Antioxidants as a preventive therapeutic option for age related neurodegenerative diseases

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Advances in our understanding for neurodegenerative mechanisms have increased significantly in last few decades. But still no novel disease modifying therapy has been developed which could prevent the disease progression and drew our attention towards the development of new alternative therapy. The major obstacle for the development of disease therapy is incomplete knowledge about neurodegenerative mechanisms. Due to the insufficient information about neurodegenerative mechanisms no standard diagnostic tests for the detection of neurodegenerative disease could be develop to date, causes delayed diagnosis and disease worsening. So far the exploratory reports and clinical data have suggested the involvement of oxidative stress, mitochondrial impairment and apoptosis as major neurodegenerative mechanisms. Investigations have elicited that once initiated the degeneration of neurons could not be arrested therefore in the scarcity of curative therapy we should approach for the preventive neurodegenerative therapy. Since oxidative stress has noteworthy involvement in neuronal death solely, and in connection to other death pathways therefore, antioxidants as preventive therapeutics might provide beneficial effects in age related neurodegenerative diseases. With this hypothesis in this review we are discussing about the use of antioxidants as a preventive treatment of neurodegenerative diseases. Such therapies may work in the preventive phase or in curative phase. However, in the symptomatic patient there may be severe damage to the neuronal networks to restore their respective functionality. As functional neuronal impairment and neuronal death are the key factors responsible for particular neurodegenerative disease therefore it is apparent that prevention of neuronal death at early stage may provide a huge clinical benefit.

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1. Neurodegenerative diseases: an overview –

Neurodegenerative disease term illustrate a range of conditions in which primarily neurons get affected or die. Neurons are the building blocks of the central and peripheral nervous system. Neurons could not reproduce or replace themselves with age therefore, when they get damaged or die they cannot be replaced and lead to specific neurodegenerative disease. Few evidences for the presence of stem cells are reported[1] but still it is not understood whether damaged neuron could regenerate or not. The Parkinson’s, Alzheimer’s, and Huntington’s diseases are the most prevalent age related neurodegenerative diseases of central nervous system involving death of specific neuronal population. The treatment of these neurodegenerative diseases might involve the re-supplementation of specific neuronal population with the help of stem cells but researchers and clinicians did not get noticeable success in this approach yet. Millions of people each year are getting affected by these neurodegenerative diseases and the incidences are increasing further significantly with the extended life expectancy. It has been reported by World Health Organisation (2006) that the number of older people of more than 65 years age are expected to increase to approximately 1 billion in 2030 worldwide. Developing countries like India and China will see the largest increase in numbers of aged persons. Therefore the percentage of aged population in developing countries would increase from 59% to 71% worldwide[2]. Since occurrence of most of the neurodegenerative
diseases is strongly associated with increasing age therefore it is anticipated that such critical situation will pose huge challenges to public health in all countries[13] would make significant impact on economy. Exhaustive research is undergoing in this field but still the enigma behind such progressive neuronal death is not well understood. Over the last several decades the studies have showed that the progression of neurodegenerative diseases involve the decreased antioxidant levels, impaired mitochondrial activity, increased oxidative damage protein, lipid peroxidation, protein modification, DNA damage and apoptosis[4-9]. Oxidative protein modifications occur at a low and persistent level in diverse cells and tissues and accumulate in aging and neurodegenerative diseases[10-19]. Since no naturally occurring experimental models for neurodegenerative diseases are available, the investigations to explore the disease mechanisms have been done in neurotoxin induced or genetically altered experimental models. Studies on these experimental models have a remarkable impact on target identification for disease treatment and enabled pre-clinical studies of novel molecules and therapies in these experimental models. Such experimental models provide opportunity to the clinical testing of a number of novel therapeutics and accelerate the efforts to develop therapies aimed at modifying the underlying neurodegenerative mechanisms in disease processes. Despite the huge progress in identifying the key factor of many neurodegenerative diseases only limited progress has been achieved yet, with respect to the treatment of patients suffering from neurodegenerative diseases. Most of the available treatments for the neurodegenerative diseases have been developed on the basis of understanding of neurochemical and impairment in neuronal network and physiology. Like for Alzheimer’s disease (AD) the available drugs have been developed on the basis of knowledge that the cholinergic neurons get damaged during disease pathology. Similarly the most successful drug levodopa for Parkinson’s treatment was developed on the basis of knowledge that in Parkinson’s disease (PD) the dopamine levels decreased due to the death of dopaminergic neurons. It should be notice that these therapies have only symptomatic effects and could not modify the diseases progression. However, the available drugs are better than nothing to provide the symptomatic relief and make the life easy of patients, up to some extent for limited duration but still we need to develop more effective therapeutics for such age related neurodegenerative diseases.

2. Oxidative stress –

Oxidative stress is a metabolic state in which excessive levels of highly reactive unstable oxygen compounds increases in the body due to unavailability of physiological antioxidants. These unstable oxygen compounds are referred to as free radicals or reactive oxygen species (ROS). ROS are highly reactive, chemically unstable and damaging to the tissues of which, they come in contact including nucleic acids, proteins and other essential building block of cell. ROS comprises nitric oxide (NO), superoxide anions hydrogen peroxide (H₂O₂), hydroxyl radical and monoxide radicals (OH·, NO·) etc. Under physiological conditions these ROS are neutralized by antioxidants enzymes of the body. Oxidative stress occurs when the level of ROS augmented significantly in comparison to physiological level, either due to pathological events or due to insufficient levels of antioxidants. ROS may be generated by endogenous or exogenous sources. Exogenous source include pesticides, solvents, alkylphenols, type-2 alkenes, metals, polycyclic aromatic hydrocarbons, dioxin, environmental pollutants, radiation, anesthetics and high oxygen environment. Endogenous ROS generated continuously under physiological conditions as a by product of aerobic metabolism. Mitochondrion is a major site of oxygen utilization in the cell and most of the ROS generated during mitochondrial oxidative phosphorylation.

2 (a) Oxidative stress and mitochondrial dysfunction in neurodegeneration

Mitochondria generate most of the cell’s energy in the form of ATP which is used as chemical energy for all the energy dependent physiological processes. It is also involved in other tasks such as signalling, cell cycle, cell death and cellular differentiation. Synthesis of ATP in mitochondrion makes it a prime target for oxidative damage which induces further mitochondrial dysfunction and ROS generation depending on the physiological imbalance. Oxygen takes part in glucose breakdown through mitochondrial oxidative phosphorylation and generates energy in the form of ATP. Mitochondrion has its own machinery for the synthesis of ATP which is essential for the cell-existence. Since neurons have high energy requirement therefore any impairment in this machinery lead to impaired ATP synthesis through perturbed oxidative phosphorylation which causes neuronal death. Neurons are hypersensitive towards the oxidative stress due to their anatomic and metabolic factors. Non-neuronal cells of brain which constitutes approximately 90% cells of the brain also require high consumption of oxygen and glucose to generate continuous ATP pool in vivo for normal functioning of brain[20]. With age the surveillance of these antioxidants decreases and thus probability of ROS generation increases significantly[21]. Along with generation of ROS the nitrogen species also generate in brain along with significant contribution of glial NADPH oxidase[22, 23]. The brain also contains high level of polyunsaturated fatty acids which are the target for the initiation of lipid peroxidation. Lipid peroxidation could further propagate the formation of reactive lipid species such as hydroxynonalenal and malonaldehyde which in turn can covalently modify the protein molecules. In most of the age related brain diseases such modifications in protein molecules have been reported[24-28].

Reports have suggested that mitochondrial dysfunction leads to oxidative stress, altered calcium homeostasis, damage or deletions of mitochondrial DNA, and consequent energy crisis which ultimately lead to neuronal death[29]. Other regulator of apoptosis also include the mitochondrial proteins viz. cell death receptors, p53, apoptosis-inducing factor (AIF), second
mitochondrial derived activator of caspases (Smac), the inhibitor of apoptosis protein (IAP) family and HtrA2/Omi[30-37]. Wang et al (1998)[38] have showed that mitochondrion integrates death signals engaged by bcl-2 family proteins and releases pro-apoptotic molecules residing in the mitochondrial intermembrane space. Activation of such resident caspase led to internucleosomal cleavage of DNA[39]. The endoplasmic reticulum, which is mainly responsible for the calcium homeostasis in cell acts in connection to mitochondria to modulate the mitochondrial pore formation and release of cytochrome-c from mitochondria[40-42]. Bcl-2 family proteins could regulate the apoptosis by modulating the release of cytochrome-c from mitochondria into the cytosol[43]. Release of cytochrome-c from mitochondria occurs through the formation of membrane channels comprising bax and the voltage dependent anion channel[44]. Rao et al (2014)[45] have reviewed the recent progress on mitochondrial transition pore formation as a potential therapeutic target for neurodegenerative diseases. Released cytochrome-c then triggers the assembly of the cytoplasmic apoptosome[46]. The apoptosome is a protein complex of apoptotic protease activating factor 1 [Apaf1], cytochrome c, and procaspase-9[47]. Apaf-1 is cytosolic protein which binds to cytochrome-c and forms an oligomeric apoptosome[48-50]. The apoptosome binds to procaspase-9 to activate it which in turn cleaves the procaspase-3 to form the caspase-3. The cytochrome-c, Apaf-1 and caspase-9 mediated apoptotic pathway is mitochondria mediated and termed as intrinsic apoptotic pathway[44]. The intrinsic mitochondria-mediated pathway is controlled by Bcl-2 family proteins[51]. However, the extrinsic apoptotic pathway involve death receptor pathway through the activation of death receptors, leading to the formation of the death-inducing signalling complex and caspase-8 activation which in turn activate the caspase-3. Caspase-8 cleaves the proapoptotic protein bid which led to its translocation, oligomerization insertion of bax into the mitochondrial membrane and formation of mitochondrial pore. ER stress and DNA damage mediated caspase-2 activation also contribute to initiation and progression of apoptosis. In normal cells this apoptotic mechanism could be antagonized with protein family of apoptosis inhibitory proteins (IAPs). Caspase-3 and 9 are the major target of the IAPs by their reversible direct interaction with caspases to block the substrate cleavage[44]. Mitochondrial protein Smac and DIABLO could inactivate the antiapoptotic action of IAPs and termed as proapoptotic proteins. Smac / DIABLO released into the cytosol to inactivate the anti-apoptotic actions of IAPs that inhibit the caspases. These are 23 kDa small proteins which release into the cytosol from the intermembrane space of mitochondria. One more protein Omi / High-temperature requirement protein A2 (HtrA2) could also act as proapoptotic protein and could inhibit the antiapoptotic activity of IAPs.

2 (b) Oxidative stress and DNA damage in neurodegeneration

ROS are very reactive to different elementary molecules of cell and could initiate cascade of cell death pathway. Oxidative over-load in microenvironment causes oxidation of lipids, proteins and DNA, and generates many byproducts such as peroxides, alcohols, aldehydes, ketones and cholesterol oxide. Augmented ROS generation could directly cause the generation of oxidized bases, DNA intra-strand adducts, DNA strand breaks and DNA protein crosslinks. ROS can modify the bases, induce inter and intra cross links, create strand break and promote DNA-protein crosslinks. Among all the DNA bases, guanine has the least oxidation potential, because of which it is frequently attacked by different reactive species. Modification of guanine can result a excess of lethal lesions that may arise due to its nitration, halogenation, alkylation, etc[52], which can induce mutagenesis and affects the DNA replication and transcription. An estimate of DNA damaging events in cell is range from $10^4$-$10^6$ per day, therefore requiring about $10^{16}$-$10^{18}$ repair events per day[53]. These repair machineries involve base reversal (BR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MR), double strand break repair (DSBR) etc.[53, 54] but still the exact mechanism of DNA repair is not well understood. However, with the increased ROS generation the physiological processes get imbalance and cause irreversible damage to the fundamental molecules of cell and consequent cell death. Mitochondrial DNA is more vulnerable to damage by ROS than nuclear DNA due to its limited DNA repair[55, 56]. DNA mutation could further augment the physiological insult after ROS mediated modification[57, 58].

In addition to DNA modification the ROS mediated protein modification also lead to loss of enzymes involved in regulation of oxidative balance in cellular system viz. glutamine synthase, superoxide dismutase. It has been showed that ROS mediated dysregulation of intracellular calcium signaling pathways affected the cell severely. Altered calcium homeostasis could further initiate the excitotoxic effects which lead to activation of glutamate receptors and neuronal apoptosis under diseased condition[59-62].

3. Antioxidant System

Human body has different antioxidant system to counteract oxidative stress by producing antioxidants, either naturally generated in situ (endogenous antioxidants metabolic antioxidants), or externally supplied through dietary supplements (exogenous antioxidants/nutrient antioxidants). The role of antioxidants is to neutralize the augmented ROS to protect the cell against their adverse effects thus to contribute in the diseases prevention.

The antioxidant system could work in two ways whether they can break the chain of death mechanisms or they could prevent the initiation of such cell death mechanisms. If the antioxidant interfere with the chain of ROS mediated death mechanism then they steals an electron from the free radical and forms a second radical. Second radical exerts same effect on another molecule and continues until the formation of non-reactive product by a chain breaking antioxidants like vitamin C, E, carotenoids etc or
it simply convert into non-oxidative stable molecule. For the use of antioxidant in preventive mode it should neutralize the ROS at initiation phase thus stabilize the transition metal radical. Reports have showed that deficiency of nutrient antioxidant is also one of the causes of number of chronic age related neurodegenerative diseases\(^{63-69}\) implicating their probable significant use as preventive therapeutics.

3 (a) Endogenous antioxidants in neurodegenerative diseases

Age-related oxidative changes are most prominent in nonproliferating cells, such as neurons and cardiac myocytes due to inability of cell division \(^{70-73}\). The synthesis of endogenous antioxidants depends on the availability of cellular pool of antioxidants. The major endogenous antioxidant enzymes which are directly involved in the neutralization of ROS and RNS are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GRx). SOD, the first line of defense against free radicals, catalyzes the dismutation of superoxide anion radical (O\(_2\)•\(^{-}\)) into hydrogen peroxide (H\(_2\)O\(_2\)) by reduction. The oxidant formed (H\(_2\)O\(_2\)) is transformed into water and oxygen (O\(_2\)) by catalase (CAT) or glutathione peroxidase (GPx). The GPx enzyme removes H\(_2\)O\(_2\) by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG). When an antioxidant destroys a free radical, this antioxidant itself becomes oxidized therefore the supplementation of endogenous antioxidants is required exogenously or endogenously. Antioxidant enzyme glutathione reductase regenerates GSH from GSSG, with NADPH as a source of reducing power. Besides hydrogen peroxide, GPx also reduces lipid or nonlipid hydroperoxides while oxidizing GSH\(^{74-77}\). Other endogenous antioxidants involve proteins and low molecular-weight scavengers, like uric acid, coenzyme Q and lipoic acid. Reports have showed that GSH is the major cellular antioxidant against ROS induced adverse effects, and its levels are closely correlated with cell survival\(^{78,79}\). GSH synthesized from glutamate, cysteine and glycine. Cysteine is the rate limiting precursor of GSH synthesis. Reports have showed the dynamic astrocytes and neuron coupling for the supply of GSH to neurons specifically for the supply of cysteine\(^{80-82}\). On the cellular level, neurons are considered to contain less glutathione than astroglial cells\(^{83}\). In vitro studies have showed that in neuronal culture the GSH concentration range from 1 nmol/mg protein\(^{84}\) to 40 nmol/mg protein\(^{85}\). It has also been reported the brain region specific GSH content in astrocytes and neurons\(^{86}\). It has been reported that astrocytes are responsible for the supply of rate limiting factor, cysteine, for the synthesis of GSH in neurons\(^{82}\) displaying an important astrocytes-neurons metabolic coupling and should be studied further.

3 (b) Exogenous antioxidants in neurodegenerative diseases

To date a number of dietary antioxidants have been used in the clinical treatments. Since the disease mechanism for most of the brain diseases is not known therefore the preventive therapy depending on the susceptible candidate for the particular brain disease could be beneficial to patients. However, the dosage and the detailed information regarding their intake should be prescribed by clinicians and if any information is scarce, it should be studied further. It has also been reported that both antioxidative and oxidative stress leading to the physiological antioxidative imbalance which could be damaging for the organism and contribute in aging processes. The beneficial effects of exogenous antioxidants have been reported in basic and clinical findings\(^{87,88}\). However, the controversial clinical reports are also available showed that antioxidant supplements did not offer beneficial effects in neurological diseases. Few report have showed that overuse of antioxidants could cause the mortality\(^{89-91}\). It has been reported that long term vitamin E supplementation could cause the adverse effects\(^{92}\). Ristow et al (2009)\(^{93}\) have showed that antioxidants could prevent the health promoting effects of physical exercise in humans. Under physiological conditions body maintain the appropriate levels of each antioxidant with rationale of cellular homeostasis but if supplemented exogenously, the overdose could interrupt that balance and cause the adverse effects. It also depends on the intake of type of antioxidant, if person is taking only one type of antioxidant than that could also interfere with the antioxidant system of body and may cause adverse effects. Following we are discussing the common exogenous antioxidants which are being used for the brain disease but still no clear cut lead has been observed by researchers and clinicians.

Vitamin E is a fat soluble vitamin with antioxidant potency with eight stereoisomers. Among eight stereoisomers only α-tocopherol is the most bioactive form in humans due to its fat soluble property thus safeguarding the cell membrane from damage by ROS/RNS. Its main role is in the protection against lipid peroxidation and clinically has been reported to prevent the ischemia and certain neurological diseases\(^{94-96}\). However, a clinical trial has showed that that daily α-tocopherol dose of 400 IU or more can increase the risk of death and should be avoided. The dietary sources of vitamin E are vegetable oils, wheat germ oil, whole grains, nuts, cereals, fruits, eggs, poultry, meat etc.

Vitamin C or ascorbic acid is a water soluble vitamin which is essentially required for collagen, carnitine and neurotransmitter biosynthesis. It could acts as antioxidant, anti-atherogenic, anti-carcinogenic and as immunomodulator \(^{97,98}\). It acts synergistically with vitamin E to neutralize the ROS / RNS. Natural sources of vitamin C are citrus fruits, green vegetables and tomatoes. It could destroy during cooking therefore the best source of vitamin C is the fresh fruits.

Beta carotene is a fat soluble member of carotenoids which can be converted to vitamin A. It is the best quencher of singlet oxygen and considered as strong antioxidant. Beta carotene is present in fruits, vegetables, germ oil etc. Lycopene is also a carotenoid possessed antiproliferative and antioxidative capacity\(^{99,100}\).
Selenium is a trace mineral found in vegetables, sea food, meat, liver, yeast and water. It forms the active site of several antioxidant enzymes including glutathione peroxidase. At low dose it could act as immunomodulator, antioxidant and anti-carcinogenic. It could provide the neuroprotection against traumatic brain injury and could modulate the oxidative stress and cytokine values. It’s essential role has been reported in Alzheimer’s and cognitive impairment.

Flavonoids are polyphenolic compounds which are present in plants. To date approximately 4000 flavonoids have been identified and classified flavanols, flavanones flavones, isoflavones, catechins, anthocyanins, proanthocyanidins. They have been reported to prevent or delay the number of chronic and degenerative ailment like stroke, aging, memory loss, inflammation and Alzheimer’s disease with their antioxidative and antiinflammatory capacity. The main sources of flavonoid are green tea, grapes, apple, cocoa, ginko biloba, curcuma etc. In neurodegenerative diseases the main preventive role of green tea is due to its anti-inflammatory property.

Essential dietary supplement include omega-3 and 6 fatty acids which promote the health. Omega-3 fatty acid helps to reduce inflammation which is almost unavoidable event in most of the neurodegenerative diseases. It could also be used in stroke, memory loss, depression and diabetic neuropathy.

4. Evidences for the beneficial use of antioxidants in neurodegeneration

Numbers of studies have been conducted related to effects of antioxidants in neurodegenerative diseases. The overview of findings has been discussed in this section. For detailed information please refer to provided respective references. Review done by Weber and Ernst for the use of antioxidants in parkinsonism (accessed through medline 1996-2005) have suggested that supplementation of antioxidants offer limited neuroprotection and therefore suggested more explorations need to be done. Review by Crichton et al. (2013) revealed that future clinical trials are warranted to elucidate the effects of a high intake of dietary antioxidants on cognitive functioning and neurodegenerative diseases. Meta-analysis by Etminan et al. (2005) suggested that intake of vitamin E, C and carotenoid could reduce the risk of Parkinson’s disease. Huang et al. (2013) have suggested the natural products as source of new leads for the treatment of AD. Flavonoids are also suggested as acetylcholinesterase inhibitors and may play as promising therapeutic molecule for the neurodegenerative diseases. However controversial reports are also available showed no co-relation in antioxidant treatment and protection against neurodegeneration. Crichton et al. (2013) have suggested that there is no correlation in habitual intake of dietary antioxidants with better cognitive performance or a reduced risk for dementia. Recently clinical trial of a nutritional formula contains α-tocopherol showed no significant improvement in cognitive performances. Albarracin et al. (2012) have also reviewed the effect of natural antioxidants in neurodegenerative diseases.

Frank et al. (2012) have reviewed the role of tocotrienols as neuroprotective dietary factors but still the information is scarce. Epidemiological studies have reported that vitamin E (ortocopherol) can prevent the AD pathology however, prospective, randomized studies have not been convincingly able to demonstrate the clinical efficacy. Dose dependent supplementation of vitamin E could offer the neuroprotective effects in AD and PD. Pham and Plakogiannis (2005) have showed that vitamin E enriched food which contains 30IU of α-tocopherol may be beneficial however, they discourage the vitamin E supplement of dose 400IU of α-tocopherol. Dysket et al. (2014) showed that mild to moderate AD could be treated with treatment of α-tocopherol. Recently Morris et al. (2015) have suggested that γ-tocopherol might have beneficial effects in AD pathology in comparison to α-tocopherol. A pilot trial of vitamin E with coenzyme Q10 in Parkinson’s patients have showed the dose dependent neuroprotective effects of vitamin E and coenzyme Q10 and the proposed highest dose was 2400 mg/day however further studies are required.

Studies in animals and in vitro models provide evidences of neuroprotective effects of vitamin E. Clinical practices are also in favour of supplementation of vitamin E in neurodegenerative pathologies. But still there are no direct answers as to whether tocopherol is worth prescribing in such neurodegenerative diseases. Casani et al. (2013) have showed that antioxidant supplementation could prevent the oxidative damage in drosophila model of Parkinson’s disease. An in vitro and in vivo study of Parkinsonism showed that antioxidants offered prevention against oxidative neuronal damage. Report by Bahadorani and Hillaire (2008) have showed that in drosophila model of h0untington’s disease the antioxidants could not offer neuroprotective effects whereas trial of α-tocopherol in HD patients have showed the beneficial effects on antioxidants. Combinative therapy of α-tocopherol with folic acid could mitigate the amyloid β induced neurotoxicity in mice model. In rotenone induced experimental model of parkinson’s diaseae the oxidative damage was blocked by the antioxidant α-tocopherol. In cellular model of AD Hagl et al. (2015) reported that rice bran extract which consist of tocopherol and tocotrienols, has showed beneficial effects on mitochondrial function and showed promising prevention of AD pathology. Study in AD patients has showed that decreased level of vitamin E reflecting involvement of vitamin E in disease pathology. Clinical assessment has showed that supplementation of α-tocopherol decreases the γ-tocopherol and therefore enhance the AD evidences. Meta - analysis done by Farina et al. (2012) have reported that vitamin E did not offer beneficial effects in treatment of AD / MCI. Isaac et al. (2008) have also reported no evidence of efficacy of vitamin E in the prevention or treatment of AD patients and cognitive impairment.
The protective role of antioxidants like vitamin C and GSH has also been suggested in neurodegenerative diseases [136, 137]. Ascorbate/vitamin C treatment in phenotype model of HD and mouse model of AD had showed neuroprotective effects [138, 139]. Study in experimental model of AD showed that vitamin C supplementation offered neuroprotective effects in AD pathology [140, 141]. Combination of vitamin C and E could also offer the neuroprotective effects in transgenic mouse model of AD [142, 143]. Study in vitro model of parkinsonism has showed that ascorbate prevents the dopaminergic neuronal death [144]. Clinical assessments for use of vitamin C are less in comparison to use of tocopherol. In vitro study has also suggested the protective effect of vitamin A in AD pathology as it could offer destabilizing effects to amyloid fibrils [145]. The use of carotenoids has also been suggested by Zhang et al (2002) [146] in PD pathology. However the carotenoids could not reduce the risk of PD but they have suggested the dose dependent neuroprotective effects in PD pathology.

The use of flavonoids as therapeutic compounds has also been suggested in learning, memory, neurocognitive performances and Alzheimer’s disease [147, 148]. Recently the beneficial effects of flavonoids have been showed for the alzheimer’s pathology in animal and in vitro experimental model [149-152]. The neuroprotective effects of rutin, a flavonoid have been reported in beta amyloid induced neurotoxicity in rats [153]. Flavonoid induced decreased acetylcholinesterase activity has also been suggested in experimental model of AD [154, 155]. Study in cellular model of AD has showed that flavonoid offered protection through antioxidation, mitochondrion protection and MAPK signal inactivation [156]. However, the further explorations are required.

5. Conclusion and Future Perspective –

In spite of the extensive research the neurodegenerative diseases are still a significant medical challenge for most of the countries. To date neurobiologist and researchers are not able to develop the therapy to prevent the disease progression. Available medications and therapies of neurodegenerative diseases could only provide the symptomatic relief up to limited time period. After treatable time span the disease remains uncontrollable and compels the patients to suffer from daily life challenges and ultimately death. The neurodegenerative mechanisms majorly involve the oxidative stress and reports have showed that it could act as initiation event for the neuronal death. However, it should be noted that treatment with antioxidant offer partial protection only during disease related pathological events. The rationale behind this partial but significant effect of antioxidant might be due to late diagnosis of disease. As we know that no peripheral diagnosis for neurodegenerative disease is available yet thus clinicians are totally depend on the behavioral, psychological and brain imaging for the disease-diagnosis. Such diagnosis and therapeutic obstacles led us to think for the alternative therapy subjected to the search of complete knowledge for the undergoing neurodegenerative mechanisms. These circumstances also draw our attention towards the need of development of early diagnosis of neurodegenerative diseases. A non-invasive diagnostic kit would really be convenient and affordable to the patients of all countries including low and middle income countries. However, it is big challenge in front of researchers as most of the neurodegenerative diseases share the common neurodegenerative death mechanisms except the death of specific neuronal population. From the evidences of oxidative stress mediated neuronal death and neuroprotective effect of antioxidants, it appears that antioxidants might be use as potent preventive therapeutic molecule for neurodegenerative diseases. Therefore it is our contention that for the immediate relief to patients and human welfare the alternative preventive therapy must be considered for the neurodegenerative diseases.

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