminution in mitochondrial content or lowered ETS is general limitation of cellular energy production. Dysfunction of single complexes of the respiratory system are often accompanied by deleterious side effects, such as loss of mitochondrial membrane potential (MMP) and subsequently decreased ATP levels, but also production of reactive oxygen species (ROS) [21]. The schematic overview of mitochondrial ROS production is depicted in Figure 1.

Apart from ROS enzymatically produced by NADPH oxidases, cytochrome P450-dependent oxygenases and xanthine dehydrogenases, mitochondria are regarded as the prime site of ROS production within cells. The ETS persistently generates ROS, which are usually kept in balance by various defence mechanisms, i.e. antioxidative molecules (e.g. glutathione (GSH) or vitamin E) and antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase), as long as ROS levels are in the physiological range. In addition, slight uncoupling of the ETC, e.g.by uncoupling proteins, may also reduce ROS production. Functional failure of this system can lead to deleterious effects, which may amplify the outcomes of mitochondrial dysfunction [22].

Thus, mitochondria play a principal role in producing energy, but also as major source of ROS. Therefore, attempts to augment mitochondrial function should be accompanied by equal attempts to limit deleterious ROS generation. Mitochondria act as signal-integrating organelles in the onset of the intrinsic apoptotic pathway. Mitochondrial outer membrane permeabilization and permeability transition result both in the release of pro-apoptotic proteins, which in turn activate caspases and cell death mechanisms further downstream [23,24]. Dysfunction of single mitochondrial enzyme complexes, ROS production, mitochondrial permeability transition pore opening (mPTP), elevated apoptosis, as well as structural alterations and a diminished mitochondrial content, play a role in brain ageing, and are believed to be crucial for the onset and progression of neurodegenerative diseases, such as AD [25-27].

OXIDATIVE STRESS AND AD

There is considerable evidence that oxidative stress is an early and critical event in the pathogenesis of AD [28-30]. For instance, isoprostanes, derived from free radical oxidation of docosahexaenoic acid, are increased in brain cortex [30-33]. Interestingly, F-2-isoprostanes, prostaglandin-like compounds derived from free radical-catalyzed peroxidation of arachidonic acid, are also elevated in the plasma, urine, and cerebrospinal fluid of patients with AD [34]. Moreover, the level of lipid peroxidation in the AD brain is dependent on the apoE genotype and level [32-36]. Increased levels of HNE and acrolein in different brain areas were also described in the hippocampus/parahippocampal gyrus and cerebellum in subjects with mild cognitive impairment as compared to control subjects [37]. Both byproducts of lipid peroxidation are known to be neurotoxic and can affect neuronal functions [38-39]. Protein carbonyls and 3-nitrotyrosine, which are the markers of protein oxidation, are also elevated in AD [40-41]. Protein carbonyls are present in both tangle- and non-tangle-bearing neurons [42], in the frontal lobe or hippocampus [43,44]. Nitrotyrosine and dityrosine cross-linked proteins are elevated 8- and 3-fold, respectively, in the hippocampus and neocortical regions of AD brain as compared to age-matched controls [45]. By using redox proteomics, specific elevation of oxidatively modified proteins has been identified in the hippocampus and the parietal lobe of the AD brain, such as R-enolase, heat shock cognate 71 (HSC 71), creatine kinase BB (CK BB), glutamine synthase (GS), and ubiquitin carboxy-terminal hydrolase L-1 (UCHL-1) [46-47]. Mitochondrial DNA had approximately 10-fold higher levels of oxidized bases than nuclear DNA. These data are consistent with higher levels of oxidative stress in mitochondria. 8-OHdG, a widely studied biomarker of DNA damage, was approximately 10-fold higher than other oxidized base adducts in both AD and control subjects. Further evidence of oxidative stress in AD is the modification of antioxidant activity in the brain. For instance, we have demonstrated that catalase activity is higher and glutathione level is lower in AD [32]. The glutathione transferase activity, which is responsible for HNE clearance, is decreased in several regions of the AD brain including the hippocampus [48]. The Aβ peptide, which is responsible for senile plaque formation in AD brain, has been reported to generate hydrogen peroxide from molecular oxygen through electron transfer interactions involving bound redox-active metal ions [49-52]. Aβ has high affinity for both copper and zinc [53], and both Aβ and APP display strong copper reductase activity, generating Cu+ from Cu2+. The original amyloid cascade hypothesis claimed that the fibrilized form of Aβ (fAβ) was the main component of senile plaques [54]. Because many processes of AD were not explained by fAβ, there is still no clear consensus on the precise nature of the toxic form of Aβ, but recent attention has focused on early protein assemblies [protofibrils, soluble oligomers, Aβ- derived diffusible ligands (ADDLs), or globular neurotoxins]. Therefore, the effects of Aβ could depend on its aggregation state [55]. On the basis of these findings, it has been proposed that Aβ acts through a biphasic neurotoxic mechanism that is conformation dependent. Besides its ability to induce oxidative stress, Aβ could also lead to activation of some redox-sensitive transcription factors such as NF-κB, extracellular protein regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 of mitogenactivated protein kinases (MAPKs) pathways.[56]. These pathways are potential targets of natural polyphenolic compounds from fruits and vegetables. Altogether, these studies and others demonstrate that oxidative stress is involved in the pathophysiology of AD; therefore, intake of antioxidants may be beneficial in the prevention of AD.

NATURAL POLYPHENOLIC COMPOUNDS: Structure, absorption and antioxidant activity

Polyphenols are a group of naturally occurring phytochemicals which are present in high amounts in fruits, vegetables, and natural products and are characterised by the presence of multiple hydroxyl groups on aromatic rings. These compounds are divided into two main categories: the flavonoids and nonflavonoids, based on the number of phenol rings and the way in which these rings interact. Among the natural polyphenols, flavonoids are the largest family and more than 2000 individual flavonoids have been isolated and identified. Classification and structure of polyphenols are presented in Figure 2. In general, they have hydroxyl, methoxyl, and/or glycosyl groups in their structures. The linked sugar is often glucose or rhamnose. The number of sugar is commonly one, but could be two or three and there are several positions of substitutions on the polyphenol. Glycosylation influences chemical, physical, and biological properties of the flavonoids and their absorption by the small intestine [57, 58]. For instance, if the phenolic compounds contain a sugar molecule, such as glucose, galactose, they will be absorbed through the small intestine by the cytosolic β-glucosides/lactase phlorizin hydroxylase. The absorption is also related to the specificity of carriers [58]. Those containing rhamnose cannot be absorbed through the small intestine. They are

degraded by the action of rhamnosidases produced by the colonic microflora. Acetylated flavonoids such as epicatechin and [57] epigallocatechin are absorbed without deconjugation and hydrolysis [58]. In the colon, each component's resistance to degradation also depends on its hydroxylation degree. Absence of the hydroxyl group in the molecule prevents its degradation while hydroxylation, such as 5,7-dihydroxylation and/or 4′- hydroxylation, enhances its tendency to degradation. Their antioxidant activity is associated with the number of hydroxyl groups and the most active possess from 3 to 6 hydroxyl groups. Hydroxylation in the C3 position seems to be detrimental for their antioxidant potency [59] and for the iron chelating [60]. In contrast, glycosylation of flavonoids reduces their ability to scavenge radicals [61]. Although, the data available on phenolics bioavailability are still limited, it has been described that the consumption of foods or beverages which are rich in polyphenols can increase the antioxidant levels in serum [62]. These results suggest that the consumption of polyphenolic compounds could have beneficial effect against oxidative-induced damages.

BIOLOGICAL ACTIONS AND MECHANISMS UNDERPINNING THE ANTIOXIDANT EFFECTIVENESS OF DIFFERENT NATURAL POLYPHENOLIC COMPOUNDS

In the following paragraphs, we will review some mechanisms and targets of the most consumed polyphenols highlighting their beneficial antioxidant effects.

A. Green Tea Catechins. Green tea is rich in flavonoids (30% of dry weight of a leaf) (*107*), with the major compounds being epigallocatechin-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC), and (-)-epicatechin-3-gallate (ECG) (Figure 2). Their antioxidants and free radical scavenging activities mainly contribute to their beneficial effects. The antioxidant potencies of these flavonoids is in the order of EGCG > ECG > EGC > EC [63]. Their powerful free radical scavenging activities relate to the gallate moiety esterified at position 3 of the C ring, the catechol group (3,4-dihydroxyl groups) on the B ring, and the hydroxyl group at positions 5 and 7 on the A ring. The galloylated catechins are more active antioxidants due to their higher phospholipid/water partition coefficients [64]. Furthermore, the free radical scavenger property increases with the number of hydroxyl groups the catechin possesses. For instance, EGCG and EC possess eight and five hydroxyl groups, respectively, and the antioxidant activity of EGCG is higher than that of EC. Moreover, their antioxidant abilities are higher than those of R-tocopherol or vitamins C and E.

It was demonstrated in a human model of BBB the pharmacokinetics of catechin and epicatechin that could cross the BBB in a time-dependent manner [65]. EGCG penetrates the BBB at a low rate and the bioavailability after oral administration was approximately 5% [66]. It should be noted that high doses of EGCG were associated to death in rat hippocampal neuron through the mitochondrial-dependent pathway [67] and also that at high concentrations it has a prooxidant/proapoptotic activity [68]. Catechins can exert their antioxidant activity through various mechanisms, one being by chelating metal ions such as copper (II) and iron (II), and therefore prevent the generation of potentially damaging free radicals. Catechins may also exert their antioxidant effects through the ultrarapid electron transfer to ROS-induced radical sites on DNA or by forming stable semiquinone free radicals. Accordingly, Levites et al. have demonstrated that prolonged administration of EGCG to mice induced a reduction in holo-APP levels in the hippocampus [69]. Moreover, after the oxidation of catechins by free radicals, a dimerized product is formed with an increased iron-chelating potential and ability to scavenge superoxide anions. The prevention of oxidative-induced damage by catechins is very effective as catechins can inhibit the ROS-induced damage by a wide variety of initiators including hydrogen peroxide, iron, paraquat, or radiolysis. Antioxidant properties of catechins were also observed in different in vivo models. For instance, rats receiving green tea extracts orally exhibited higher levels of antioxidant enzymes such as glutathione peroxidase and reductase, superoxide dismutase, and catalase [70]. These effects on antioxidant levels were also investigated in human. It has been evidenced that after 42 days of the consumption of 2 cups of green tea, containing approximately 250 mg of total catechins, a significant increase in plasma total antioxidants was observed, whereas the plasma peroxide level decreased [71]. Catechins also decreased oxidative stress by inhibiting the activity of xanthine oxidase [72], a ROS-generating system. Catechins can also protect lipids from oxidation in the liver, serum, and brain [70]. For instance, it has been demonstrated that catechins could protect against lipid peroxidation induced by 6-hydroxydopamine, hydrogen peroxide, and iron [73]. These antioxidant effects are observed in vitro with concentrations ranging from 1 to 50 μM. However, with higher concentrations (100-500 μM) and in the presence of copper (II) or iron (III), EGCG exacerbated oxidative stress, cytotoxicity, and DNA damage induced by hydrogen peroxide [74-76]. However, considering that Aβ can induce mitochondrial dysfunction, it was also demonstrated

that EGCG treatment is able to restore mitochondrial respiratory rates, altered mitochondrial membrane potential, and ROS production or ATP levels [77]. Overwhelming evidences from increasing publications reports the ability of EGCG to modulate multiple biological pathways. Indeed, it has been shown to regulate several biomedically important targets and to exert neuroprotection in many ways. In addition to the antiinflammatory properties, EGCG exerts protection by regulating different survival genes and controlling numerous antioxidant protective enzymes [78]. Advanced glycation end-products are involved in the neuronal injury associated with several neurodegenerative disorders. EGCG increased SOD activity and protected against glycation end products induced neurotoxicity by decreasing ROS and MDA [79]. Over the past decade, intense focus has been placed on the processes of APP proteolysis and Aβ metabolism as possible targets for AD therapy. Various synthetic and naturally occurring compounds have been analyzed for their efficacy in the modulation of these pathological events. Among them, EGCG is able to regulate the proteolytic processing of APP both in vitro and in vivo [80]. Green tea catechins, especially ECGC, also reduced the activation of a number of signaling pathways such as p38 and JNK of MAPKs [81] and induce the phosphorylation of protein kinase C [82-86] and phosphatidylinositol-3-kinase (PI-3 kinase)-Akt [87], and these modulations may mediate some of the neuroprotective effects of EGCG. Intraperitoneal administration of EGCG attenuated brain Aβ neuropathology and improved cognitive function in a transgenic AD mouse model [88]. In particular, EGCG inhibits the fibrillogenesis of Aβ through the binding to the natively unfolded polypeptides and preventing their conversion into toxic aggregates intermediates [89]. A further study revealed that through the inhibition of extracellular signal-regulated protein kinase (ERK) and NF-kβ pathways, the treatment with EGCG in mutant AD mice improved memory function enhancing the α-secretase function and reducing the activities of β-and γ-secretases with subsequently decrease in the levels of Aβ [90]. The total concentration of epicatechin and metabolites was estimated to be about 0.4 nmol/g of brain tissue, but the investigators state that the concentrations were too low to quantify accurately [91]. Some in vivo studies have shown that 0.33% of EGCG administration can reach the brain [92] and that frequent consumption of green tea enables the body to maintain a high level of catechins. EGCG has a wide array of biological effects and it is a promising compound which has been proven efficacious in AD animal models.

B. Resveratrol. Resveratrol is a non-flavonoid polyphenolic found in grapes, red wine, and berries. The concentration of resveratrol in red wine is in the range of 1.5-3 mg/L [93]. There are two isomeric forms of resveratrol, the biologically inactive *cis*-resveratrol and the most biologically active *trans*resveratrol (*trans*-3, 4, 5-trihydroxystilbene). Interestingly, several epidemiological studies indicate an inverse correlation of wine consumption and incidence of AD [94-96]. Many studies reported that the central nervous system (CNS) is one of the resveratrol's targets. This compound is able to pass the BBB [97] but the bioavailability is low because it is quickly metabolized into glucuronide and sulfate conjugates. After oral administration of resveratrol, it is rapidly metabolized (within 2 h, with a peak in <30 min) to glucuronide acid and sulfate conjugates in the liver and intestinal cells [93]. More than 90% of total resveratrol, given as pure aglycone, circulates in the plasma in the conjugated form, and glucuronidation predominates the metabolism of resveratrol. These results indicate that the circulating forms of resveratrol are predominantly modified metabolites and not the original aglycone. Therefore, the antioxidant and anti-inflammatory activities and the effect on cell signaling of the original aglycone compound seem to be considerably diminished due to its extensive and rapid metabolism. However, the biological activities of the circulating form and their functions remain to be determined, particularly their implication in neuroprotective effects. Indeed, resveratrol appears to reach the brain as was shown in one rat study exposing 250 g males to 50 mg/kg [3H]- *trans*-resveratrol by oral gavage [98]. The concentrations found in the whole brain after 2 and 18 h were about 0.03 and 0.01%, respectively, of the original dose, suggesting that distribution to the brain is minimal. In several in vitro studies, resveratrol has been recognized for its powerful antioxidant properties. At the cellular level, resveratrol could protect PC12 cells against Aβ-induced toxicity and prevent the accumulation of intracellular ROS [99]. Resveratrol can also protect SH-SY5Y neuroblastoma cells and primary hippocampal neuronal/glial cells from H2O2, NO, and Aβ-induced toxicity [86,100–102]. Interestingly, resveratrol exhibited its neuroprotective effects when it was used in pretreatment, in cotreatment, or in post-treatment. Regarding the radical-scavenging activity, structural studies and theoretical calculations demonstrate that in the antioxidant reaction of resveratrol the hydroxyl group at the 4'- position is much easier to subject to oxidation than other hydroxyl groups [103]. Intraperitoneally administration of resveratrol exerts neuroprotective properties upregulating several endogenous antioxidant enzymes such as SOD and

CAT [104]. Prolonged administration of resveratrol improves colchicine-induced cognitive impairment, reduces MDA and nitrite levels, and restores depleted GSH [105]. However, it is important to emphasize that resveratrol can exhibit prooxidant activities in the presence of transition metal ions such as Cu2+, leading to oxidative breakage of cellular DNA [106]. At the cellular level, resveratrol could protect PC12 cells against Aβ-induced toxicity and prevent the accumulation of intracellular ROS [107]. The NF-κB pathway is also a target of resveratrol. Since NF-kβ signaling activation plays an important role in the neurodegeneration, another link between AD and neuroprotective activity of resveratrol is its ability to reduce the expression of genes modulated by NF-kβ, such as iNOS, prostaglandin E2 (PGE2), as well as cathepsin and NO [108]. Moreover, resveratrol was found to activate AMPK and reduce cerebral Aβ levels and deposition in the mice cortex [109]. Using electron microscopy and biochemical methods, it was reported that resveratrol prevents the abnormal expression of peroxiredoxins, but also mitochondrial structural abnormalities in a mouse model of primary AD and Aβ-incubated mouse neuroblastoma cells [110].

C. Curcumin. Curcumin is a major chemical component of turmeric (*Curcuma longa*) and is used as a spice to give a specific flavor and yellow color to Indian curries and in food preservation. Interestingly, the prevalence of AD in people aged 70-79 years in India is 4.4-fold less than in the United States [111]. Turmeric is derived from the rhizome, or root, of the plant. There is substantial in vitro evidence indicating that curcumin has potential antioxidant, anti-inflammatory, and antiamyloid activities [112]. For instance, curcumin could inhibit lipid peroxidation [113], activate glutathione *S*-transferase [114], or induce heme oxygenase-1 (HO-1) [115]. HO-1 induction occurs through the antioxidant response element (ARE) [116]. Curcumin could also chelate the redox active metals iron (Fe2+) and copper (Cu2+) [117]. Curcumin is also a suppressor of iNOS and a potent inhibitor of NF-κB and AP-1 activation [118-120]. The structural features of curcumin that can contribute to the antioxidant activity are the phenolic and the methoxy group on the phenyl ring and the 1, 3-diketone system. Moreover, the antioxidant activity of curcumin increases when the phenolic group with a methoxy group is at the ortho position [121, 122]. The orthomethoxy group can form an intramolecular hydrogen bond with the phenolic hydrogen, making the H-atom abstraction from the orthomethoxyphenols surprisingly easy [123]. The H abstraction from these groups is responsible for the remarkable antioxidant activity of curcumin. Moreover, the reactions of curcumin with free radicals produce a phenoxyl radicals and a carbon-centered radical at the methylene CH_2 group [124]. Additional experimental reports supporting the antioxidant property of curcumin were provided by Lim and coworkers using an AD transgenic mouse model which demonstrated that curcumin reduces brain levels of oxidized proteins containing carbonyl groups [125]. *In vivo*, the antioxidant activity of curcumin may be mediated through antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Curcumin has been shown to serve as a Michael acceptor, reacting with glutathione (GSH) and thioredoxin [126]. Depletion in cellular GSH levels is an important measure of oxidative stress, which is implicated in the pathogenesis of AD. A study on postmortem brain of AD patients has revealed decreased levels of GSH in some area of the brain [127]. Also, the GSH levels were low in the red blood cells of male AD subjects, confirming an association between GSH and AD [128].Noteworthy, there are some studies reporting the restorative effect of curcumin on GSH depletion. For instance, it was demonstrated that curcumin is able to replenish the intracellular GSH pool by changing the nuclear content and/or activation of specific transcription factors such as 12-tetradecanoate 13-acetate (TPA-) responsive elements (TRE) and electrophilic response element (EpRE) [129]. Moreover, curcumin enhances the antioxidant enzyme activities of SOD and CAT in the striatum and mid-brain of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine- (MPTP-) injectedmice [130]. Taking into account that *in vivo* evidence showed that peroxynitrite induces Alzheimer-like tau hyperphosphorylation, nitration, and accumulation [131], it was reported that curcumin mediates the direct detoxification of reactive nitrogen species such as peroxynitrite, thus exerting an antioxidant activity [132]. Furthermore, the pieces of evidence to support a role of oxidative stress in AD brain with elevated levels of lipid peroxidation increasing [133]. Oxidative damage of lipids generates toxic aldehydes such as 4-hydroxy-2-nonenal (4- HNE) and malondialdehyde (MDA) leading to cell death. Important cytopathologies in AD brain include a decreased activity of all electron transport chain complexes [134]. In particular, complex IV decreases in AD, which causes release of oxidants during mitochondrial electron transport [135]. It was reported that excessive Aβ binds to regulatory heme, triggering functional heme deficiency and causing the key cytopathologies of AD. Additionally, Aβ-heme complex is a peroxidase and curcumin significantly inhibits the peroxidase activity of Aβ-heme [136]. The Tg2576 mouse model of AD exhibits impaired

mitochondria metabolic activity in the spinal cord and curcumin partially suppressed the mitochondrial impairment reversing motor function deficits [137]. Interestingly, curcumin treatment abrogates lipid peroxidation protecting mitochondria from oxidative damage and apoptosis in cortical neurons [138].

Moreover, curcumin has been also shown in PC12 cells to provide protection against the deleterious effects of 4-HNE on mitochondrial redox metabolism, cytochrome c release, and DNA fragmentation [139]. The increased level of oxidative stress in AD is reflected by the increased brain content of iron (Fe2+) and copper (Cu2+) both capable of stimulating free radical formation. In addition to its properties of quencher, curcumin showed to be able to bind Cu2+ and Fe2+ ions [140]. Since these redox-active metals ions can intensify Aβ aggregation, curcumin may prevent this aspect of AD pathogenesis. Other reports suggested that curcumin regulates Fe2+ metabolism by modulation of Fe2+ regulatory proteins; therefore it may act as an iron chelator [141]. Significantly, *in vivo* studies reported that another divalent metal cation such as zinc (Zn2+) is highly enriched in Aβ plaques [142,143] but its role in the amyloid landscape is still poorly understood and under investigation. However, even though curcumin more readily binds to the redoxactive metals such as Cu2+ and Fe2+, it was also reported relatively weak affinity for the redox-inactive metal Zn2+ which might exert a small protective effect against Aβ by inducing metal chelation [140].

CONCLUSION

Overall, oxidative stress is at the forefront of Alzheimer disease (AD) research. In living cells, when the formation of intracellular reactive oxygen species exceeds the cells' antioxidant capacity, oxidative stress can arise, resulting in damage to cellular macromolecules such as proteins, lipids and DNA. When ROS is not removed efficiently, it would be detrimental to neurons exacerbating neurodegeneration. Epidemiological studies suggest that dietary habit and intake of antioxidants can affect the incidence of neurodegenerative disease such as AD. Although multiple drugs for AD are now available, none of them are able to slow down, halt, or cure the neurodegeneration in AD. Thus, natural polyphenolic compounds having potent antioxidant activity can serve to be the promising candidates in effectively treating and/or preventing AD. This would greatly benefit millions of people and help in warding off the dementia epidemic that is upon us.

ACKNOWLEDGEMENT

We wish to express our profound gratitude and appreciation to the teachers of Shri guru ram rai institute of technology and sciences for providing their guidance and support at each and every step.

.

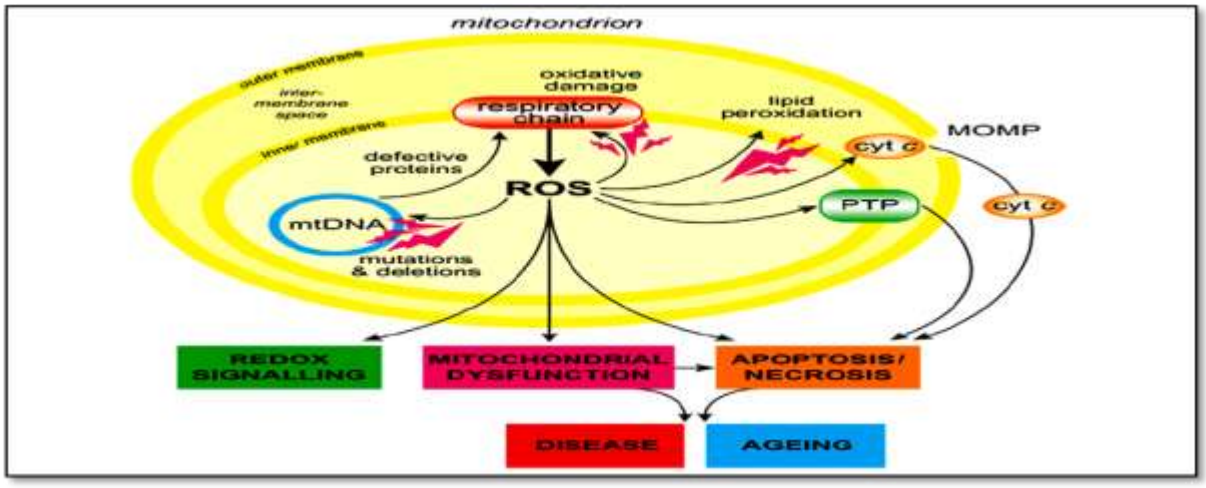

Figure 1 Overview of mitocondrial ROS production

ROS production by mitocondria can lead to oxidative damage to mitocondrial protiens, membranes and DNA (mDna) impairing the ability of mitocondria to synthesize ATP and to carry out their wide range of metabolic functions, including the tricaboxylic acid cycle, fatty acid oxidation, the urea cycle, amino acid metabolism, haem synthesis and iron- sulfur- centre assembly, that are central to the normal operation of most cells. Mitochondrial oxidative damage can also increase the tendency of mitocondria to release intermembrane- space protiens such as cytochrome c (cyt c) to the cytosol by mitocondrial outer membrane permeabilization (MOMP) and thereby activate the cells apoptotic machinery. In addition, mitochondrial ROS production leads to induction of the mitocondrial permeability transition pore (PTP), rendering the inner membrane permeable to small molecules in situations such as ischemia/reperfusion injury. Consequently, it is unsuprising that mitocondrial oxidative damage contibutes to a wide range of pathologies, in addition, mitocondrial ROS may act as modulatable redox signals, reversibly affecting the activity of a wide range of functions in the mitocondria, cytosol and nucleus [21].

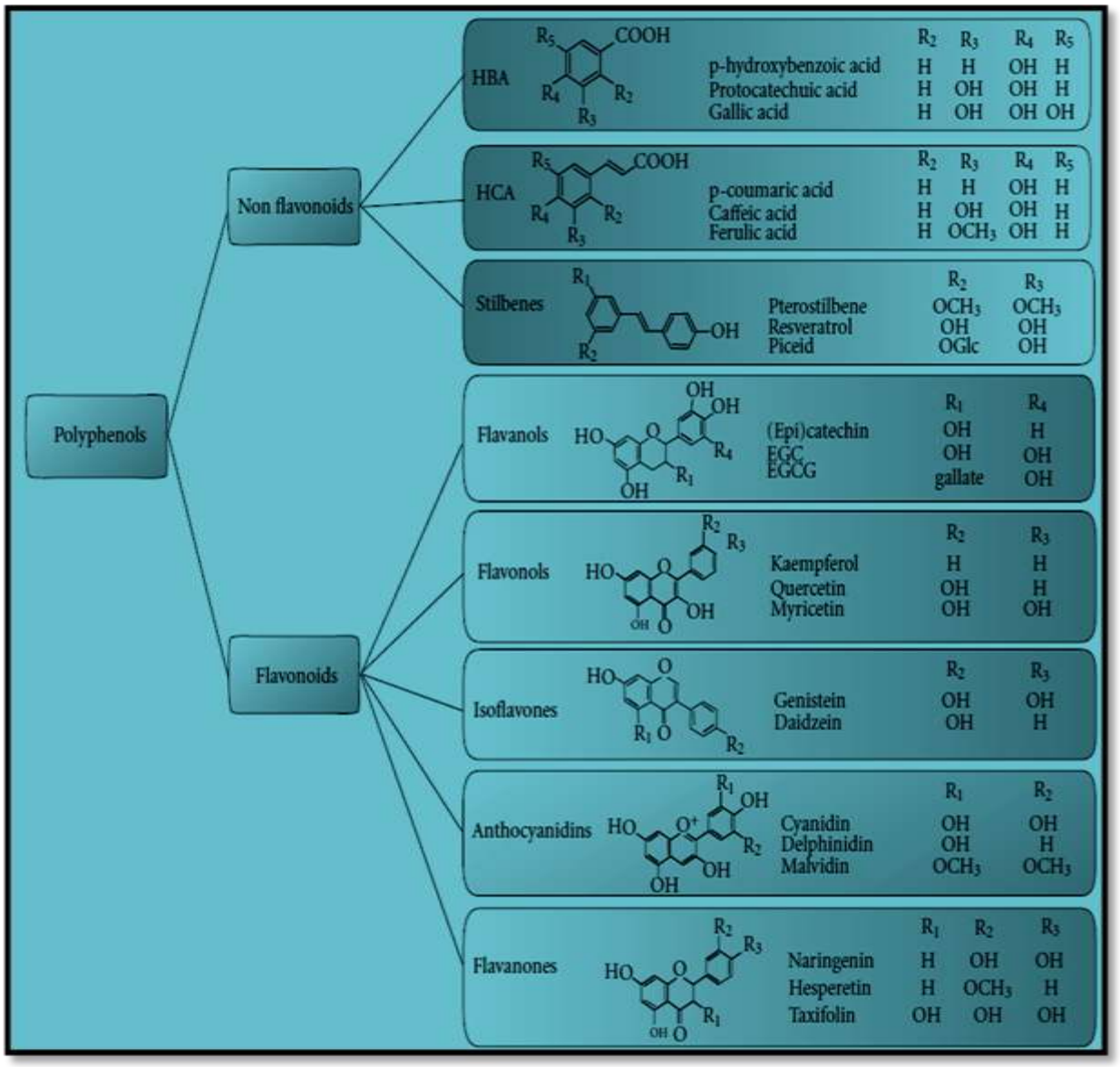

Figure 2: Classification and structures of polyphenols

Polyphenols are a group of naturally occurring phytochemicals which are present in high amounts in fruits, vegetables, and natural products and are characterised by the presence of multiple hydroxyl groups on aromatic rings. These compounds are divided into two main categories, the flavonoids and non flavonoids, based on the number of phenol rings and the way in which these rings interact. For the flavonoid group, the major differences between the individual groups arise from the hydroxylation pattern of the ring-structure, the degree of saturation of the C-ring, and the substitution of the 3-position. HBAs, hydroxybenzoic acids; HCAs, hydroxycinnamic acids [144].

REFERENCES

[1] Carrasquillo MM et al. Nat Genet, 2009; 41:192-198.
[2] Brookmeyer R et al. Alzheimers Dement, 2007; 3:186-191.
[3] Lovell MA, Markesbery WR. J Neurosci Res, 2007; 85:3036-3040.
[4] Mecocci P et al. Arch Neurol, 2002; 59:794-798.
[5] Minghetti L et al. J Neuroinflammat, 2006; 3:4.

[6] Rinaldi P et al. Neurobiol Aging, 2003; 24:915-919.
[7] Resende R et al. Free Radic Biol Med, 2008; 44:2051-2057.
[8] Shan X, Lin C L. Neurobiol Aging, 2006; 27:657-662.
[9] Dumont M, Beal MF. Free Radic Biol Med 2011; 51:1014-1026.
[10] Kowaltowski AJ et al. Free Radic Biol Med, 2009; 47:333-343.
[11] Muller WE et al. Mol Neurobiol, 2010; 41:159-171.
[12] Fukui H et al. Proc Natl Acad Sci U.S.A. 2007; 104:14163-14168.
[13] Wadsworth TL et al. J Alzheimers Dis, 2008; 14:225-234.
[14] Butterfield DA et al. Free Radic Biol Med, 2007; 43:658-677.
[15] Ramassamy C. Eur J Pharmacol, 2006; 545:51-64.
[16] Luchsinger JA, Mayeux R. Lancet Neurol, 2004; 3:579-587.
[17] Muller WE et al. Mol Neurobiol, 2010; 41(2-3):159-171.
[18] Nijtmans LGJ, Ugallde C, van den Heuvel LP, Smeitink JAM. Function and dysfunction of the oxidative phosphorylation system. In: Koehler C, Bauer MF (Eds) Mitochondrial function and biogenetics. Springer Inc., Heidelberg: 2004, pp. 149-167.
[19] Brand MD et al. Free Radic Biol Med, 2004; 37(6):755-767.
[20] Smeitink J et al. Nat Rev Genet, 2001; 2(5):342-352.
[21] Murphy MP. Biochem J, 2009; 417(1):1-13.
[22] Harper ME et al. Acta Physiol Scand, 2004; 182(4):321-331.
[23] Martinou JC. Dev Cell, 2011; 21(1):92-101.
[24] Rasola A et al. FEBS Lett, 2010; 584(10):1989-1996.
[25] Napoli E et al. Antioxid Redox Signal, 2006; 8(3-4):506-516.
[26] Bilsland LG et al. J Neurochem, 2008; 107(5):1271-1283.
[27] Casley CS et al. Neurobiol Dis, 2002; 10(3):258-267.
[28] Chai CK.. Am J Alzheimers Dis. Other Dementia, 2007; 22:37-41.
[29] Markesbery WR. Arch Neurol, 1999; 56:1449-1452.
[30] Christen Y. Am J Clin Nutr, 2000; 71:621S-629S.
[31] Nourooz-Zadeh J et al. J Neurochem 1999; 72:734-740.
[32] Ramassamy C et al. Free Radic Biol Med 1999; 27:544-553.
[33] Ramassamy C et al. Neurobiol Dis, 2000; 7:23-37.
[34] Montine KS et al. J Neuropathol Exp Neurol, 1998; 57:415-425.
[35] Pratico D et al. Ann Neurol, 2000; 48:809-812.
[36] Montine KS et al. Am J Pathol, 1997; 150:437-443.
[37] Williams TI, Lynn BC, Markesbery WR, Lovell MA. Neurobiol Aging, 2006; 27:1094-1099.
[38] Lovell MA, Xie C, Markesbery WR. Neurobiol Aging, 2001; 22:187-194.
[39] Qin Z, Hu D, Han S, Reaney SH, Di Monte DA, Fink AL. J Biol Chem, 2007; 282:5862-5870.
[40] Sultana R, Perluigi M, Butterfield DA. Antioxid Redox Signal, 2006; 8:2021-2037.
[41] Butterfield DA. Brain Res, 2004; 1000:1-7.
[42] Smith MA et al. Nature, 1996; 382:120-121.
[43] Pamplona R et al. J Biol Chem, 2005; 280:21522-21530.
[44] Aksenov MY et al. Neuroscience, 2001; 103:373-383.
[45] Hensley K et al. J Neurosci, 1998; 18:8126-8132.
[46] Castegna A et al. J Neurochem, 2002; 82:1524-1532.
[47] Castegna A et al. Free Radic Biol Med, 2002; 33:562-571.
[48] Lovell MA, Xie C, Markesbery WR. Neurology, 1998; 51:1562-1566.
[49] Huang X et al. Biochemistry, 1999; 38:7609-7616.
[50] Butterfield DA. Free Radic Res, 2002; 36:1307-1313.
[51] Behl C, Davis JB, Lesley R, Schubert D. Cell, 1994; 77:817-827.
[52]Tabner BJ et al. J Biol Chem, 2005; 280:35789-35792.
[53] Wang L, Colon W. Biochemistry, 2007; 46:5562-5569.
[54] Hardy JA, Higgins GA. Science, 1992; 256: 184-185.
[55] Tamagno E et al. Free Radical Biol Med 2006; 41:202-212.
[56] Tamagno E et al. Free Radical Biol Med, 2003; *35*:45-58.
[57] Rice-Evans CA, Miller NJ, Paganga G. Free Radic Biol Med, 1996; 20:933–956.
[58] Scalbert A, Williamson G. J Nutr, 2000; 130:2073S-2085S.
[59] Huguet AI, Manez S, Alcaraz MJ. Z Naturforsch [C], 1990; 45:19–24.

[60] Van Acker SA et al. Free Radic Biol Med, 1996; 20: 331-342.
[61] Fukumoto LR, Mazza G. J Agric Food Chem, 2000; 48:3597-3604.
[62] Frankel EN, Waterhouse AL, Kinsella JE. Lancet, 1993; 341:1103-1104.
[63] Guo Q, Zhao B, Li M, Shen S, Xin W. Biochem Biophys ,Acta 1996; 1304: 210-222.
[64] Caturla N et al. Free Radical Biol Med, 2003; 34:648-662.
[65] Faria A, Pestana D, Teixeira D et al. Food and Function, 2011; 2(1):39-44.
[66] Lin LC, Wang MN, Tseng TY, Sung JS, Tsai TH. J of Agric and Food Chem, 2007; 55(4):1517-1524.
[67] Yin ST, Tang ML, Deng HM et al. Naunyn-Schmiedeberg's Archives of Pharmacol, 2009; 379(6):551-564.
[68] Wang JH, Cheng J, Li CR, Ye M, Ma Z, Cai F. Int J Mol Sci, 2011; 12(1):742-754.
[69] Levites Y, Amit T, Mandel S, Youdim M. B. FASEB J, 2003, 17, 952-954.
[70] Skrzydlewska E, Augustyniak A, Michalak K. Alcohol, 2005; 37:89-98.
[71] Erba D, Riso P, Criscuoli F, Testolin G. Nutrition, 2003; 19:545-548.
[72] Bickford PC et al. Brain Res, 2000, 866:211-217.
[73] Guo S, Bezard E, Zhao B. Free Radical Biol Med, 2005; 39:682-695.
[74] Elbling L et al. FASEB J, 2005; 19:807-809.
[75] Furukawa A, Oikawa S, Murata M, Hiraku Y, Kawanishi S Biochem Pharmacol, 2003; 66:1769-1778.
[76] Oikawa S, Furukawaa A, Asada H, Hirakawa K, Kawanishi S. Free Radical Res, 2003; 37:881-890.
[77] Dragicevic N, Smith A, Lin X et al. J Alz Disease, 2011; 26(3):507-521.
[78] Mandel S, Youdim MBH. Free Radical Biol and Med, 2004; 37(3):304-317.
[79] Lee SJ, Lee KW. Biol and Pharmaceutical Bulletin, 2007; 30(8):1369-1373.
[80] Levites Y, Amit T, Youdim MB, Mandel S. J Biol Chem, 2002; 277:30574-30580.
[81] Kim S J et al. J Nutr Biochem, 2007; 32(10):1720-1725.
[82] Levites Y, Amit T, Mandel S, Youdim MB. FASEB J, 2003; 17:952-954.
[83] Bastianetto S, Yao Z X, Papadopoulos V, Quirion R. Eur J Neurosci, 2006; 23:55-64.
[84] Rezai-Zadeh K et al. J Neurosci, 2005; 25:8807-8814.
[85] Obregon DF et al. J Biol Chem. 2006; 281:16419-16427.
[86] Bastianetto S, Brouillette J, Quirion R. Neurochem Res, 2007; 18 (9):587-596.
[87] Koh SH et al. Neurotoxicol, 2004; 25:793-802.
[88] Rezai-Zadeh K, Arendash GW, Hou H et al. Brain Res, 2008; 1214:177–187.
[89] Ehrnhoefer DE, Bieschke J, Boeddrich A et al. Nature Struct and Mol Biol, 2008; 15(6):558-566.
[90] Lee JW, Lee YK, Ban JO et al. J Nutrition, 2009; 139(10):1987–1993.
[91] Abd El Mohsen MM et al. Free Radic Biol Med, 2002; 33:1693-1702.
[92] Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Carcinogenesis, 1998; 19: 1771-1776.
[93] De la Lastra CA, Villegas I. Mol. Nutr. Food Res. 2005; 49:405-430.
[94] Lindsay J et al. Am J Epidemiol, 2002; 156:445-453.
[95] Orgogozo JM et al. ReV Neurol (Paris), 1997; 153:185-192.
[96] Truelsen T, Thudium D, Gronbaek M. Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study. Neurology, 2002; 59:1313-1319.
[97] Baur JA, Pearson KJ, Price NL et al. Nature, 2006; 444(7117):337-342.
[98] Abd El-Mohsen M et al. Br J Nutr, 2006; 96:62-70.
[99] Jang JH, Surh YJ. Mutat Res, 2001; 496:181-190.
[100] Savaskan E et al. Gerontology, 2003; 49:380-383.
[101] Han YS, Zheng WH, Bastianetto S, Chabot JG, Quirion R. Br J Pharmacol, 2004; 141:997-1005.
[102] Bastianetto S, Zheng WH, Quirion R. Br J Pharmacol, 2000; 131:711-720.
[103] Caruso F, Tanski J, Villegas-Estrada A, Rossi M. J of Agric and Food Chem, 2004; 52(24):7279-7285.
[104] Mokni M, Elkahoui S, Limam F, Amri M, Aouani E. Effect of resveratrol on antioxidant enzyme activities in the brain of healthy rat. Neurochemical Research, 2007; 3(6):981-987.
[105] Kumar A, Naidu PS, Seghal N, Padi SSV. Pharmacol, 2007; 79(1):17–26.
[106] de la Lastra CA, Villegas I. Biochem Society Transactions, 2007; 35(5):1156-1160.
[107] Jang JH, Surh YJ. Mutat Res, 2001; 496:181-190.
[108] Kim YA, Lim SY, Rhee SH et al. Int J Mol Med, 2006;17(6)-1069-1075.
[109] Karuppagounder SS et al. Neurochem Int, 2009; 54(2):111-118.
[110] Manczak M, Mao P, Calkins MJ et al. J of Alzheimer's Disease, 2010; 20(2):S609-S631.
[111] Ganguli M et al. Arch Neurol, 2000, 57, 824–830.
[112] Menon V P, Sudheer AR. AdV Exp Med Biol, 2007; 595:105-125.
[113] Wei QY, Chen WF, Zhou B, Yang L, Liu Z L. Biochem Biophys Acta, 2006; 1760:70-77.

[114] Nishinaka T et al. Toxicol Lett, 2007; 170:238–247.
[115] Motterlini R, Foresti R, Bassi R, Green C J. Free Radic Biol Med, 2000; 28:1303-1312.
[116] Hayes JD, McMahon M. Cancer Lett, 2001; 174:103-113.
[117] Baum L, Ng A. J Alzheimer's Dis. 2004; 6:367-377.
[118] Bengmark S. JPEN-J Parenter Enteral Nutr, 2006; 30:45-51.
[119] Singh S, Aggarwal BB. J Biol Chem, 1995; 270:24995-25000.
[120] Shishodia S, Singh T, Chaturvedi MM. AdV Exp Med Biol, 2007; 595:127-148.
[121] Itokawa H, Shi Q, Akiyama T, Morris-Natschke SL, Lee KH. Chinese Med, 2008; 3(11):1-22.
[122] Motterlini R, Foresti R, Bassi R, Green CJ. Free Radic Biol and Med, 2000; 28(8):1303-1312.
[123] Chen WF, Deng SL, Zhou B, Yang L, Liu ZL. Free Radic Biol and Med; 50(3):484.
[124] Barzegar A, Moosavi-Movahedi AA. PLoS ONE, 2011:6(10), Article ID e26012.
[125] Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. J of Neuroscience, 2001; 21(21):8370- 8377.
[126] Adams BK, Cai J, Armstrong J et al. Anti-Cancer Drugs, 2005; 16(3):263-275.
[127] Gu M, Owen AD, Toffa SEK et al. J of the Neurol Sci, 1998; 158(1):24-29.
[128] Liu H, Harrell LE, Shenvi S, Hagen T, Liu RM. J of Neurosci Research, 2005; 7(6):861-867.
[129] Dickinson DA, Iles KE, Zhang H, Blank V, Forman HJ. FASEB Journal, 2003; 17(3): 473-475.
[130] Rajeswari A. Europ Review for Medic and Pharmacol Sci, 2006; 10(4): 157-161.
[131] Zhang YJ, Xu YF, Liu YH et al. FASEB J, 2006; 20(9):1431-1442.
[132] Iwunze MO, McEwan D. Cellular and Molecular Biol, 2004; 50(6):749-752.
[133] Smith DG, Cappai R, Barnham KJ. Biochimica et Biophysica Acta, 2007; 1768(8):1976-1990.
[134] Parker WD Jr, Parks J, Filley CM, Kleinschmidt BK- DeMasters. Neurology, 1994; 44(6):1090-1096.
[135] Mutisya EM, Bowling AC, Beal MF. J of Neurochem, 1994; 63(6):2179-2184.
[136] Atamna H, Boyle K. PNAS, 2006; 103(9):3381-3386.
[137] Seo JS, Leem YH, Lee KW, Kim SW, Lee JK, and Han PL. J of Alz Disease, 2010; 21(1):263-276.
[138] Zhu YG, Chen XC, Chen ZZ et al. Acta Pharmacologica Sinica, 2004; 25(12):606-1612.
[139] Raza H, John A, Brown EM, Benedict S, Kambal A.Toxicol and Applied Pharmacol, 2008; 226(2):161-168.
[140] Baum L, A. Ng. J of Alz Disease, 2004; 6(4):367-377.
[141] Jiao IV Y, Wilkinson J, Christine Pietsch E et al. Free Radic Biol and Med, 2006; 40(7):1152-1160.
[142] Bush AI, Pettingell WH, Multhaup G et al. Science, 1994; 265(5177):1464-1467.
[143] Stoltenberg M, Bush AI, Bach G et al. Neuroscience, 2007; 150(2):357-369.
[144] Vauzour D. Oxidative Med and Cellular Longevity, 2012; 1-16.