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Neuroprotective potential of phytomedicines by qualitative and quantitative analysis of antioxidants

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Abstract:

Neuroprotection is an umbrella term including various processes to remove noxious stimuli and substances that can damage the brain and/or neuronal cells, thus lead to the onset of neurological disorders. Phytomedicines are potential phytochemicals (polyphenols, alkaloids, terpenes, quinones, flavonoids, catechins, coumarins, saponins etc.) that may alleviate a neuronal disease or disorder. Over production of Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS) leading to oxidative stress is a central feature of most of neurodegenerative disorders. To fight against this oxidative stress, human body has some protective mechanisms as antioxidants. The antioxidants are substances that have an extra electron to donate to impart stable nature to reactive species.

Introduction:

Neurological disorders include malfunctioning in both central nervous system (CNS) and peripheral nervous system (PNS) or in any part of both the systems. In neurodegenerative diseases, synaptic transmission of information is disrupted either by decline in number of neurons or by removal of myelin sheath (Pérez-Hernández, J. et al., 2016). The term neurodegeneration is for progressive loss of structure and function of neurons, resulting in degeneration and/or death of neuron cells. As per World Health Organization (WHO), globally 24.3 million people have dementia, with addition of 4.6 million new cases each year. Number of people affected would double every 20 years to 81.1 million by year 2040 (WHO, 2006).

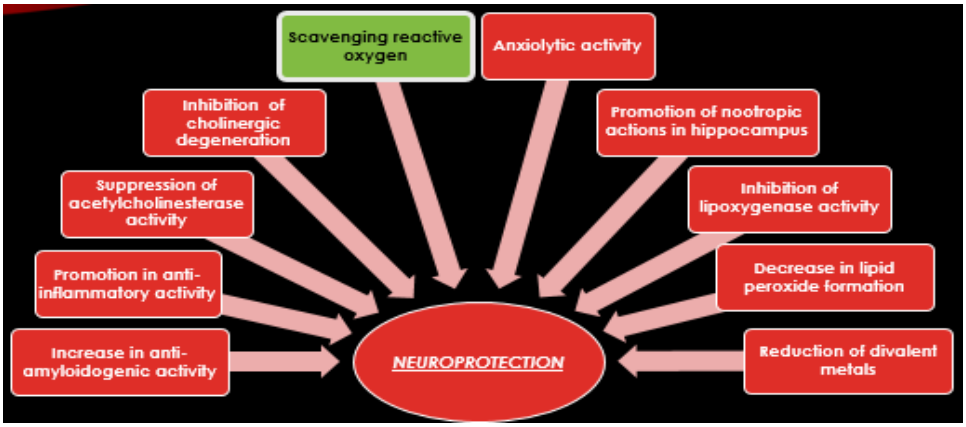

Figure 1: Various mechanisms of neuroprotection including scavenging Reactive Oxygen/Nitrogen radicals.

Phytomedicines can prevent or provide effective protection to the nervous tissue by its neuroprotective properties that delay the onset of neurodegenerative disorders by increasing amyloidogenic activity, promoting anti-inflammatory activity, suppressing acetylcholine esterase activity, inhibiting cholinergic degeneration, scavenging reactive oxygen species, anxiolytic activity, promoting the nootropic actions in hippocampus, inhibiting lipoxygenase activity, reducing the divalent metals and decreasing the lipid peroxidation activity. Reactive oxygen species can lead to sequential reduction to superoxide, hydrogen peroxide and hydroxyl radicals (Apel, K. & Hirt, H., 2004). Reactive oxygen species are thought to be responsible for accumulation of biomolecules and thus lead to synaptic dysfunction (Yoo, K.Y. & Park, S.Y., 2012). Oxidative stress increases by consequences of a mismatch between the production of free radical and the free radical scavenging ability of the cell. Previous experimental models and human brain studies suggest oxidative stress may play an important role in neurodegenerative diseases.

DPPH assay is mostly being used and is easy, simple and reasonably costly method. Principle behind DPPH assay is donation of hydrogen atom by antioxidant molecule to free radical (Molyneux, P. 2004), which gives stability to it and prevent damage to be happened.

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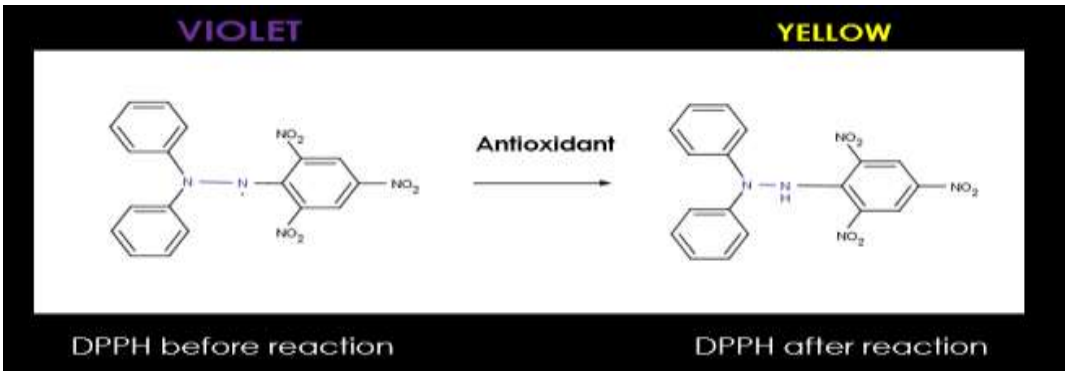

Figure 2: DPPH reaction in presence of Antioxidant

Phytomedicines again witnessed the interest from last decade due to its neuroprotective role in one or another way. However, the proper mechanism is still not well understood by scientific investigations. Phytochemicals are used from ages as in specific herbal formulas but the synergistic effects are still need to be investigated by scientific procedures.

Phytomedicines in association with Reactive Oxygen Species (ROS)

Oxidative stress may play an important role in neuronal degeneration in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis (ALS). Alteration in free radical scavenging system may also contribute to oxidative stress (Simonian, N.A. & Coyle, J.T., 1996). The phytosciences are different from the other biomedical sciences in that instead of testing a hypothesis, researchers try to determine whether plants commonly used in traditional medicine bring benefits for health. Various plants and their isolated phytochemicals have been used for treatment of various learning and memory disorders by herbal formulas in "Rasayan drugs" (Pattewar, A.V. et al., 2011). The medicinal plants used for treatment of Alzheimer's disease focus on Ayurvedic system, where the nervous system related disorders are being called as "Vata Vyadhi". Ayurvedic plants called nervines and their constituents strengthen the functional activity of nervous system (Rao, R.V. et al., 2012). Phytomedicinal properties of Ashwagandha (Withania somnifera), an antioxidant, antidepressant and neuroprotective, has remarkable stress relieving capacity better than many drugs used to treat depression and anxiety (Kiefer D., 2015). Polyphenols, alkaloids and terpenes are mainly three classes of phytochemical compounds with neuroprotective properties (Pérez-Hernández, J. et al., 2016).

Reactive Oxygen Species (ROS)

Oxidative stress is a result of mitochondrial dysfunction and enzymatic processes and it is believed to cause accumulation of damaged proteins, lipids, carbohydrates and nucleic acids. Mitochondria have been suggested to play a major role in ageing in view of their central role in energy production. Mitochondria regulate apoptosis as well (Schaffer, S. et al., 2012).

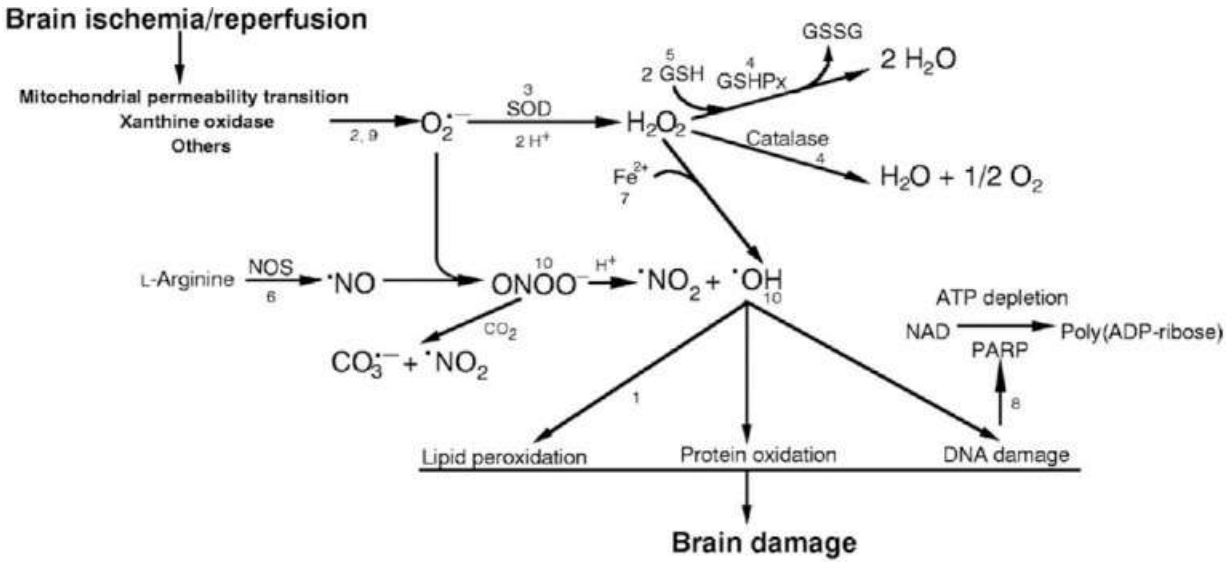

Figure 3: Biochemical reactions of ischemia/reperfusion brain injury. (Source: Neuroprotection and antioxidants, Maria Lalkovičová* and Viera Danielisová, 2016).

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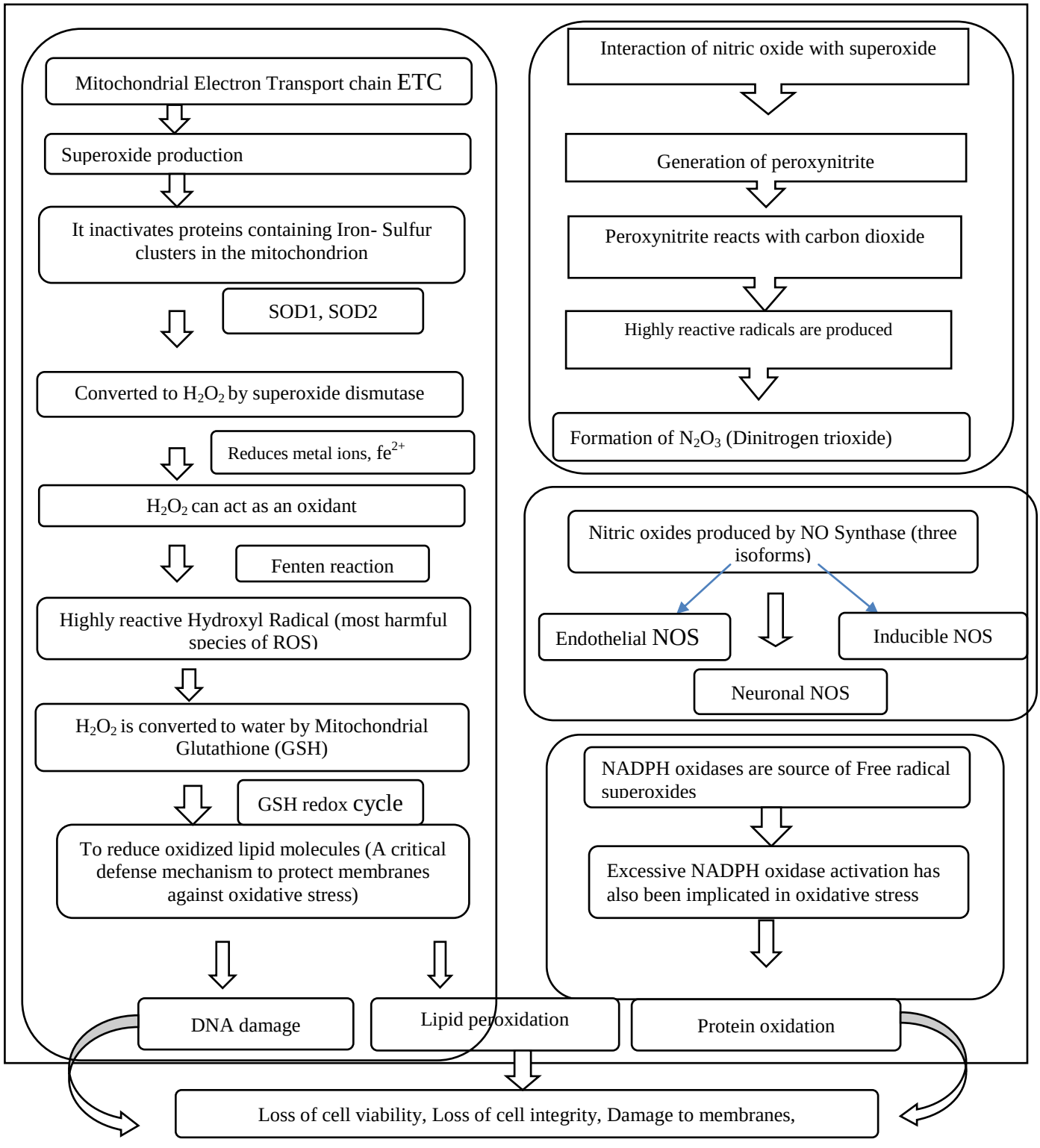

Figure 4: Sources and action of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

Nutritional antioxidants:

Phytochemical or nutritional antioxidants are playing an important role in neuroprotective, neuroregenerative, reversing cellular damage and slowing down the process of neuronal loss. General neuroprotective nutritional antioxidants are polyphenols, quinones, flavonoids, catechins, coumarins and ascorbic acid retarding neuronal loss thus delaying onset of nuerological disorders (Kumar, G.P., & Khanum, F., 2012).

Antioxidant	Source	Action
Resveratrol	Grapes, wine, and peanuts	Suppression of ROS and BBB instability
Ascorbic acid	Oranges, Papaya, Grape fruit and citrus juices	Major antioxidant transports from the blood into the brain extracellular fluid.
Vitamin- E (α-tocopherol)	Almonds, Sunflower seeds and spinach etc.	Blocks the chain reaction of lipid oxidation Protective effects against ischemic events, such as cerebral infarction. Vitamin E reduces the generation and availability of NO and O_2^- in brain tissue.
Selenium	Sunflower seeds, whole grain (Rye) Mushrooms Seafood, Fish(Tuna)	Maintains physiological functions. Important component of antioxidant enzymes such as glutathione peroxidase (GPx) and thioredoxin reductase (TrRx).
CoQ10	Spinach, Broccoli and cauliflower	Inhibit ROS generation for protection of neuronal cells.
Albumin	Peanut butter	It decreased infarction volume.
Polyphenols	Fruits and beverages; tea, red wine, cocoa, and coffee	Protect neurons against injury induced by neurotoxins. An ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function. Decrease in oxidative stress
flavonoids	Ginger	Reduced brain infarction following focal brain ischemia.
Statins (high doses)		potentially neuroprotective in ischemic stroke statins may reduce lipoprotein oxidation
Melatonin		Free radical scavenger and antioxidant Reduces inflammatory response, and BBB permeability

Table 1: Common antioxidants, their source and their actions.

Enzymatic antioxidants:

Enzymatic Antioxidants are Superoxide Dismutase (SOD), Glutathione peroxidases and Catalase. In the mammals, three distinct form of SOD have been identified e.g. Copper zinc Superoxide Dismutase encoded by SOD1 gene (Cu/Zn SOD), Manganese Superoxide Dismutase encoded by SOD2 gene (MnSOD) and Extracellular Superoxide Dismutase encoded by SOD3 gene (ECSOD). These forms of SOD exhibit similar functions, but characteristics of their protein structure, chromosome localization, metal cofactor requirements, gene distribution, and cellular compartmentalization are distinctly different from one another (Lu Miao and Daret K. St. Clair, 2009). Glutathione Peroxidases is a family of multiple isozymes that catalyze the reduction of H_2O_2 or organic hydroperoxides to water or corresponding alcohols using reduced glutathione (GSH) as an electron donor. Catalase is a ferriheme-containing enzyme that is responsible for the conversion of hydrogen peroxide (but not other peroxides) to water.

Non-enzymatic antioxidants:

Glutathione is a major antioxidant present in brain It consists of a tripeptide of glutamate, cysteine and glycine characterized by a reactive thiol group and γ-glutamyl bond. Vitamin E is one another molecule that can act as antioxidants. The role of vitamin E in the central nervous system is not fully understood although it is a lipid soluble molecule with antioxidant function.

Conclusion:

The fine-tuned balance among generation and elimination of ROS is essential for maintenance of its physiological level and normal functions in the human body. Its especially the mitochondria, the "Power House of Cell" which generate ROS in the cell. Both enzymatic and non-enzymatic systems maintain a constant ROS level in the cell. Among many, the one way for maintaining the normal levels of ROS to exert physiological function is through modulation of gene signaling pathways, such as activation of protein kinases and deactivation of phosphatases. A misbalance of the ROS level has deleterious effects as hypo-production of ROS in a living cell, is unable to carry out certain physiological functions while in contrast, the high levels of ROS by either through over-production or restricted elimination, puts a living organism under an oxidative stress condition. Abnormally high level of ROS may modify several biomacromolecules, affecting lipid peroxidation, misfolding of protein and DNA damage and thus leading to mutations. The role of ROS is hallmark to several notorious neurodegenerative diseases. Free radicals are amenable to pass freely through the plasma membrane and result in membrane leakage and ultimately cell death. ROS. On the ground of high oxygen

consumption of neurons, more ROS can accumulate in the brain and therefore results in kinds of neurodegenerative disease. The affected brain region and modified hallmark proteins by excessive ROS seem to determine the type of the disorder.

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