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THE ROLE OF ANTIOXIDANTS AND THEIR RELATED ENZYME IN PROTECTIVE RESPONSE TO CEREBRAL ISCHEMIA REPERFUSION INJURY

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ABSTRACT: In aerobic organisms, oxygen is essential for sufficient energy production but self-contradictory, produces chronic toxic stress in cells. So, protective techniques must exist for removal of toxic free radicals which are byproducts of oxygen. Diverse protective systems have evolved to enable adaptation of antioxidant activity. Tissues and organs have different rates of metabolic activity and oxygen consumption. Their levels of antioxidants are also different. Such is the case with glutathione (GSH) and cysteine, which are lower in the brain than the liver, kidney, or muscle. Investigations of oxidative responses in different complex organisms such as mammals, organs, and tissues which contain distinct antioxidant systems and this may form the basis for differential susceptibility to toxic agents. Notable advances have been made in our understanding of these distinct systems, with several antioxidant systems and their regulatory pathways being described at the cellular level, thus understanding the pathways leading to the induction of antioxidant responses will enable development of strategies to protect against oxidative damage.

INTRODUCTION: In oxygen requiring organisms, oxygen is essential for sufficient energy production but self-contradictory, produces chronic toxic stress in cells. So, protective techniques must exist for removal of toxic oxygen byproduct called as free radicals. Diverse protective systems have evolved to enable adaptation to antioxidant. 5% or more of inhaled O_2 is converted to reactive oxygen species (ROS) such as H_2O_2, O_2 and OH by univalent reduction of oxygen so these antioxidant defence systems are very critical for survival of both prokaryotic and eukaryotic organisms.

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The outcome of oxidative stress (OS) is seen when production of reactive oxidative species (ROS) surpass more than the capacity of cellular antioxidant defences to remove these toxic species (free radicals). Tissues and organs have different rates of metabolic activity and oxygen consumption. Their levels of antioxidants are also different. Such is the case with glutathione (GSH) and cysteine, which are lower in the brain than the liver, kidney, or muscle. Investigations of oxidative responses in different complex organisms such as mammals, organs, and tissues contain distinct antioxidant systems, and this may form the basis for differential susceptibility to toxic agents.

Notable advances have been made in our understanding of these distinct systems, with several antioxidant systems and their regulatory pathways being described at the cellular level.

Antioxidants (free radical scavenger) act as scavenging reactive oxygen species (ROS) (that is SOD removing Oxygen), by inhibiting their formation (by blocking activation of phagocytes), by binding transition metal ions and preventing formation of OH and/or decomposition of lipid hydro-peroxides, by repairing damage (*e.g.* α-tocopherol repairing peroxyl radicals and so terminating the chain reaction of lipid peroxidation) or by any combination of the above two. All of these conditions, along with the aging process are associated with OS due to elevation of ROS or insufficient ROS detoxification [1].

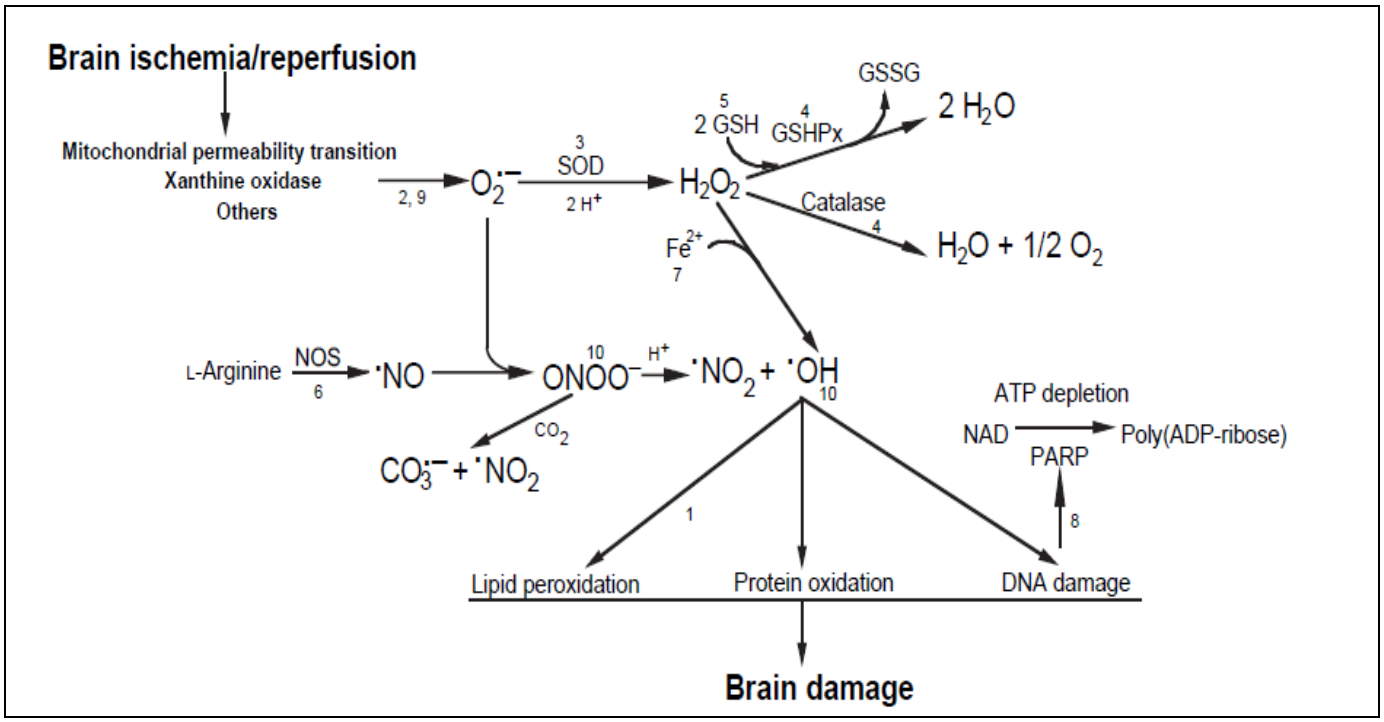

FIG. 1: MECHANISM OF BRAIN ISCHEMIA AND REPERFUSION INJURY

Mechanism of Brain Ischemia and Reperfusion Injury: Brain ischemia/reperfusion indicates various opportunities for the formation of reactive oxygen/nitrogen species which results in tissue injury. So, simultaneously various site-specific targets for therapeutic intervention are explained. It is clear that inhibition of a single pathway may be insufficient to provide protection against oxidative stress. (1) Inhibition of lipid peroxidation; (2) inhibition of xanthine oxidase; (3) the superoxide dismutase's (SOD) and their mimetic; (4) catalase and glutathione peroxidase (GSHPx); (5) glutathione (GSH) mimetic; (6) nitric oxide synthase (NOS) inhibition (7) metal chelates (8) poly(ADP-ribose) polymerase (PARP) inhibitors (9) mitochondrial permeability transition inhibitors; (10) spin traps and Peroxynitrite scavengers. O^-_2 (superoxide); CO^-_3 (carbonate radical); H_2O_2 (hydrogen peroxide); glutathione disulphide; OH (hydroxyl radical); NO_2 (nitrogen dioxide); NO (nitric oxide); $ONOO^-$ (Peroxynitrite); NAD (Nicotinamide adenine dinucleotide)

Inhibition of Lipid Peroxidation: During cerebral ischemia, free fatty acid concentrations are enormously increased, the largest increase in that of arachidonic acid [2, 3]. The calcium ions activate phospholipases C and A2 resulting in phospholipid hydrolysis, while the synthesis of phospholipids requires ATP. Results in ischemia-induced Ca^{+2} influx and energy failure promote free fatty acid release which is associated with membrane damages. Free carboxylic acid metabolism alternative adverse effects include inhibition of oxidative phosphorylation [4, 5], oxidative conversion of free arachidonic acid *via* the cycle-oxygenase pathway to eicosanoids (*i.e.* thromboxane's and prostaglandins) [6], generating of free radical and lipid peroxidation-mediated chain reactions [7, 8] and cytotoxicity from lipid peroxidation products which may stimulate apoptosis. Increased NO concentrations associated with ischemia may have dual effects on lipid peroxidation. The reaction of NO with superoxide causes formation of peroxynitrite which initiates lipid peroxidation *via*

reaction of lipids with its decomposition products hydroxyl radical and nitrogen dioxide [9, 10]. NO directly inhibit lipid peroxidation by intercepting alkoxy and peroxyl radical intermediates thereby terminating chain propagation reactions. Despite it is difficult to confirm that lipid peroxidation is a primary and contributor to ischemic cell death.

Inhibition of Xanthine Oxidase: ATP metabolism directs to an accumulation of hypoxanthine [11] during ischemia, calcium ion stimulated proteases cause irreversible partial cleavage of xanthine dehydrogenase to xanthine oxidase, which in turn catalyzes oxidation of hypoxanthine to xanthine. XO further oxidizes xanthine to produce uric acid, superoxide, and hydrogen peroxide [12]. Allopurinol is oxidized by XO to oxypurinol, which binds to the active site of xanthine oxidase causing xanthine oxidase inhibition.

The Superoxide Dismutase and their Mimetic: There are three major endogenous superoxide dismutases. Cu Zn-SOD (SOD1) is primarily found in the cytosolic and lysosomal fractions but is also in the mitochondrial intermembrane space [13]. MnSOD (SOD2) is found in the mitochondrial matrix. Both Cu Zn-SOD and MnSOD are available in neuronal tissue. Copper Zinc-SOD minimizes the ischemic damage results from ischemia/reperfusion [14]. So, MnSOD targeted deletion worsens the outcome from both temporary and permanent middle cerebral artery occlusion [15, 16]. Cu,Zn- SOD overexpression inhibit post-ischemic mitogen-activated protein kinase activation, resulting the bad cell death signaling pathway caspase activation [17], mitochondrial cytochrome with release of DNA fragmentation and polymerase (PARP) activation.

Extracellular SOD (SOD3) is also expressed in the brain but in lower concentrations when it is compared to SOD1 or SOD2. EC-SOD, a tetrameric protein which is secreted into extracellular compartment ECSOD a heparin-binding domain that allows adherence to the glycocalyx. EC-SOD is supposed to provide defence against superoxide present in the extracellular space. The relatively low EC-SOD concentration in whole-brain may mislead with respect to its importance to ischemic events. The extracellular compartment is very small and thus EC-SOD concentration in the extracellular compartment may be sufficient to provide biological relevance.

Glutathione Depletion: Glutathione is a tripeptide (g-L-glutamyl-L-cysteinylglycine) that is the reductant for glutathione peroxidase. Oxidation of the cysteine sulfhydryl groups combines two glutathione (GSH) molecules with a disulfide bridge to form glutathione disulfide (GSSG). NADPH-dependent glutathione reductase catalyzes the recovery of glutathione. The brain maintains a high ratio of GSH/GSSG for antioxidant defence. Depletion of all the total glutathione and a decreased GSH/GSSG ratio are the markers for oxidative stress in ischemic brain and as long as 72 hrs may be required to restore concentrations to normal values by an ischemia insult [18, 19].

Nitric Oxide Syntheses Inhibition: Three nitric oxide synthases (NOS) defined endothelial (eNOS) and neuronal (nNOS) localization, or ability to be upregulated when induced (iNOS). At first, the field was confusing because NOS inhibitors were not selective and were given in heavy doses. Pharmacologic eNOS inhibition would be expected to worsen outcome, secondary to cerebral vasoconstriction and reduced blood flow. This is supported by studies of eNOS-deficient mice [20] that have worsened ischemic outcomes. An upregulation of eNOS activity by treatment with 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (e.g. simvastatin) caused increased intra-ischemic blood flow and reduced infarct size [21, 22] confirmed that neuronal production of nitric oxide contributes to ischemic cell death.

Metal Chelates: The free iron stored in ischemia brain is released from protein storage, providing that substrate for the iron-catalyzed Haber–Weiss reaction, results in hydroxyl radical formation from hydrogen peroxide. Iron chelates such as desferrioxamine are logical candidates to probe the role of these reactions in the ischemic brain.

Poly (ADP-ribose) Polymerase Inhibitors: Poly (ADP-ribose) is synthesized from NAD by PARP and then is degraded by poly (ADP-ribose) glycohydrolase (PARG). PARP is activated in response to DNA damage as a repair mechanism but can also causes NAD and ATP depletion,

potentially exacerbating ischemic injury. Sources of DNA damage is likely to be peroxynitrite formation from superoxide and nitric oxide, mediated by NMDA receptor activation [23, 24]. Cu, Zn-SOD overexpressing mice does not exhibit post-ischemic PARP activation [25].

Mitochondrial Permeability Transition Inhibitors: The concept is relatively new that the mitochondrial permeability transition (MPT) pore plays a crucial role in response of the brain to ischemia [26, 27]. Ca^{2+} overload causes translocation of cyclophilin-D from the matrix to the MPT pore that activates the pore allowing influx of solutes from the matrix to the intermembrane space [28]. Persistent MPT allows mitochondrial swelling and disruption of the outer mitochondrial membrane which intend in loss of the hydrogen ion gradient, and failure of oxidative phosphorylation. Other factors, include oxidative stress, opens the MPT pore. Therefore, oxidative stress can cause MPT which in turn heightens oxidative stress. It attracts to speculate that MPT allows the release of proapoptotic factors (*e.g.* cytochrome *c*) into the cytosol [29]. However, release of proapoptotic factors has been shown to be MPT-independent [30].

Antioxidants: Antioxidants are the substances which protect the cells from damage caused by free radicals (unstable molecules made by the process of oxidation during normal metabolism). Antioxidants include beta-carotene, lycopene, vitamins A, C, and E, and other natural and manufactured substances.

- It reduces free radicals.
- It stimulates the growth of normal cells.
- Protects cells against premature and abnormal aging.
- Helps fight age-related molecular degeneration.
- It supports the body immune system [31].

First Line Defence Antioxidants: These are the collection of antioxidants that act to suppress or prevent the formation of free radicals or reactive species in cells. It is very fast in neutralizing any molecule with the potential of developing it into a free radical. Major three key enzymes are superoxide dismutase, catalase, and glutathione peroxidase. These enzymes respectively catalyze the dismutasion of superoxide radical, breakdown hydrogen peroxides and hydroperoxides to harmless molecules (H_2O_2/alcohol and O_2).

Second Line Defence Antioxidants: This cluster of antioxidants is usually stated as scavenging antioxidants. They scavenge active radicals to inhibit chain initiation and break chain propagation reactions. They neutralize or scavenge free radicals by donating electron to them, and in the process become free radicals themselves but of lesser damaging effects.

These 'new radicals' are easily neutralized and made completely harmless by other antioxidants in this group. Most antioxidants including ascorbic acid, uric acid, glutathione, which are hydrophilic and alpha-tocopherol (vitamin E), ubiquinol which is lipophilic belong to defence antioxidants.

Third Line Defence Antioxidants: This category of antioxidants comes into role after free radical damage has occurred. They are new enzymes which repair the damage caused by free radicals to biomolecules and reconstitute the damaged cell membrane. These are a group of enzymes for repairing of damaged DNA, protein, and lipids, they include DNA repair enzyme systems (polymerases, glycosylases, and nucleases), proteolytic enzymes (proteinases, proteases, and peptidases) located in both cytosol and mitochondria of mammalian cells.

Fourth Line Defence Antioxidants: Basically it involves an adaptation mechanism in which they utilize the signals required for free radicals production and react to prevent the formation or reaction of such free radicals. The signal generated from the free radical induces the formation and transport of an antioxidant to the right site [32].

Antioxidants Include:

Vitamin A:

- This is fat-soluble vitamin which is essential for growth, maintenance of visual function, reproduction and differentiation of epithelial tissue.
- Includes compounds- retinol and its ester.
- Beta carotene protects dark green, yellow and orange vegetable and fruits from solar radiation damage.

- Excellent scavenger of singlet oxygen during photosynthesis.
- Plays a vital role in suppressing carcinogenesis by increasing immunity to the tumor through several mechanisms.
- Examples such as carrots, squash, sweet potatoes, peaches, and apricots are rich sources of beta-carotene.

Vitamin C:

- Vitamin C is a water-soluble antioxidant, essential micronutrient for metabolic functions of body.
- Interact directly with radicals thus preventing damage to the cell membrane.
- Widely used supplements and helps strengthen the immune system.
- Vitamin in rich in citrus fruits, green vegetables, raw cabbage, and tomatoes.

Vitamin E:

- It is a lipid-soluble vitamin.
- Occurs in plasma as a variety of tocopherols.
- Compared to other lipophilic, it is the most efficient antioxidant in lipid phase. Sources include wheat germ oil, nuts, seeds, whole grain and fish liver oil [33, 34].

Antioxidants in Natural Plants:

***Curcuma longa*:** *Curcuma longa* of family Zingiberaceae is used as a dietary spice, coloring agent in foods and textile. The main functional compound is curcumin which has been reported to reduce blood cholesterol, prevents low density lipoprotein oxidation, inhibits platelet aggregation, suppresses thrombosis, myocardial infarction, rheumatoid arthritis, multiple sclerosis (MS), alzheimer's disease, inhibits human immuno-deficiency virus (HIV) replication, enhances wound healing, protects from liver injury, increases bile secretion, protects from cataract formation, pulmonary toxicity, and fibrosis [35]. Curcuma species are largely being used in various food products because of their antioxidant properties. These species contain essential oil, which includes terpenes, alcohols, ketones, flavonoids, carotenoids, and phytoestrogens [36].

***Zingiber officinale*:** Ginger comes from the plant *Zingiber officinale* which is of rhizome family Zingiberaceae, consumed as a delicacy, medicine, or spice. 6-Zingirols is the major compound of Zingiber species and has reported having high antioxidant activity, known to enhance high-density lipoprotein in diabetic rats [37], reduced lipid peroxidation tissues [38] and possess scavenging and high chelating capacity. Moreover, Zingiber extract commonly used in curry powder, sauces, gingerbread, carbonated drink, and in preparation of dietaries due to its high antioxidant activity [39]. *Zingiber officinale* contains phenolic compounds (gingerol) having antioxidant activity which is even greater than α-tocopherol.

***Morus alba*:** *Morus alba*, family Moraceae is often known as white mulberry, is short-lived, fast-growing, small to medium-sized tree. The species is native to northern China, widely cultivated and naturalized elsewhere. Phenols and flavonoids rich fraction of *Morus alba* have shown beneficial effect against lipoproteins and delayed the onsets of atherosclerosis. The roots of *Morus alba* is one of the main constituents of Chinese drug named as ''Sohaku-hi'' which helps in reducing the plasma sugar level in mice. Some of the flavonoids that are obtained from leaves of *Morus alba*, such as quercetin 3-(6-malonyglucoside) attenuate the arthrosclerosis lesion development in LDL receptor deficient mice through enhancement of LDL resistance to oxidation modification [40].

***Podophyllum hexandrum*:** *Podophyllum hexandrum* often known as Himalayan Mayapple or Indian Mayapple is native to Himalaya and is found between altitudes of 2,800–3,500 m as. This plant contains podophyllotoxin, having an antimitotic effect (interferes with cell division and thus prevent the growth of cells). The roots contain several significant anticancer lignans, including podophyllin and berberine. The roots are also antirheumatic. Radioprotective and antitumor properties in *Podophyllum hexandrum* extract-treated animals were reported [41]. The aqueous extract of the species reported protecting kidney and lung tissue against CCl_4 induced oxidative stress [42]. Studies of various proteins associated with inhibition of apoptosis in the spleen of male Swiss albino strain 'A' mice by immunoblotting, has been reported [43]. *In-vitro* studies using human hepatic carcinoma cell lines has revealed its ability to stabilize the state of mitochondrial oxidative burst,

decreased TBARS, time-dependent inhibition of gamma radiation-induced leakage of electrons in the mitochondrial electron transport chain (*etc*.) *via* reduction in ROS and NO Generation and simultaneously enhancement in the thiol status via neosynthesis [41, 44].

***Myrica esculenta*:** *Myrica esculent'a* Buch–Ham ex. D. Don' of family Myricaceae, is commonly known as 'kappa' and is one of the wild edible and medicinally important plant growing between 900 and 2,100 m as in IHR. The species are widely accepted among the local people for its delicious fruits and its processed products. Some species contain antioxidant phenolic compounds, such as gallic acid, catechins, hydroxybenxoic acid, and coumaric acid. Also, the fruits of the species possess strong reducing properties and free radical scavenging properties with ABTS and DPPH assay which showed a significant relationship with phenolic and flavonoids content [45].

Habenaria edgeworthii: *Habenaria edgeworthii*, (Family-Orchidaceae) commonly named as Virdhi, grows in open grassy land in a mountainous region in IHR with an altitudinal range of 1,500- 3,000 m as. Species is traditionally used in burning sensation, hyperdipsia, fever, cold, asthma, anemia, insanity, cataplexy, leprosy, skin diseases, anorexia, Helminthiasis, emaciation, hematemesis, Gout, and general debility. The tubers are sweet, refrigerant, emollient, intellect promising aphrodisiac, and depurative, and appetizer, anthelminthic, rejuvenating, and tonic. It is one of the components of 'Astvarga', which is mainly used in preparation of 'Chyavanprash' and used to cure cough, cold, calcium deficiency and anemia.

The main properties of Chyavanprash are protection against strain, stress and restore youth, vitality and give strength and stamina. These properties are attributed to the presence of phenolic compounds in the species [46]. Total phenolic content contributed a strong share in ferric reducing radical scavenging properties by DPPH and ABTS assay [47].

***Valeriana jatamansi*:** *Valeriana jatamansi* Jones syn *V. wallichi* (Family Valerianaceae) commonly referred to as 'Tagar or Indian valerian, is a wild herb commonly distributed in subtropical and temperate Himalaya. The species is grown in temperate zone of the western Himalaya at an altitudinal range of 1,200-3,300 m as. These species are used as an aromatic, stimulant, carminative, and anti-spasmodic in Ayurveda medicine especially in the preparation of Sudarshan churan, Darsan gaylep, Papalyasava, *etc*. The plant is widely known for its use in anxiety, insomnia, epilepsy, failing reflexes, hysteria, neurosis, sciatica, tranquilizer, emmenagogue, diuretic, and hepatoprotective [48]. Plant extract of *V. jatamansi* has been reported to attenuate stress, anxiety, and symptoms of depression [49]. The species has found beneficial for cerebrospinal system, hypochondriasis, insomnia, migraines, nervous unrest, nervous tension, neuralgia, and neuroasthemia. Valerian is reported for depressant action on the central nervous system and antispasmodic activity [50].

Pharmacological screening of valerian and some other components of Valeriana showed that the sedative action can be attributed to the essential oil and valepotriates fractions [51]. Valerenic acid inhibits the enzyme system which is responsible for central catabolism of GABA and the valerian extract releases [3H] GABA by reversal of the GABA carrier, which is Na (+) dependent and Ca (2+)-independent [52]. The valepotriates (valtrate and didrovaltrate) of the species have been reported to exert a spasmolytic effect [53]. *V. jatamansi* essential oil exhibited antimicrobial activity against a large number of pathogenic bacteria and antifungal activity against fungal pathogens [54]. Antiinflammatory activity of the species in both methanolic and ethanolic extract are reported and are known to inhibit inflammation mediators, such as histamine, serotonin, prostaglandins, and bradykinins, *etc*. [55]. These species have shown strong antioxidant activity in different types of system models, such as, scavenging of DPPH, ABTS+, nitric oxide, hydroxyl radical, peroxinitrite, non-enzymatic superoxide radicals, and prevent oxidative DNA damage [56].

***Acorus calamus*:** *Acorus calamus* Linn. commonly referred to as sweet flag or 'Bach' in India, is grown wild in abundance ascending to 2,200 m in the Himalaya. These species are widely used for the treatment of epilepsy, chronic diarrhea, dysentery, bronchial and abdominal tumors and as analgesic for the relief of toothache or headache

and for oral hygiene to cleanse and disinfect teeth, relief the effects of exhaustion or fatigue.

Methanolic extract showed that during exposure of noisy environment ROS generation led to increasing in corticosterone, lipid peroxidase, and sulphoxide dismutase, but decrease in catalase, glutathione peroxidase, glutathione, protein thiols, vitamins C and E levels, in both the ethyl acetate and methanolic extract of *A. calamus* changes in the brain is observed induced by noise-stress. The species showed potent against fish pathogen *Aeromonas hydrophila* [57]. The antifungal activity of crude methanolic extract of *A. calamus* was reported [58]. The essential oil of *A. calamus* exhibited antibacterial activity against the phytopathogenic bacteria and antioxidant activity of crude methanol extract of rhizome and leaf extract of *A. calamus* is also reported [59].

***Roscoea procera*:** *Roscoea procera*, family Zingiberaceae, is one of the important Himalayan medicinal plant distributed from Himachal Pradesh to Arunachal Pradesh between 1,800 and 3,000 m as. It is traditionally used as a tonic in seminal debility, malaria and in many other folk medicines. This species is one of the ingredients of a polyherbal formulation 'Ashtavarga' which is used in the preparation of Ayurveda formulation 'Chyavanprash'. Chyavanprash is categorized into Rasayana group of drugs which is having a rich source of antioxidants, good hepatoprotective and immunomodulating agent with nutritive, antiaging, and many other medicinal properties. Also this species showed ferric reducing antioxidant properties and free radical scavenging properties with ABTS and DPPH assay which showed a significant relationship with phenolic and flavonoids content [47].

***Berberis asiatica*:** *Berberis asiatica*, family Berberidaceae is used for traditional system of medicine since the historical time. In modern system of medicine, the species is being used for preparation of drugs to cure various diseases, including eye-related disorders, intermittent fevers, as well as malaria, promoting the flow of bile, jaundice, inflammation of the gall-bladder, improving appetite, digestion, and assimilation. In addition, the fruits of this species are well known for edibility value.

Various inhibitor phytochemicals like xantho-phylls, α-carotene, β- carotene, water-soluble vitamin, and phenoplast content have been according to the species [60]. Extract of Berberis species controls glucose homeostasis through gluconeogenesis and oxidative stress [61].

***Picrorhiza kurroa*:** *Picrorhiza kurroa*, family Scrophulariaceae, it is an important medicinal herb in Ayurvedic medicine. The roots are a rich source of various chemical compounds such as picrorhiza, kutkin, D-mannitol, glycosides, cucurbitacin, kutkisterol, steroids, and vanillin acid. The species is used for the treatment of liver cirrhosis, ascites, treatment of jaundice, constipation, dyspepsia, and promotes stomach actions and provides strength. The root extract was found cytotoxic and was able to target cells toward apoptosis [62]. Roots were also reported to be useful in therapeutic action on gastric ulcer [63]. Cardioprotective effect of P. kurroa against adriamycin-induced cardiomyopathy and low dose of combined methanolic extract of P. kurroa possess good hepatoprotective activity against paracetamol induce liver damage [64].

***Bergenia ciliata*:** *Bergenia ciliata* is a perennial herb found in the Himalayan region between 900 to 3,000 m as. The species is commonly used as a poultice, treating boils, curing diarrhea and vomiting, treatment of fever, cough, menorrhagia, excessive uterine hemorrhage and pulmonary infections and kidney stone. The herbal formulations, (The Himalaya Drug Company, India) Cystone, Calcuri (Charak Pharmaceuticals, Bombay, India), and Chandraprabha Vati (Baidyanath, India) proved clinically to dissolve urinary calculi in the kidney and urinary bladder [65]. Rhizome extracts of the species were found to possess antioxidant activity, including reducing power, free radical scavenging activity, and lipid peroxidation inhibition potential as well as DNA protection [66].

Synthetic Drugs Used in Cerebral Ischemic Stroke:

Emoxipin: Emoxipin is an antioxidant synthetic drug which is used in the treatment of patients with ischemic disorders of cerebral circulation. The drug produced a beneficial clinical effect in patients with lacunar and cardio embolic strokes of moderate severity. The therapeutic effect of emoxipin

increased endogenic antioxidant activity and thus improved a clinical status of the patients. The protective effect of carnosine was demonstrated in experimental acute hypobaric hypoxia and cerebral ischemia in human. So, it was further concluded to recommend inclusion of both emoxipin and carnosine in a combined treatment of ischemic disorders of cerebral circulation [67].

Endocannabinoid: Endocannabinoid consist of ligands which are endogenous lipid-based retrograde neurotransmitter which binds to cannabinoid receptors proteins, that is anandamide and 2-arachidonoyl glycerol (2-AG), receptors (CB1, CB2), transporters and enzymes, responsible for the synthesis [N-acylphosphatidylethanolamine-phospholipase D, diacylglycerol lipase (DGL)] and degradation of these lipid mediators [fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase] [68]. The multiplicity of eCB actions, mainly occurs in the brain, under both physiological and pathological conditions. In presynaptic vesicles ECBs are not stored rather, they are produced 'on-demand' when increased intracellular Ca^{++} is the major intracellular trigger for synthesis. The primary ligands produced in the brain are anandamide [69] and 2-AG [70], which activate both the CB1 and CB2 receptors. Brain tissue concentrations of 2-AG are approximately 200-fold higher than those of anandamide [71] and the rank order for the distribution of both eCB in different areas is similar: highest in brainstem, lower in cortex, diencephalon and cerebellum's receptor in the brain is totally responsible for psychoactive effects of the cannabinoids. These receptors have been shown to be localized presynaptically on GABAergic interneurons and glutamatergic neurons [72-74].

ECBS as Neuromodulators of Excitotoxicity: Hyperactivation of the NMDA receptors by extracellular excitatory amino acids like glutamate implicated in the cellular events leading to neuronal death and decline in function following traumatic or ischemic brain injury [75-76]. Agents modulating glutamate transmission were developed, targeting as antagonists to NMDA receptors [77-79], that could theoretically ameliorate the harmful effects of excessive glutamate. Based on the location of the CB1 receptors on presynaptic terminals of glutamatergic synapses and the inhibitory nature of their signaling, eCBs and other CB1 agonists as neuromodulators of glutamate releases, as modulators of excitotoxicity continuing numerous brain disorders. A crucial component of cell survival, activated by CB1 receptors, is the PI3K/Akt pathway. Acute administration of THC increases the Ser473 phosphorylation of hippocampus, striatum, and cerebellum. This effect is blocked by the selective CB1 antagonist rimonabant [80]. Activation of this pathway could modulate the expression and activity of genes involved in cell survival, highlighting the CB1-induced neuroprotection afforded by endogenous and synthetic CB1 agonists. The synthetic cannabinoid agonist HU-210 coupled to extracellular signal; regulated kinase (ERK) activation. It stimulated the PI3K downstream targets protein kinase B (PKB), as shown by its phosphorylation in Thr 308 and Ser 473 residues and Raf-1 [81]. The findings of CB1-induced ERK activation is mediated by PI3KIB is of important consequences in the control of cell death/survival decision.

ECB in Neuroinflammation: The massive glutamate release after traumatic or ischemic brain injury followed by robust production of ROS within minutes of injury [82] and the inflammatory cytokines initiating the brain inflammatory response are up-regulated within hours [83]. In LPS-stimulated macrophages, a widely used model for an *in-vitro* inflammatory response, 2-AG suppressed the formation of tumor necrosis factor-α (TNF-α) and ROS. Also, using LPS-stimulated mice as *in-vivo* assay, TNF-α was significantly inhibited by 2-AG [84]. TNF receptors recruit, upon ligand activation, multiple intracellular adapter proteins that activate the transcription factor NFκB, a key regulator of the inflammatory response [85]. This factor is composed of homo and heterodimers including p65 which contains a translocation domain in its C-terminal end and p50.

Inactive NFκB is retained in the cytosol where its activity is tightly regulated by members of the IκB family. NFκB thus released translocate into the nucleus and activates various pro-inflammatory genes. In the brain, CB2 receptors are predominantly in non-neuronal cells, upregulated mainly under neuroinflammatory conditions. Their levels in the brain may also increase under

conditions that lead to peripheral immune cells infiltration. Whereas in healthy condition the normal expression of CB2 is hardly detected, they are up-regulated in activated microglia [86] leading to increased cell proliferation along with reduction of the release of pro-inflammatory agents such as TNF-α and NO.

ECBS as Vasomodulators of the Cerebro-vasculature: 2-AG and the cerebro micro-vasculature 2-Arachidonoyl-glycerol were shown to cause hypotension, which may be attributed to its hyperpolarizing properties [87]. It has been suggested that induction of 2-AG release in endothelium occurs in parallel to nitric oxide (NO) and involves activation of cholinergic receptors [88]. Nitric oxide, the most effective endothelium derived relaxing factor (EDRF), and endothelial derived hyperpolarizing factor (EDHF) [89] have a close functional relationship with ET-1 in regulating the endothelial-dependent capillary and microvascular responses in the brain [90].

Semi-Synthetic Drugs Used in Cereberal Ischemic Stroke:

Minocycline and Neuroprotective Effect: Minocycline is a semi-synthetic, tetracycline-class antibiotic used to treat various bacterial infections such as pneumonia, meningitis, *etc*. It is less preferred than tetracycline doxycycline. It is also used for the treatment of acne and rheumatoid arthritis, effective against gram-positive and -negative infections. Cerebral ischemia leads to memory impairment that is associated with loss of hippocampal CA1 pyramidal neurons. Neuronal inflammation and oxidative stress might imply in the pathogenesis of ischemia/reperfusion damage upon addition to its own anti micro bacterial properties it also applies neuroprotective effects over cerebral ischemia, brain injury, amyotrophic lateral sclerosis, Parkinson's disease, kainic acid treatment, Huntington' disease, and multiple sclerosis. Minocycline has been focused as an agent over neurodegenerative disease since it was first reported that minocycline has neuroprotective effects in animal of ischemic injury. Inhibit microglial activation and are neuroprotective in global brain ischemia.

The mechanisms of minocycline for neuroprotection are *via* the inhibition of mitochondrial permeability-transition mediated cytochrome c release from mitochondria, the inhibition of caspase-1 and -3 expressions, and the suppression of microglial activation, involvement in some signalling pathways, metalloprotease activity inhibition, because of the high tolerance and penetrating into the brain, minocycline has clinically tried for some neurodegenerative diseases such as stroke, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease [91].

Neuroprotective Effect of Minocycline on Cognitive Impairments Induced by Transient Cerebral Ischemia *via* Anti Inflammatory and Anti-Oxidant Properties: Memory shortage is the most visible symptom of cerebral ischemia that is associated with loss of pyramidal cells in CA1 region of the hippocampus. Oxidative stress and inflammation may cause pathogenesis of ischemia/ reperfusion (I/R) damage. Minocycline, a semi-synthetic tetracycline-derived antibiotic, has both anti-inflammatory and antioxidant properties. Minocycline minimizes the increase in escape latency time and in swimming path length induced by cerebral I/R. Further, the ischemia-induced reduction in time spent in the target during the investigational trial increases by treatment with minocycline. Minocycline also reduced the levels of MDA and pro-inflammatory cytokines in the hippocampus in rats subjected to I/R. Minocycline has neuroprotective effects on memory deficit induced by cerebral I/R in rat, probably via its anti-inflammatory and antioxidant properties [92].

CONCLUSION: Oxidative stress is nothing but the imbalance between oxidants and antioxidants. In favor of the oxidants which are formed as a normal product of aerobic metabolism and also during pathophysiological conditions can be produced at an elevated rate. Both enzymatic and non-enzymatic strategies were involved in antioxidant defense and antioxidant efficacy of any molecule depends on the co-oxidant.

The antioxidant properties of several vitamins like vitamin A, C, and E as well as carotenes, oxi carotenoids, and ubiquinols in their lipid phase has been understood in recent years. Low molecular mass antioxidant molecules that include nuclear as well as mitochondrial matrices, extracellular fluids,

and so forth have been studied vividly to understand how they accelerate the body defense significantly.

It is now clear that oxidants play a major role in brain damage in cerebrovascular diseases. The successful development of SOD-1, a unique opportunity to study the oxidant mechanisms underlying the complex neuronal responses to ischemic insults. The activities of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) constitute a first-line antioxidant defence system which plays a key and fundamental role in the total defense mechanisms and strategies in biological systems.

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