



ISSN (E): 2277- 7695

ISSN (P): 2349-8242

NAAS Rating: 5.03

TPI 2020; 9(6): 412-424

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[www.thepharmajournal.com](http://www.thepharmajournal.com)

Received: 17-04-2020

Accepted: 22-05-2020

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## Natural bioactive products with antioxidant properties useful in neurodegenerative diseases

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DOI: <https://doi.org/10.22271/tpi.2020.v9.i6f.4803>

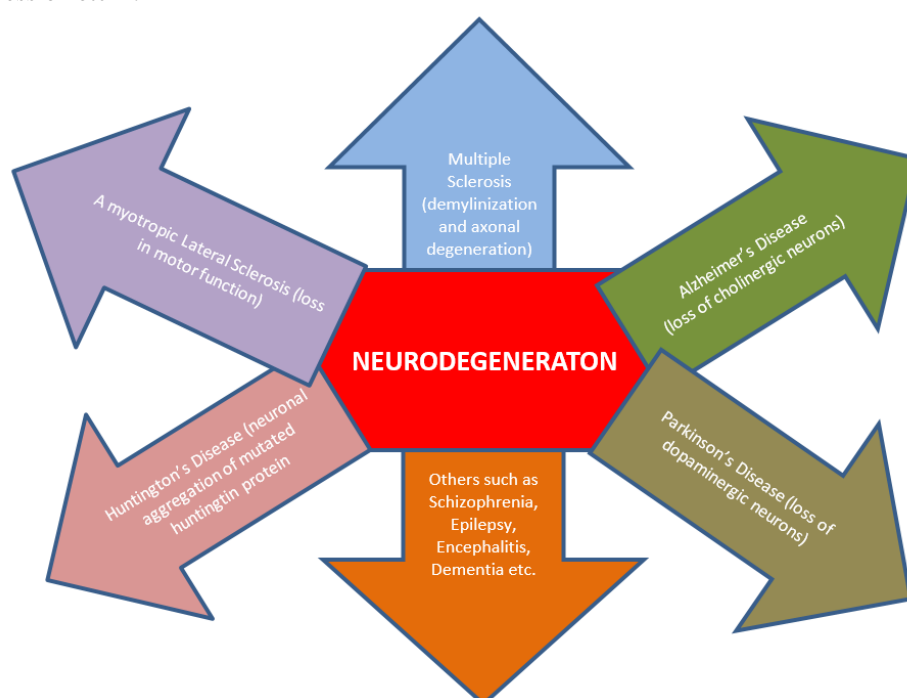
### Abstract

Oxidative stress is one of the principal causes behind the progression of several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, neurosclerosis and others. Reactive oxygen species and reactive nitrogen species are the major reduced moieties produced during the cellular oxidative stress which are responsible for the neural damage and death. Therefore, the compounds or group of compounds which are capable of limiting the concentration of these reduced form of oxygen commonly known as antioxidants can be the promising elements in controlling or recovering the neurodegenerative diseases. This article deals with various naturally active antioxidants which have been evidenced in the management of the neurodegenerative diseases. In this context, we have concluded the role of polyphenols, alkaloids, vitamins, terpenoids and several other bioactive compounds in the preventive and curative measures of different neurological disorders.

**Keywords:** Neurodegenerative disease, polyphenols, Alzheimer's disease, Parkinson's disease, vitamins

### Introduction

The neurodegenerative diseases are the major group of pathophysiological conditions which include either alterations in the neuronal structures or stiffening of the neurons (Neurosclerosis) or the loss of the neurons itself. These conditions are generally characterized either due to accumulation of protein, or inflammation or oxidative stress in the CNS which lead to cause various behavioral changes such as cognition impairment, motor dysfunction, depression etc <sup>[1]</sup>.



**Fig 1:** Major Neurodegeneration with possible etiology

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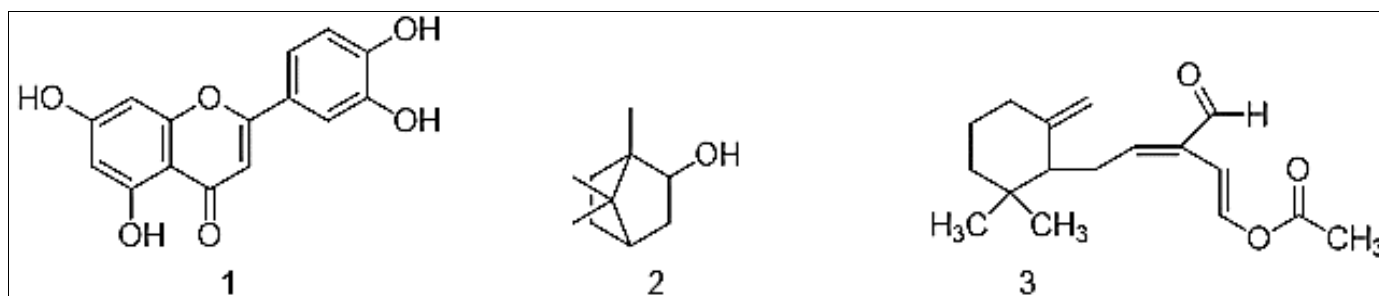
Sometimes, damage to the BBB (Blood Brain Barrier), insufficient synthesis or depletion of the neurotransmitters due to enhance activity of the enzymes, autophagia, etc. may also be the etiology behind the neurodegeneration. The most commonly known diseases due to improper generation and progression of the neurons are Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) etc. (refer fig. 1) Neurodegenerative diseases cause a substantial burden over the globe because of communicable conditions such as meningitis & Japanese encephalitis as well as non-communicable conditions such as AD, PD, HD, cerebrovascular diseases etc. [2]. The various substrates which are taken by the body to generate energy are being oxidized by using molecular oxygen and in the meanwhile, these oxygen molecules get converted into reduced form of oxygen (Reactive Oxygen Species or ROS) such as peroxide and superoxide radicals. In various circumstances, superoxide radicals react with nitric oxide (NO) to produce peroxynitrite radicals (OONO<sup>-</sup>), commonly called as Reactive Nitrogen Species (RNS) [3]. ROS and RNS are to be considered as the possible factors of neurodegeneration and can also be formed under various stressed conditions such as

- Continuous direct contact with UV radiations
- Metal catalyzed reaction in the body
- Product produced by neutrophils and macrophages during inflammation
- Products produced during electron transport chain reaction in mitochondria, etc. [4].

Apart from this, it has been surveyed that poor life-style is one of the major factor behind the generation of such oxidative stress and progression of various neurological disorders [5]. These reduced form of oxygen acts as a double edged sword in the biological system. They behave as the soldiers and encounter all the infectious agents when present at lower concentration in the body. But these can cause stress in the activation of neuron factor-kappa B in the brain even cause damage to various organs of the body when present at higher concentration [6]. Their concentration and action are enzymatically or non-enzymatically controlled by the special defense mechanism of the various cells present in the different organs of the body [7]. Superoxide dismutase and glutathione peroxidase are the few enzymes available on the

either sides of the mitochondrial membrane (major free radical site) which scavenge the aggravate number of free radicals. Among the various non-enzymatic antioxidant (refer Table 1), vitamin C (8) & vitamin E (16) play the most important role but in different types of condition [8]. For example, vitamin C combines with superoxide in the aqueous environment where as vitamin E combines effectively with the same but in the non-aqueous phase. On contrary,  $\alpha$ -lipoic acid is a natural reducing agent which can act in both types of situation. Fruits like pomegranate, apricot etc. vegetables like tomato, potato, carrot etc., nuts like walnut, peanut etc. & beverages such red wine, green tea are certain substance which are essential to maintain the redox system in the body or specifically brain [9, 10]. Therefore, the antioxidant pools available naturally in the physiological system often requires some nourishments and support in order to encounter the produced free radicals which can be done by the above mentioned items. There are various species of plants and even microorganisms which are rich in the compounds accessible to reduce the blackballed concentration of free radicals and balance the cellular redox of the system. Flavonoids and other polyphenols [11], terpenoids, alkaloids, are the secondary metabolites which are helpful in the management of the CNS diseases. For example,

- Luteolin, which is a flavonoid, has been reported its vital function in the treatment of multiple CNS disorders such as inhibition of mast cell degranulation, protection against mitochondrial damage, activation and proliferation of microglia etc.
- Vitamin supplementation has been informed in the modulation of clinical symptoms of Parkinson's disease.
- Borneol has been shown its efficacy in the amelioration of BBB permeability, thus acting as neuroprotector [12]. Similarly, water habitants have been also shown some tremendous effects in the modulation of neurodegenerative diseases.
- Onchidal which is an acetate ester isolated from mollusc *Onchidella binneyi*, has been shown its ability to inhibit acetylcholine esterase enzyme, therefore it can be helpful in the management of AD [13]. In this section, we will discuss about various natural compounds and their derivatives responsible for the amelioration in the severe CNS disorders.



**Table 1:** Natural exogenous antioxidants [14]

Natural exogenous sources of Antioxidants						
Polyphenols		Alkaloids	Vitamins	Terpenoids	Others	
Flavonoids Flavonols, Flavanones, Flavones, Isoflavonoids, Anthocyanidins	Polyphenolic acid Ferulic acid, p- Coumaric acid, Gallic acid, Ellagic acid	Vindolicine, Boldine, Tetrandine, Caffeine	Vitamin A Vitamin C Vitamin E	Carotenoids, Lycopene	<b>Proteins</b> Albumin, Ceruloplasmin, Hepatoglobin, Lectoferrin, etc.	<b>Non proteins</b> (Bilirubin, Ubiquinol, Uric acid)

### Class of Natural Antioxidants useful in the management as well as treatment of various CNS disorders

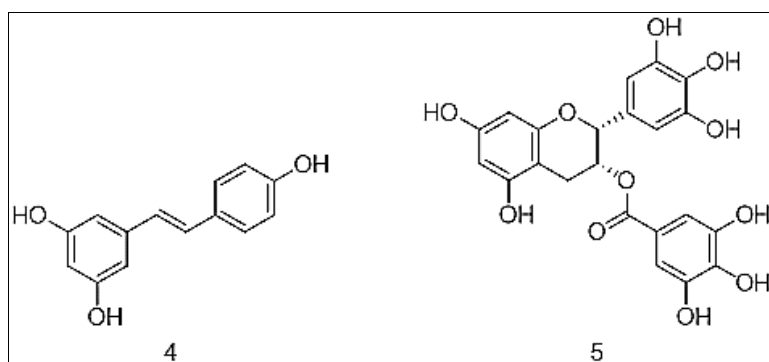
**1. Polyphenols:** Neurodegenerative problems are being majorly associated with the aging effects which gives an idea to reduce the oxidative stress responsible for the aging as well as to treat mentioned malady. For such purpose, polyphenolic compounds produce very promising effect by reducing the various free radicals resulted from the oxidative stress. Flavonoids such as anthocyanins, flavonols, flavones, flavanones, isoflavonoids, flavanols come under this class of compounds where as lignans, stilbenes, phenolic acids are the examples of non-flavonoid polyphenols. These are considered as broad spectrum compounds since they act through multiple mechanisms in order to prevent and manage various neurodegenerative problems. The possible ways through which polyphenols can act are as follows:-

- By acting through antioxidant pathways
- By modulating the various neurotransmitters and enzymes such as acetylcholine esterase
- By acting on the amyloidogenic pathways
- By interacting with signalling pathways
- By inhibiting NMDA (N-methyl-d-aspartate) neurotoxicity <sup>[15]</sup>, but our major focus will be on its first

above mentioned mechanism only.

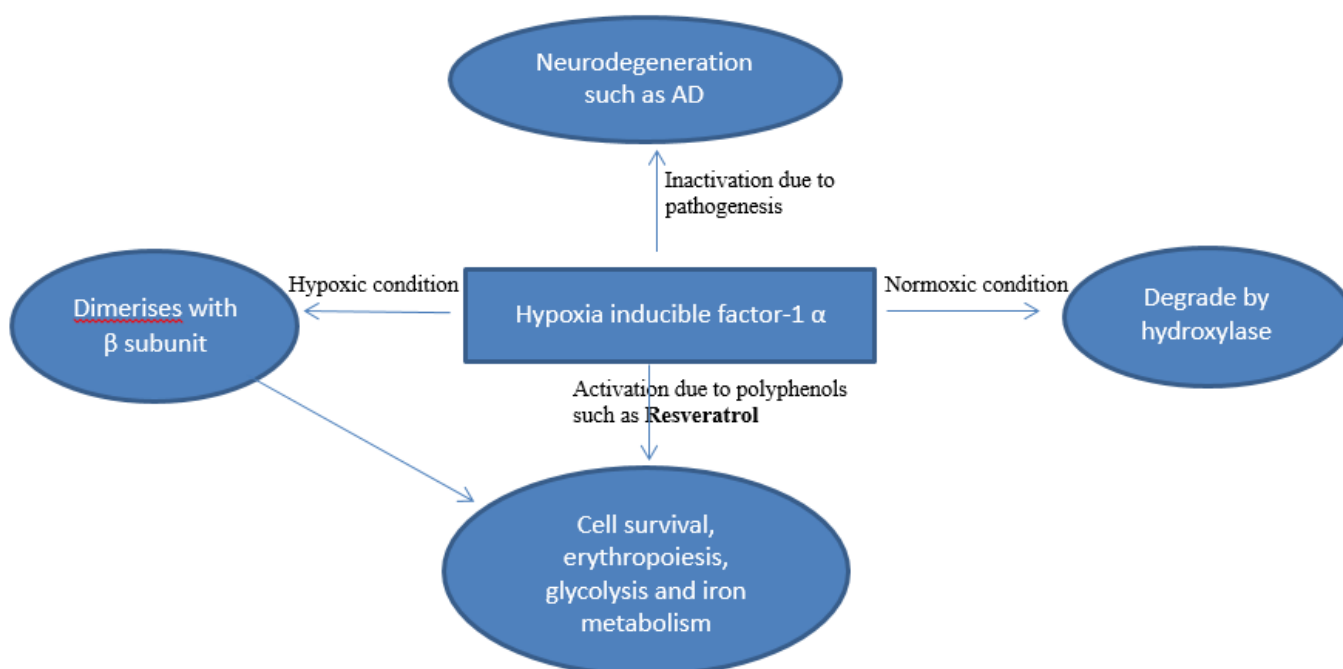
As we have already discussed various categories of polyphenols, it has been found that the antioxidant action of different types of polyphenols exist through different mechanisms in different types of cell lines studied. The reported pathways through which polyphenols reveal its antioxidant properties are follows:-

- HIF-1 $\alpha$  (Hypoxia Inducible Factor-1 alpha) Pathways-** This pathway is responsible for the transduction and expression of the genes responsible for inducing the mediatory survival condition for the cells. Two subunits, i.e.  $\alpha$  &  $\beta$  <sup>[16]</sup> have been found and studied in which  $\alpha$  is related with oxygen regulating capacity while  $\beta$  (also known as aryl hydrocarbon receptor nuclear translocation) is dimerised with  $\alpha$  subunit under hypoxic condition which subsequently binds to the target genes involved in the cell survival, glycolysis, angiogenesis, erythropoiesis and iron metabolism (refer Fig. 2) <sup>[17]</sup>. Polyphenols like resveratrol (4) and catechins such as EGCG (epigallocatechin gallate) (5) act through the induction of HIF-1 $\alpha$  pathways.



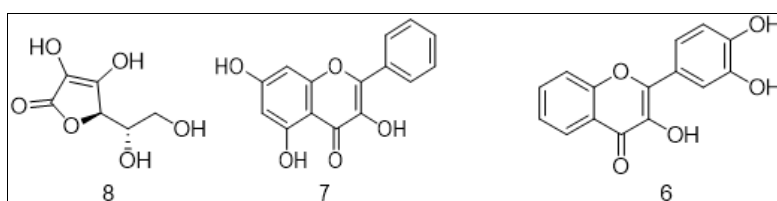
And in several studies, direct relationship between hypoxia and production as well as accumulation of amyloid- $\beta$  protein, responsible for the pathogenesis of AD, is obtained <sup>[18]</sup>.

Therefore, the compounds helpful in the activation of HIF-1 $\alpha$  can play the ideal role in the management of AD too.



**Fig 2:** Behaviour of HIF-1 $\alpha$  in different conditions

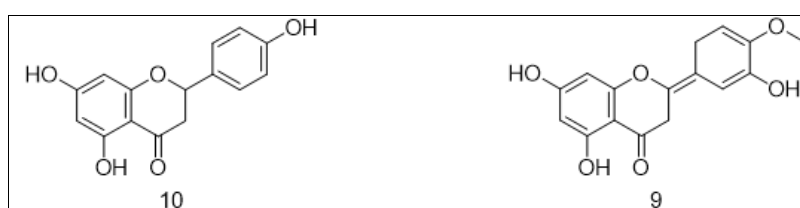
- i) **ROS Modulation:** This is an additional mechanism through which polyphenols can show their antioxidant properties by regulating the reactive oxygen species which are responsible for the deterioration of various cell organelles in the central nervous system [19]. Further, these species are reported to reduce the various metal ions in the brain which is one of the symptomatic behaviours found in various neurodegenerative diseases such as AD, PD etc. EGCG, a major constituent in the Japanese green tea has been found as most effective in reducing the hydroxy radicals, superoxide radicals, peroxy radicals, nitric oxide, lipid free radicals and even 1, 1-diphenyl 1-3-picrylhydrazyl free radicals. The chemistry behind such kind of behaviour of EGCG is the presence of the plenty of hydroxy groups in its structure which can act as both hydrogen donor as well as hydrogen acceptor [20].
- ii) **Metal Chelation:** Lipid peroxidation starts to occur in the brain under various stressed condition which can be



inhibited via chelation of the metal ions such as ferrous ion by the various antioxidants like vitamin E and vitamin C (8) [15]. These metals actually catalyze the oxidation of even natural antioxidants which is proceeded through the free radicals formation. Therefore, a special account of flavonoids are used in order to remove or cage such metals. Flavonoids possess 3-OH group are believed to be shown with better activity when compared with 5-OH group moiety. The presence of catechol ring also demonstrate better activity than the presence of 5-OH group which can be clearly understood by considering fisetin (6), a good iron chelator. The dual combination of 4-keto and 3-OH groups in the flavonoid structure is also responsible for the better chelating properties as seen in the case of galangin (7) [21]. By observing such kind of studies based on the structure related activities, we can expect a broad range of compounds which can make chelations with these transition metals.

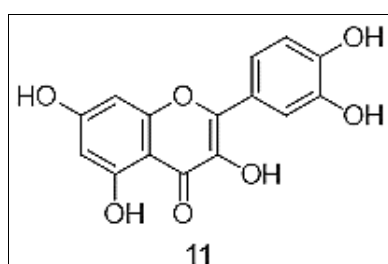
- iii) **Cell signals Alteration:** There are number of cell signal pathways which are responsible for the cell survival and apoptosis under different circumstances. The major of these pathways are PI3K (phosphoinositide-3 kinase), PKA (protein kinase A), MAPK (mitogen activated protein kinase), tyrosine kinase, Akt/PKB (Akt/protein kinase B) etc. Polyphenols act on the ATP binding sites of these cascades such as mitochondrial ATPase, calcium plasma membrane ATPase, protein kinase A, protein kinase C, topoisomerase & benzodiazepine binding sites of GABA-A receptor and cause change in either phosphorylation or expression of the targeted genes [15]. Among all the mentioned pathways, MAPK is the most

general pathway through which polyphenols produce their actions. The subclass of polyphenols such as hesperetin (9), and naringenin (10) possibly show its neuroprotective activity by inhibiting the kinases enzymes [22]. Furthermore, resveratrol is established to show its neuroprotective activity by modulating the expression of SIRT1 (sirutin) as suggested in the mice models of AD & HD [23]. In addition, resveratrol as well as huperzin A & EGCG are also found to be responsible for the overexpression of protein kinase C which leads to cause reduction in the amyloid protein which is a major target in the treatment of AD [24].



Quercetin (11) is a polyphenolic compound which has been reported for showing its immense activity to inhibit the PI3/Akt/PKB pathways which ultimately inhibit the synthesis of proapoptotic proteins say Bcl 2 (B-cell lymphoma 2) and alleviate the longevity of the neuronal cells [25, 26]. However,

different polyphenols are being informed to target a large number of the protein kinases and other mediators of the cell signalling pathways which makes the understanding of the mechanism little bit complicated.



**2. Alkaloids:** Besides polyphenols, alkaloids have also shown its promising effect on treating neurodegenerative problems in *in vitro* and *in vivo* models of rats. The fruitfly (*Drosophila melanogaster*) model, associated with neurodegeneration such as AD or PD is the most demanded model in the field of CNS related studies. The possible reason behind this, might be its similarity in term of genetic elements with that of humans [27]. And it is a well-known mythology that the green leafy vegetables are not only good for nutritional care but also good as a medicinal benefit. In this regard, a study has been performed on the alkaloid extract of the leaves of *Gnetum africanum* (African Jointfir), commonly known as Okazi in Nigeria. In this study, the extract is examined on the Mn induced neurotoxic model of fruit flies and it is observed that the survival rate and the locomotor function of these flies enhance. Actually, this plant has been under traditional uses such as fever, ulcer & diabetes and also demonstrated hypolipidemic, hypoglycemic, antioxidant, and anti-inflammatory properties [28, 29].

As per the analysis, Manganese induces the neurotoxicity in the mentioned model via the following ways:-

- Elevation in the ROS level
- Elevation in the NO (nitric oxide) level
- Induction in the metal catalysis

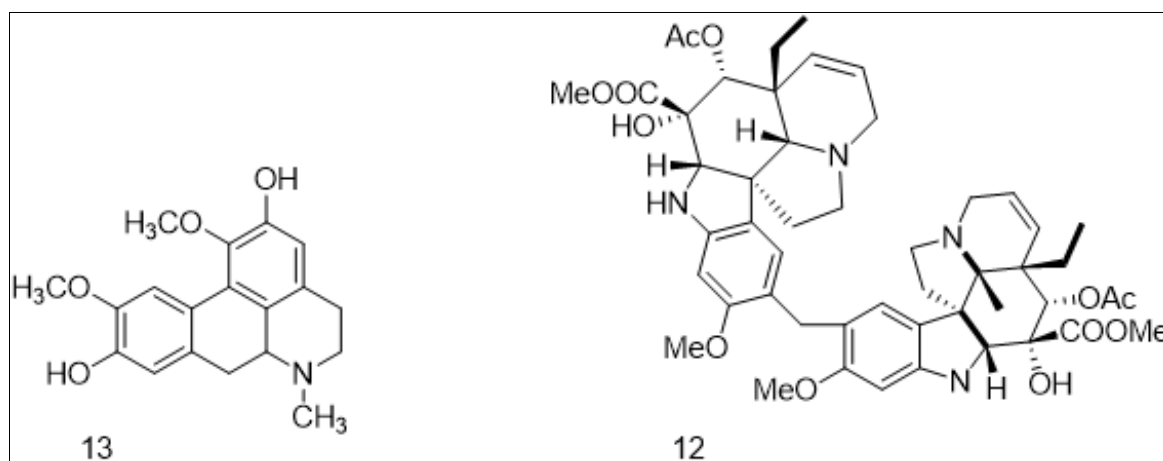
As we have already discussed that these free radical are cytotoxic and can damage various neurons and related transmitters. Therefore, the moiety which can ameliorate such free radicals will be very beneficial in order to treat various neurodegeneration. And the alkaloid extract of African jointfir is found to be able to decrease such elevated free radicals and besides, it is also reported to inhibit the acetylcholine esterase enzyme in the *in vitro* study of fruitfly model [30]. It produces

a conception to employ this extract to treat neurodegenerative disease such as AD and dementia because inhibiting acetylcholine esterase enzyme will lead to increase the life span of acetyl choline which is responsible for the cognitive ability, memory/learning, motor function and locomotion [31]. The effect is found to be much better when the model is being cotreated with Mn sample.

And it is a well-known fact that  $Fe^{+2}$  is responsible for the ROS production which causes the cell damage. But in this model Mn has induced neurotoxicity by competing with the ferrous ion i.e through non-redox pathway [32]. Since there is the chemical similarity between Fe and Mn so it can be expected the jointfir extract to chelate Mn as well [31].

Apart from producing immune response, cell proliferation and differentiation, NO is also being reported as a proinflammatory mediator [33]. And according to the study, the alkaloid extract of African Jointfir is able to ameliorate the elevated level of NO which suggests its anti-inflammatory property [30]. So in this way, this extract can be an innovative candidate for the isolation purpose obtaining possibly a novel or known compound which is active in treating neurodegeneration.

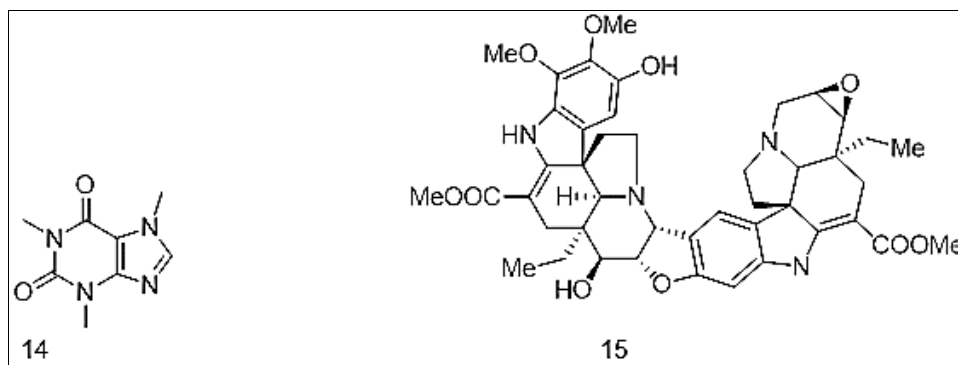
There are several other alkaloids such as vindolicine (12) which is isolated from leaves extract of *Catharanthus rosea* [34], tetrandine which is a benzyloisoquinoline alkaloid [35], boldine (13) from the bark of *P. boldus* [36], photoberberine and aporphine alkaloids from the *Mahonia aquifolium* [37] and several others have been reported with antioxidant properties in different free radicals productive models. In fact, boldine (10-100 $\mu$ M) has been shown its efficacy in ameliorating the peroxidative production which is observed by decreased in the visible luminiscence due to the reduction of TBARS (thiobarbituric acid reactive species) formation, and oxygen consumption in the *in vitro* model of rat's brain [36].



Vindolicine has revealed its scavenging activity when examined under DPPH, ORAC and peroxide induced free radicals assays in the  $\beta$ -TC6 cell lines of mouse pancreatic model. These assays have been performed taking quercetin as the control and it is reported that this alkaloid is much less active when compare with the standard one [34].

As we know the caffeine (14) is one of the known compound useful in the memory enhancement and cognition improvement. There are several dietary sources of caffeine

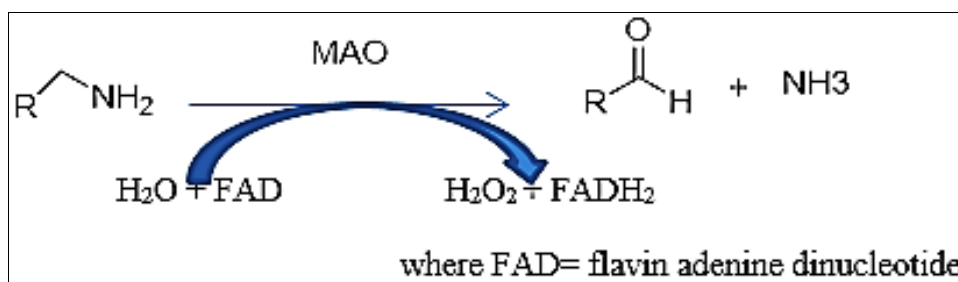
such as caffeinated soft drinks, chocolates, cocoa etc. [38]. In one of the study, the synergistic effect of caffeine on the anticholinesterase activity of Donepezil has been observed in the *in vitro* model of the rat. It is found that caffeine 50-100 mg/kg body weight of the rat models causes the drastic enhancement of the anticholinesterase activity of Donepezil in addition with its antioxidant property as well [39]. In this study, alone caffeine is reported to inhibit the cholinesterase enzyme at concentration.



In another study, Sasazawa and coworkers worked on conophylline (15), one of the novel compound of that time and reported its autophagical activity. This compound was found to be active in suppressing the aggregation of the proteins responsible for the neurodegenerative disease such synuclein in PD or huntingtin in HD in m-TOR (mammalian target of rapamycin) independent manner<sup>[40]</sup>. In this way, this compound was found to be effective in eluding the cell death while treating any neurodegenerative disease as in case of neurotoxin, MPP<sup>+</sup> (1-methyl-4-phenylpyridinium). This

experiment was done in the rat pheochroma PC12 cytochrome cells of PD model.

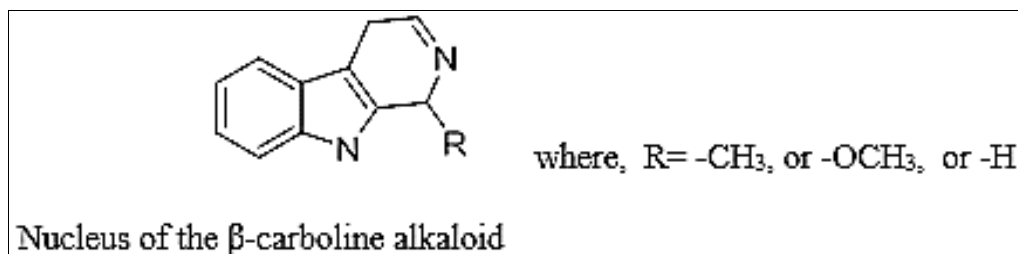
Alkaloids are also being reported to inhibit the enzyme known as monoamine oxidase enzymes (MAO), a member of flavin dependent metabolic enzymes. This possess two isozymes such as MAO-A & MAO-B and are responsible for the conversion of the various biogenic and xenobiotic amines into its oxidative products as well as peroxide radicals as byproduct (refer Fig. 3)<sup>[41]</sup>.



**Fig 3:** Oxidation of amines by MAO

And, the produced peroxide as usual causes oxidative stress to the neurons which leads to the various neurological disorders. Therefore, inhibiting this enzyme present on the mitochondrial membrane will be a good protective in order to treat and manage different neurodegenerative diseases such as HD, PD, AD and dementia. The subcategories of alkaloids which can act as MAO inhibitors are: a. indole alkaloids such as  $\beta$ -carboline & monoterpene alkaloids, b. isoquinoline alkaloids such as jatrorrhizine & berberine, c. piperidine

alkaloids, i.e. guineensine & piperine, d. tropane alkaloids such as atropine & hyoscyne etc.  $\beta$ -carboline alkaloid such as harmaline from *Peganum harmala* is found to be counteracted both the isozymes of MAOs and various derivatives have been studied in order to raise the selectivity. For example, selective MAO-A inhibitors are effective in treating the depression but selective MAO-B inhibitors are used frequently to treat Parkinson's disease.



**3. Vitamins:** Vitamins are the organic compounds that cannot be or partially synthesized by the body which are very essential for the health and well-being. The diets deficient in vitamins, other antioxidants and unsaturated fatty acids lead to increase the susceptibility to neurodegenerative problems<sup>[42]</sup>. Different types of diseases can occur even when a single vitamin is missing in the body such as night blindness due to vitamin A, beri-beri due to vitamin B, scurvy due to vitamin C, rickets due to vitamin D and so on<sup>[43]</sup>. But the major vitamins which are nutritious for the central nervous system are

vitamins C, D & E. These vitamins play a major role in maintaining the health of the neurons and also help in avoiding the various mechanisms which can cause various neurodegenerative diseases such as cognitive impairment, AD or PD. According to the Food and Nutrition Board, the elderly people associated with various neurological disorders can take up to 2000 mg/day and 1000 mg/day of vitamins C & E respectively in order to avoid any toxicity.<sup>[44]</sup>

**a. Vitamin C:** This vitamin is termed alternatively with

ascorbic acid, dehydroascorbic acid or any other ascorbate. The list of the components in which ascorbic acid is found are the citrus fruits say lemon, broccoli, pepper, cauliflower and potatoes [43]. The most known disease caused due to deficiency of vitamin C is scurvy which is characterized by athralgias, bleeding and improper wound healing. Ascorbic acid or vitamin C is the compound having capability to ameliorate the free radicals produced during any oxidative stress. And it is found in a study that this compound can increase the viability of peroxide induced PC 12 cells in a dose dependent manner [45]. Vitamin C shows the scavenging activity in the aqueous environment and can act as the modulator of the Vitamin E scavenging activity.

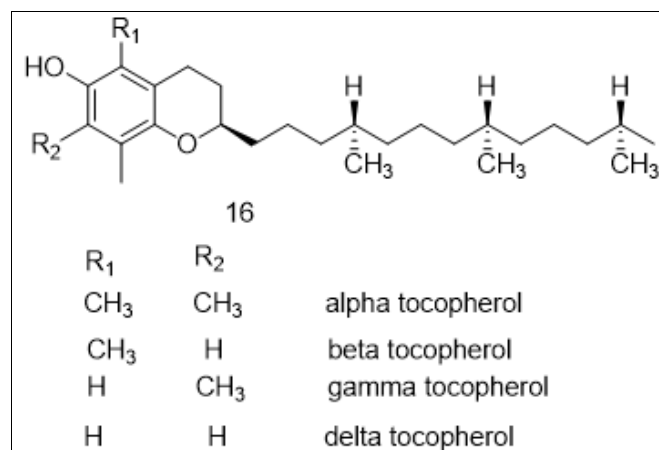
In a study, it is found that chronic alcoholism is the cardinal feature in FAS (Fetal Alcohol Syndrome) which is associated with the decrease in the dopamine level & probably oxidative stress causing various neurodevelopmental deficiencies in the fetus [46]. Therefore the hippocampal part of pregnant Sprague-Dawley rats were cultured & exposed with ethanol & PTZ (pentylentetrazol) and the effect of vitamin C was observed. Vitamin C showed its neuroprotective property by reducing the damage caused by ethanol and PTZ at gestational day 17.5. Furthermore, it was revealed that the cotreatment (vitamin C+ PTZ+ alcohol) effectively improves the prenatal development by reducing PTZ and alcohol induced apoptotic neurodegeneration. Besides, increase in the cell proliferation and cell survival by inducing the anti-apoptotic proteins say Bcl-2 were the additional merits observed in that particular experiment [47]. But the dose of the vitamin C is very much important to be considered here as it should not interfere with the naturally occurring oxidative process probably important for the fetus [48].

Vitamin C has been investigated to treat the numerous CNS disorder as follows:-

- i) **Alzheimer's Disease:** As we know this disorder is the effect of both genetic and lifestyle combination characterized by the accumulation of amyloid- $\beta$  protein in the brain. In a study, it is observed that the alzheimer's patients are found to have lower plasma and CSF (Cerebrospinal Fluid) ascorbate level [49, 50]. It has been evidenced that the orally administered ascorbate can protect the CA1 area of hippocampus of the rat's brain from the oxidative damage. It was also found that the SH-SY5Y neuroblastoma cells could be protected from apoptosis induced by  $\beta$ -amyloid protein [51, 52]. The ascorbate has also been reported to act as acetylcholine esterase inhibitor, the most prominent way to treat AD [53].
- ii) **Parkinson's Disease:** Ascorbate has been found to improve the durability of levodopa which can then be converted into dopamine and can raise the dopamine level in the elderly patients which is a key line of treatment in the PD [54]. The oxidative stress induced by MPP<sup>+</sup> (1-methyl-4-phenyl pyridinium) in various Parkinson models is reportedly protected by the ascorbate administration [55].
- iii) **Huntington's Disease:** It has been found the release of the ascorbate declines in the brain of the mice express genes for the Huntington's disease which can be reverted by administering the ascorbate injection [56].

**b. Vitamin E:** Vitamin E, also known as tocopherol is a group of lipid soluble tocol or tocotrienol derivatives. Out of which,  $\alpha$ -tocopherol is the most concerned compound for the human health [43]. Although the clinical deficiency of

vitamin E is not very common yet the only known disease due to primary deficiency of vitamin E is AVED (Ataxia with vitamin E deficiency) caused due to the mutations in the TTP (Tocopherol Transfer Protein) [57, 58]. TPP is a protein which is physiologically available to facilitate the selective secretion of  $\alpha$ -tocopherol from hepatocytes to the lipoproteins that deliver the vitamin to the non-hepatic tissues [59]. Cholestatic liver disease, short bowel syndrome, cystic fibrosis, abetalipoproteinemia, Tangier's disease etc. are the fat malabsorption disorder which are generally caused due to secondary vitamin E deficiency [60-63]. The structure of tocopherol has already been discussed in this chapter and its metal chelating activity is described. The evidences of the reaction of vitamin E with the peroxy radicals suggests its *in vivo* antioxidant properties to prevent any tissue damage [64]. In fact, vitamin E is the most important lipid soluble antioxidant in plasma and Red Blood Cells which protects lipid from its peroxidation [65]. In different study, it has been mentioned that vitamin E works as a chain antioxidant which inhibits the polyunsaturated fat in the membrane and plasma lipoproteins to initiate any free radical reaction [66]. In this section, we will discuss about the role of vitamin E in different neurological disorder management and the possible mechanism behind.

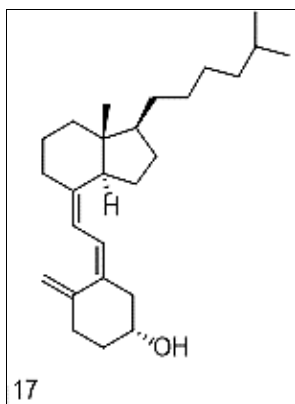


In one of the study, the capacity of quenching singlet oxygen by different tocopherols was observed and the following sequence was obtained:- alpha tocopherol > beta tocopherol > gamma tocopherol > delta tocopherol [67]. The possible chemistry behind this antioxidant activity of tocopherol is the presence of 6-OH group in the chromanol ring (see above) because the activity diminishes or completely vanishes as this -OH group is replaced by any ester or ether [68].

The effect of intake and concentration of vitamin E in the brain have assessed its importance towards the neurological function and its efficiency in different studies. In a study, the role of vitamin E in the inhibition of the neurotoxicity due to accumulation of the amyloid beta protein is demonstrated [69, 70]. The decrease in the vitamin E concentration due to any external or internal stimuli such as any bacterial infection, exposure to any toxins, or metabolic changes such as increased in homocysteine etc. could increase free radical reaction, alter the normal brain function and speed up the progression of dementia in AD [44, 71, 72]. This developed an idea to consider tocopherol's ability to protect neurons from oxidative stress which is documented in multiple studies [73, 74].

**c. Vitamin D\*:** It has been a long time when vitamin D has

shown its role in the neuroimmunomodulation and reported to have multiple biological targets (VDR, i.e., vitamin D receptor) in order to overcome with any of the CNS disorders [75]. Vitamin D (17) (especially cholecalciferol, i.e. vitamin D<sub>3</sub>) can be synthesised in the skin under the exposure of ultraviolet rays and therefore often avoided to consider it into the classical definition of vitamins [76].



The major source of vitamin D are fat fish flesh, fish liver oil, milk, eggs of hen etc. and the major function of vitamin D is to maintain the calcium and phosphorus level by altering their absorption in the small intestine, maintaining the equilibrium with the bones and modulating the immune system [77]. The deficiency of vitamin D is majorly characterized by rickets in the children and osteomalacia in adults [43]. And the list of the functions reportedly performed by the application of vitamin D in order to treat various neuropathologies but not through antioxidant pathways are as follows:-

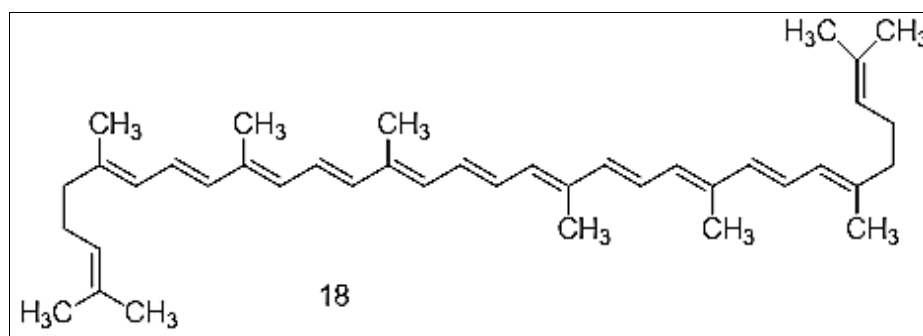
- i) In a study done by J. Brown & company, it has been demonstrated that the vitamin D can play a vital in stimulating the synthesis of neurotrophic agents such as neurotrophin 3, nerve growth factor, glial cell-line derived neurotrophic factor and other important moieties which help correspondingly in the neuronal growth in *in vitro* rat hippocampal cell cultures [78]. This neuroprotective action of vitamin D was found to be either due to the regulation of calcium dependent voltage channels or synthesis of calcium related cytoplasmic proteins such as calbindin [79, 80].
- ii) Vitamin D has been reported in eluding the VDR-dependent immunosuppression including rise in the cytokine level, macrophages and polynuclears in the mice model by inhibiting the expression of major proteins

involved in the autimmune process of the nervous system [79, 81].

- iii) Furthermore, it was found that the public associated with the higher altitude region & born during winter season, are more susceptible to get the disorder, Schizophrenia. Lower amount of 1, 25-dihydroxy D<sub>2</sub> (active form of vitamin D) in the maternal plasma which deteriorate the neuroformation and favoring the occurrence of psychosis, could be the possible reason behind such scenario [82, 83].
- iv) In several other studies, the correletaion between vitamin D and depressive subjects is established. According to which, the subjects with deficiency of 25-hydroxy D<sub>2</sub> & 1,25-dihydroxy D<sub>3</sub> concentration in their body are prone to have depression [84-86]. In another study it was found that the seasonal depressive subjects given with 100000 IU of vitamin D showed better results when compared with the same subjects treated with phototherapy [87].
- v) An article has confirmed the reduction of the seizure episodes in epilepsy while treating with vitamin D supplementation [81]. This can be justified by considering the mechanism of action of valproic acid (commonly used in epilepsy), which is an inhibitor of cytochrome P450, an enzyme responsible for the catabolism of 25-hydroxy D<sub>2</sub> to inactive form [88].

**4. Terpenoids:** These are the class of compounds which are identified as the integral multiple of isoprene units (C<sub>5</sub>H<sub>8</sub>) and then named accordingly such as monoterpenoid, sesquiterpenoid, diterpenoid, sesterpenoid, triterpenoid and so on. Terpenoids have also some historical evidences of antioxidant and antiinflammatory properties which can lead their importance in neurological background [89]. The presence of the huge number of alternate double bonds is possibly the factor behind the free radical scavenging activity of terpenoids [90].

Lycopene (18), a terpenoid which is enriched in the variety of substance such as tomato, potato, water-melon, apricot etc. has established its antioxidant or free radical scavenging activity is more than that of β-carotene and tocopherols [91]. An inverse relationship between serum lycopene concentration and lipid oxidation has been demonstrated and found that instant absorption of tomato lycopene reduces the possibility of oxidative damage to the lipids, proteins, DNA etc. [92]. Lycopene is supposed to act as an antioxidant which may reduce the dementia symptoms attributed in AD by ameliorating the degree of disturbance in antioxidant balance [93].



Studies have investigated that lycopene has the potential to cross the BBB and can act on neurons directly or indirectly through modulating the addition of peroxy radicals to the polyene chains, electron capture by pigment, hydrogen

abstraction from allylic positions [94, 95].

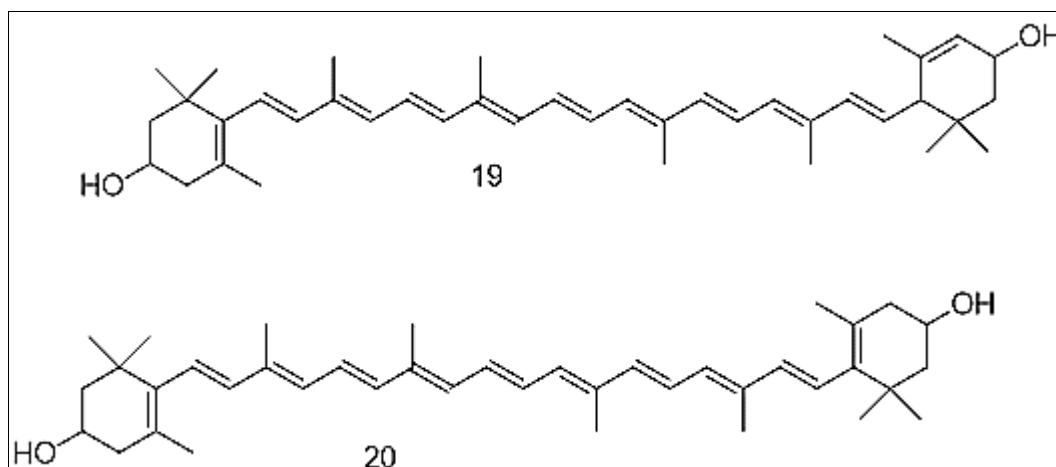
One of the investigations has suggested the role of terpenoids in the neuroprotection of transient global cerebral ischemic (tGCI) rats. This study was based on Lupeol, a pentacyclic



triterpenoid isolated from the leaves of *Hygrophila auriculata* and some of its fractions. This plant is marked as 'Rasayana' in Ayurveda which means drugs for the treatment of neurological disorders. Furthermore, the ethanolic terpenoid fraction of this plant has been reported to reverse the reduction in the glutathione (GSH) activity in cortex and hippocampal regions of the brain [96]. GSH is responsible for the synthesis and release of various molecules such as glutamate and GABA which coordinate the NMDA & non-NMDA activity [97]. And it is found in various studies that the deficiency of glutamate and related compounds lead to cause neurological impairments [98]. In another study, the application of Curcuma oil (isolated from the rhizomes of *Curcuma longa*) on the transient focal ischemic brain of rats was demonstrated with the reduction in

the concentration of reactive oxygen species and peroxynitrite which significantly showed its antioxidant properties. Therefore, this can be employed in order to delay the neuronal death [99].

Lutein (19) and zeaxanthin (20) are the two compounds of the same abovementioned class have been found in association with neural performance. These are the plant pigments possibly helpful in maintaining the MPOD (Macular Pigment Optical Density), the retinal carotenoids which have direct relationship with the modulation of brain health and cognition strength. In a study, it has been found that the preadolescents with higher MPODs tend to respond superior in a given cognitive load as compared with that of adolescents with lower MPODs [100].



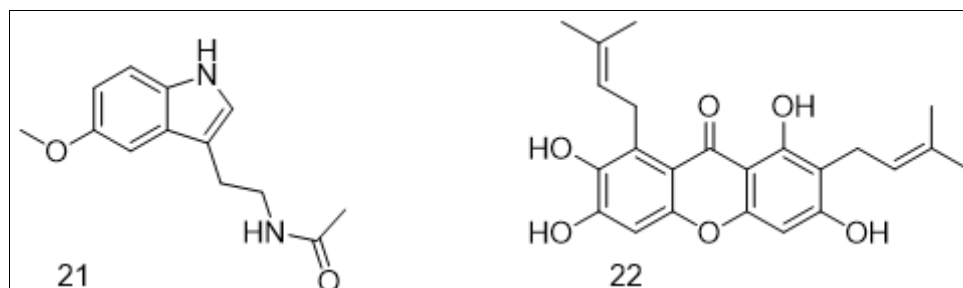
The *in vivo* effect of POJ (pasteurized orange juice; 2 varieties, i.e. Cara Cara & Bahia) on the transgenic alzheimer's model of *C. elegans* was observed and concluded its resistive property towards oxidative stress by acting through the transcription factor SKN-1. Besides, it was found that POJ was responsible for the delayed  $\beta$ -amyloid induced paralytic symptoms and boosted the longevity of the neurons. Furthermore, the obtained results were more effective for the Cara Cara rather than the Bahia possibly due to its higher content of carotenoids such as zeaxanthine, lycopene,  $\beta$ -carotene etc.

**5. Others:** In a study, melatonin (21) which is naturally occurring hormone responsible for the regulation of sleep cycle, is found to be responsible for the direct or indirect benefits in AD. The effect was proposed due to its anti-amyloidogenic property, interaction with apolipoprotein E4, and  $\beta$ -amyloid antagonism [101-103]. The major external sources of melatonin are fruits & vegetables (potatoes, cucumber, pomegranate, asparagus, apricot etc.), grains (rice & barley) and nuts & seeds (walnuts, peanuts, flax seeds) [9].

Several fractions of the leaves of *Ginkgo biloba* have been reported with antioxidant property and found toxic to  $\beta$ -amyloid protein and reducing the NO induced neuronal death [104]. This effect was probably due to the various flavonoids and terpenoids which further demonstrated the cognition enhancing property in AD [105].

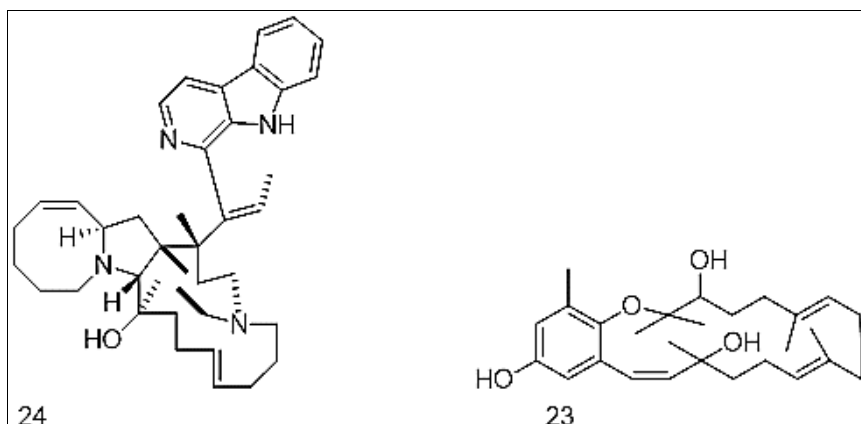
In various studies it has been established the people with frequent intake of coffee and cigarette have minimum risk of PD. It has been investigated that nicotine consumption stimulates the release of dopamine in the striatum and preserves the nigral neurons & striatal dopamine level in animals. It has been informed that caffeine and the related compound theophylline are the adenosine  $A_{2A}$  receptor antagonist which lead to improve the motor function in the PD patients [106, 107].

$\gamma$ -mangostin (22), a major compound from the fruits of *Garcinia mangostana* has been found effective in reducing the neurotoxicity by inhibiting the peroxide induced ROS generation, DNA fragmentation, and lipid peroxidation [108].



Even the marine creatures have been considered as the excellent source of antioxidant compounds which can play a vital role in the management of various neurological maldies [109]. A macrocyclic compound (23) isolated from an algae *Sargassum micracanthum* has shown its antioxidant potential and can be clamied to reduce the free radicals produced

during oxidative stress in any neurodegenerative disease, say AD [110]. Another compound from marine source, i.e., manzamine-A (24) has been marked as antineurogenic compound with potent anti-inflammatory and low toxicity properties [110].



In a study, the action of green tea extract on N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine induced Parkinson's mice model was observed. The study concluded that the extract was responsible for reduction in the loss of dopaminergic neurons in substantia nigra along with the increment of striatal dopamine and tyrosine hydroxylase levels. The possible cause behind this property was supposed to be due to the presence of (-)-epigallocatechin-3-gallate in the extract which is a well-known polyphenolic compound [111].

### Conclusion

Neurological disease is considered to be the second leading cause of deaths after cardiovascular disease [112]. Therefore, it should be a centre of attention in order to keep people healthy and free from any CNS maladies. And there has been plenty of evidences behind the role of oxidative stress in various kinds of neurodegenerative diseases such as AD, PD, HD and so on. But it is a truth that the gap between the clinical and preclinical evidences of treatment by using single antioxidant in such neurodegenerative diseases has been observed so many times [113]. Therefore, it has been suggested that use of multiple antioxidant can play a vital role in treating any neurological disorder rather than the use of single antioxidant [114]. In this context, it can be assumed to use fruits, vegetables, ginkgo extract, and beverages such as green tea, POJ will be a better option in order to treat any neurological disease since these contain multiple antioxidants. Although, this chapter concluded various polyphenols, alkaloids, vitamins and terpenoids as the major natural bioactive antioxidants which can be used to provide prophylactic as well as curative treatment in the various neurodegenerative diseases such as AD, PD, HD, & so on. Furthermore, this manuscript has dealt with various compounds originated from the marine creatures which had been proven descent antioxidants and could be a pivotal neuroprotective agents.

### Acknowledgements

The authors are thankful to the staff of R.K College of Pharmacy for their continuous support and inspiration.

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