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Natural antioxidants and nutraceuticals to fight against common human diseases: an overview

Madhumita Chowdhury[1], Sagarika Chowdhury[1], Ashmita Bhattacherjee[1], Chandrima Roy[1], Riya Sarkar[1], Krishnendu Adhikary[2], Rajkumar Maiti[3] and Prithviraj Karak[3*]

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ABSTRACT

To fight against some common illnesses, antioxidants have always taken central role. Antioxidants are constantly available in our daily diet. Vitamin E and Vitamin C are two common natural antioxidants that are mostly present in fruits and vegetables. By lowering free radicals produced by oxidative stress situations, antioxidants play a significant role in minimizing diabetes-related health issues and maintaining optimal insulin generation. Vitamin E, Vitamin C, selenium and other antioxidants are also very much efficient against diabetes mellitus. Oxidative stress leads to the liver's dysfunction and many others disorders like liver cirrhosis. In order to avoid neurological diseases and the advancement of atherosclerosis, using dietary supplements such as vitamin E and vitamin C that directly interact with oxidative stress and free radicals are recommended. In this article we have focused on different diseases and the effects of naturally occurring antioxidants to prevent those diseases.

Keywords: Antioxidants, Liver disease, Parkinson's disease, Atherosclerosis, Diabetes

[1]Department of Biotechnology, Paramedical College Durgapur, West Bengal, India.

[2]Departmentof Interdisciplinary Science, MS Swaminathan School of Agriculture, Centurion University of Technology and Management, Odisha, India.

[3]Department of Physiology, Bankura Christian College, Bankura, West Bengal, India.

***Correspondence author:**

E. mail: drpkarak@gmail.com

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Section: Research Paper
ISSN 2063-5346

INTRODUCTION

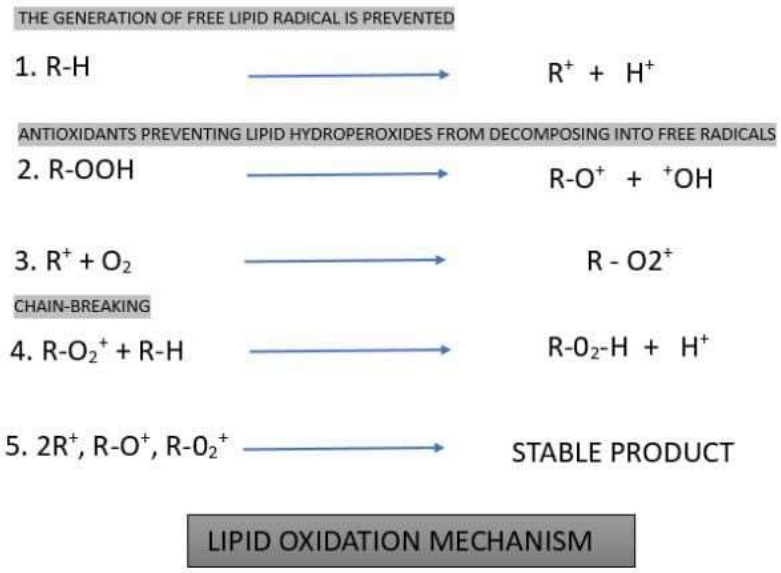
Antioxidants are substances that prevent or slow down the damage caused by free radicals in cells known as free radical scavengers. Commonly found natural antioxidants in fruits, vegetables, nuts and whole grains are present in Table 1.

Table 1: Sources of some natural antioxidants

Antioxidants	Sources
Vitamin C	Berries, Citrus fruits and vegetables
Carotenoids	Papaya, apricots and carrots.
Flavonoids	Oilseeds, lettuce, black tea and citrus fruits.
Vitamin E	Palm oil, nuts, eggs, vegetables and whole grains.
Catechins	Green tea, berries and oil seeds.

Natural antioxidants are substances produced by living things that have the power to reduce oxidative stress by controlling free radicals, neutralizing their effects, preventing the free radicals' ability to start free chain reactions and preventing lipid peroxidation (Figure 1).

Figure 1: Lipid oxidation mechanism represents the way anti-oxidant works to prevent diseases [1].



There is promise for natural antioxidants to alleviate and stabilize uncontrolled oxidative stress and balance of cells. Thus, natural antioxidants can lessen the harmful effects of certain oxidative conditions pathologically caused by stress [1]. Artificial antioxidants are BHA (Butylated hydroxy anisole), BHT (Butylate dihydroxy toluene), PG (Propyl gallate) is more effective than natural antioxidants and is produced by the Nrf2-Keap1 (Nuclear factor erythroid 2 and Kelch-like erythroid cell-derived protein with CNC homology [ECH] associated protein 1) are signaling pathway (Table 2) (Figure 2) [2].

Section: Research Paper
ISSN 2063-5346

Figure 2: Nrf2-Keap1- ARE signaling pathway.

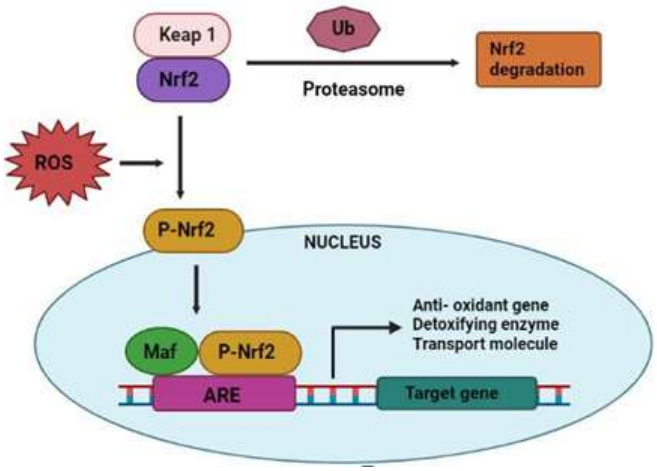


Table 2: Dosage of vitamins as antioxidants and their efficiency [2]

Antioxidants	Dosage	Efficiency
Vitamin E	About 450 mg/day to 500 mg/day	It helps in lowering the lipid peroxide level in liver.
Vitamin C	About 550 mg twice a day	Vitamin C along with metformin results in the reduction of fasting blood sugar level.
Vitamin E + Vitamin C	Vitamin C about 50 mg to 60 mg/day and vitamin E 150 mg Twice-a-day for about 5 weeks	Helps in the reduction of lipid peroxidation in liver to a large extent.
Selenium	About 0.5 µg/day	It helps in there duction of oxidative stress in the body.

Antioxidants and Diseases

Diabetes Mellitus

Diabetes mellitus is a serious metabolic disorder caused by two underlying causes: β-cells in the pancreas being unable to produce insulin in adequate amounts and the body not able to utilize insulin properly [3]. Antioxidants like vitamin E, vitamin C, selenium *etc*. are very effective in reducing problems associated with diabetes and maintain in optimum production and utilization of insulin (Table 3) [4].

Section: Research Paper
ISSN 2063-5346

Table 3: Vitamin E enriched food items [4].

Food Sources	Vitamin E content (mg/100g)
Sunflower oil	41
Almond	25
Wheat germ	16.5
Olive oil	16
Safflower oil	33
Spinach	2.2

Antioxidants against Diabetes

Oxidative stress is the main cause of diabetes mellitus due to the excess formation of free radicals in the body. It is caused by an improper balance between the increased number of free radicals and decrease in antioxidant defenses, leading to micro vascular complications and tissue damage. Endothelial cells are vulnerable to the adverse effects of diabetes due to their complex antioxidant system, which is decreased in type 2 diabetes. Antioxidants can be addressed by the use of various antioxidants [5]. Some antioxidants which are beneficial against diabetes mellitus like selenium is a naturally occurring antioxidant that has been found to be helpful in glucose metabolism, activating protein required for insulin synthesis. This is due to an increase in glucose tolerance and alteration in the function of gluconeogenic enzymes [6]. Vitamin E is a highly active lipophilic antioxidant that helps to control free radical levels in the body. It is made up of tocopherols and tocotrienols and plays a major role in defending a cell against oxidative damage [7]. It also decreases hepatic lipid peroxide levels and improves the OGTT (Oral Glucose Tolerance Test) in diabetic conditions. Vitamin E also lowers the complications of the macrovascular system and microvascular systemin patients suffering from diabetes [4]. Vitamin E is helpful at regulating diabetes in rats, according to recent studies. All of the rodents were discovered to have diabetes three days after the injection, with blood glucose levels greater than 250 mg/dl [8]. However, the blood glucose levels of the treated rats were also under control. The mortality rate of untreated rats was greater than that of vitamin E treated rats.

Atherosclerosis

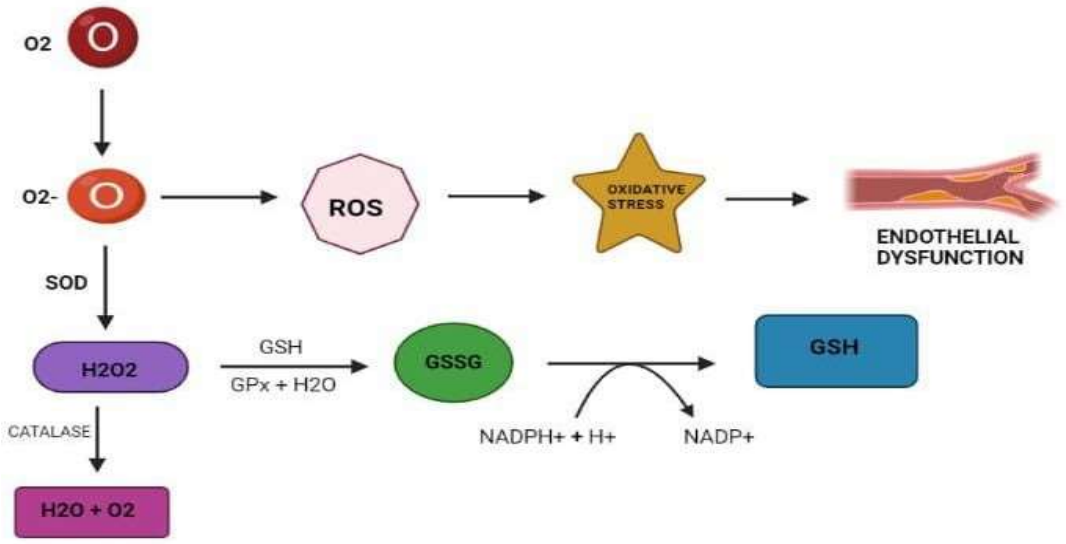
Atherosclerosis is a type of chronic, progressive, complex inflammatory disease that causes arteries to become narrow due to buildup of plaque on the arterial walls. It is caused by damage to the endothelium which is caused by various factors such as smoking, high blood pressure or high levels of glucose, fat and cholesterol in blood. Antioxidants plays an important role in preventing atherosclerosis by reducing oxidative stress, reducing the generation of ROS (Reactive Oxygen Species), preventing formation of plaque in the arterial wall and reducing the bioavailability of nitric oxide [9].

Role of antioxidants and its effect on atherosclerosis

Defense mechanism of antioxidants occurs in two processes; primary defense mechanism by endogenous enzymes like SOD (Superoxide Dismutase) and glutathione scavenge free radicals and convert H_2O_2 (Hydrogen peroxide) into H_2O (Water) and O_2 (Oxygen), which is reduced to form glutathione (Figure 3).

Section: Research Paper
ISSN 2063-5346

Figure 3: Antioxidant defense mechanism



[GSH- Glutathione; GPx- Glutathione peroxidase; GSSG- Glutathione disulfide.]

Secondary defense mechanism by vitamin C and vitamin E have a particular role in this mechanism by scavenging free radicals. Apart from these, nuclear enzyme acts a secondary defense mechanism.

Ganoderma lucidum is a traditional medicine used as antioxidants, anticancer, immune-stimulatory, antimicrobial, anti-inflammatory and energy enhancing agent (Table 4) [10]. β-glucan is mainly composed of β-D-glucose and acts as an antioxidant in atherosclerosis disease.

Table 4: Composition of *Ganoderma lucidum* [10].

Compounds	**Content [mg/100g]**
Vitamin B_1	3.50
Vitamin B_2	17.5
Vitamin B_6	0.8
Niacin	62
Calcium	830
Phosphorus	4.2
Iron	81
Choline	2.0

Superoxide Dismutase (SOD) reduces atherosclerotic wound size by reducing free radicals and preventing the expression of Vascular Cell Adhesion Molecule-1 (VCAM-1) and Monocyte Chemoattractant Protein-

Section: Research Paper
ISSN 2063-5346

1(MCP-1) [11]. Malondialdehyde (MDA): MDA damages blood vessels and increases free radicals [9].

Circulating Endothelial Cells (CEC): CEC increases endothelium injury, acting as a biomarker for atherosclerosis. Endothelial Progenitor Cells (EPC): EPCs are associated with atherosclerosis and act as biomarkers [9]. Vitamin E, vitamin C, vitamin B, vitamin A and carotenoids have preventative effects against atherosclerosis. Vitamin C is a water-soluble antioxidant that scavenges free radicals and improves endothelium, reducing cardio vascular disease (CVD) [12]. Vitamin A and carotenoids are antioxidants that reduce cholesterol levels and reduce endothelium dysfunction, inhibiting CVD [9]. Vitamin E is a fat-soluble vitamin with important roles in various diseases [13].

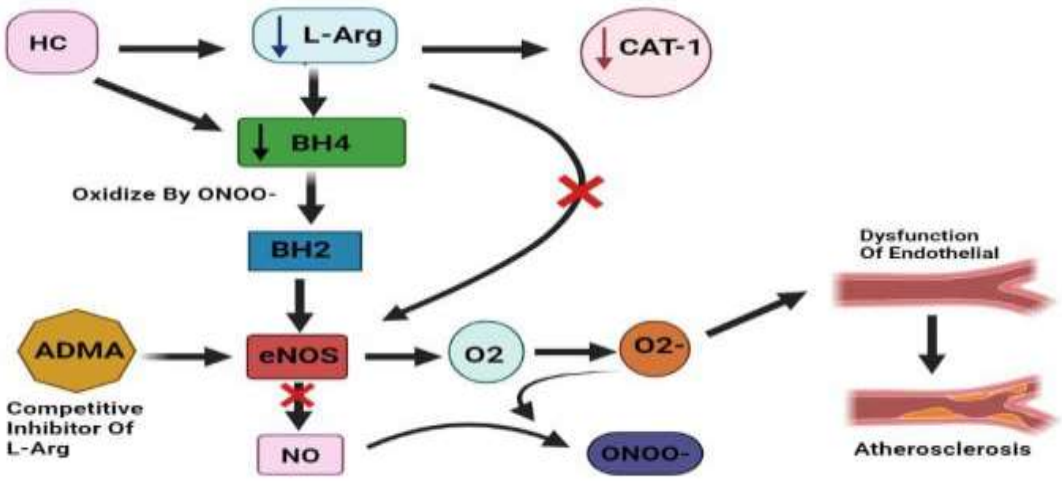
Role of vitamin E in cardiovascular disease

Vitamin E has a preventing role in CVD through its down regulation of CD36 (cluster of differentiation 36), NFkB (Nuclear factor kappa B) signaling, PKC (Protein Kinase C) signaling [14], c-jun phosphorylation, and Nrf2(Nuclear factor erythroid 2 related factor 2), ABCA-1(ATP-binding cassette sub-family-A member 1) and PPAR-γ (Peroxisome proliferator activated receptors), LXRα (Liver X receptor). Different vitamin E compounds have different antioxidative effects, with α-tocopherol decreasing the activity of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase and γ-Tocopherol scavenging free radicals [15].

Role of vitamin E in atherosclerosis

Vitamin E has a major role in atherosclerosis, reducing hypercholesterolemia, inhibiting HMG-COA (Hydroxymethyl glutaryl-coenzyme A reductase inhibitor) reductase, producing NO (nitric oxide) from endothelial cells, inhibiting the penetration of leukocyte/monocyte to sub-endothelial space, reducing the activity of CAT-I (cationic amino acid transporter 1) and upregulating NOS (nitric oxide synthase) proteins expression to prevent BH4 (tetra hydro biopterin) oxidation [16] (Figure 4).

Figure 4: Atherosclerosis is form by homocysteine



Oxidized LDL (OxLDL) in the subendothelial space of arterial wall leads to atherosclerosis. α-Tocopherol

Section: Research Paper
ISSN 2063-5346

down regulates the CD36 receptor to prevent the formation of fatty streaks in the arterial walls [17]. Polyphenols and related phenols are synthetic antioxidants that have a potential beneficial effect in atherosclerosis by preventing ROS formation, scavenging ROS, increasing eNOS expression and reducing NO oxidation [18].

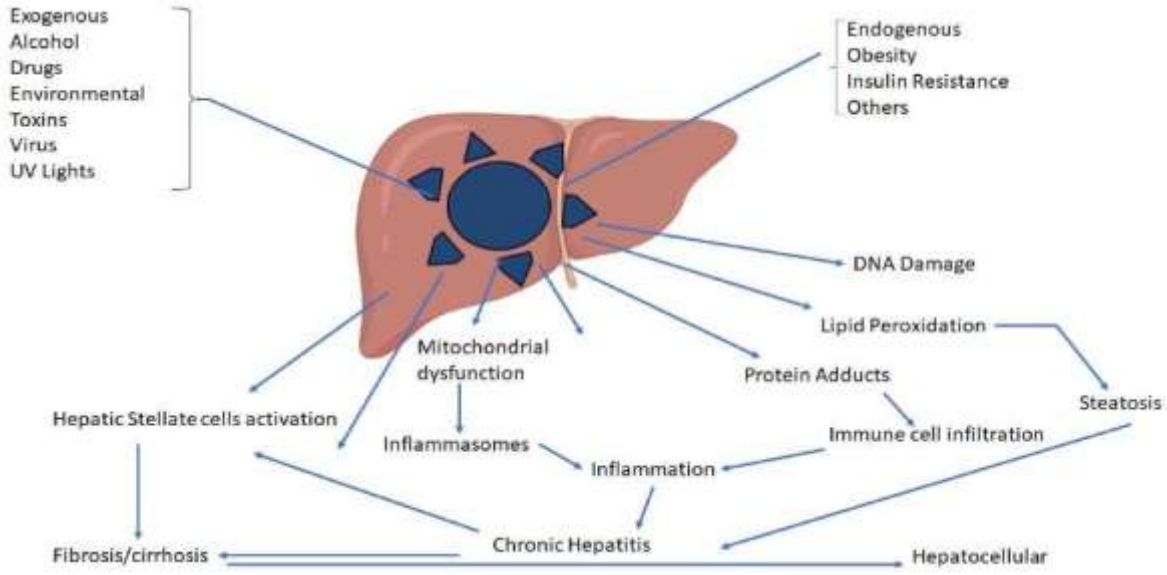
Liver cirrhosis

Liver cirrhosis is a chronic liver damage caused by hepatitis, chronic alcoholism, and other causes, leading to liver failure. Antioxidants are used to balance the ratio of free radicals in the liver, and herbal agents are also beneficial for liver cirrhosis. Alcohol consumption is a major cause of liver cirrhosis, but many other causes have been recognized [19]. Liver fibrosis can occur from numerous conditions, and is connected to viral hepatitis and portal central in bridging fibrosis. Fibrosis can be cured if diagnosed in early stage, but cirrhosis is serious scarring of liver tissue that hampers normal functioning and blocks the normal blood flow. Mesenchymal stem cells can differentiate, perform immunomodulation, and release bioactive molecules to cure organ diseases caused by tissue injury or decadence. Use of hucMSC-Ex can improve liver function and increase survival, but it can't help in the fundamental credit of differentiation into hepatocytes [20]. HucMSC-EX was found to suppress liver tumors after 8 months of injection, even though doses of 250 and 200 were sufficient to enhance liver fibrosis and injury healing [21].

Antioxidants and their effect on liver cirrhosis

Oxidative stress is caused by an imbalance of cell antioxidants, which can lead to liver failure and death [22]. (Figure 5) explain the causes of this oxidative stress and how it invites other diseases to occur in our body which ultimately leads to liver cirrhosis and which further may lead to cancer of liver.

Figure 5: How oxidative stress causes various diseases [22].



Antioxidants are essential for maintaining the balance of oxidative stress in the body. They reduce the oxidative stress, maintain normal functioning and the stability, and have anti-inflammatory, membrane stabilization and anti-apoptotic characteristics [23]. Research has shown that antioxidants in diet improve the

Section: Research Paper
ISSN 2063-5346

anthropometric conditions, lipid profiling and reduces hepatic fat accumulation. Zinc is beneficial for curing chronic liver disease, and vitamin E has a great role in curing liver disease [24]. Treating rats or mice with liver disease with different causative agents and natural or artificial antioxidants can have beneficial effects (Table 5).

Table 5: The effect of antioxidant in liver diseases [25].

Model (Prevent/Treatment)	Material	Effect	Dose (Dose-Effect)	Bioactive Compounds
Rats treated with ethanol diet	Green tea	Enzymes, non-enzymatic antioxidants; lipids and protein oxidation	7g/L in Ethanol Lieber-DeCarli diet	Epicatechin gallate
Rats treated with ethanol	*Ziziphus mauritiana* leaf	ALT, AST, ALP, total bilirubin, CAT, GSH-Px, glutathione reductase and SOD	200 and 400 mg/kg of body weight	Tannisns, saponins and phenolic compounds
Rats sub-chronically exposed to ethanol	Methanolic extract from *Hammada scoparia* leaves	Aminotransferase, glycogen-synthase kinases-3 beta, lipid peroxidation, GSH-Px	140g/kg in diet	Total phenols
Mice with acute alcohol-induced liver injury	Peduncies of *Hovenia dulcis*	ALT, AST, MDA, SOD, GSH-px	100, 350 and 600mg/kg	Non-starch polysaccharide
Rats treated with ethanol	Methanolic extract from *Hammada scoparia* leaves	Aminotransferase, glycogen-synthase kinases-3 beta, lipid peroxidation, GSH-Px	200mg/kg	Phenolic compounds
Mice with alcoholic liver damage	Jujube honey	Lipoprotein oxidation, AST, ALT, MAD, 8-hydroxy-@-deoxy guanosine; GSH-Px	27 and 54g/kg	Phenolic acids
Mice with alcohol induced hepatotoxicity	Freeze dried, germinated and fermented mung beans	Antioxidant level, NO	200 and 1000mg/kg	
Chronic ethanol exposure in rats	Virgin olive oil	Transaminase levels hepatic lipid, Peroxidation, GSH-Px, SOD and CAT	5% (wt/wt) in diet	Tocopherols, chlorophyll, total polyphenols

Section: Research Paper
ISSN 2063-5346

Special emphasis on vitamin E for the treatment of liver cirrhosis

Vitamin E is a fat-soluble vitamin that appears in multiple forms and is utilized by the human body. Its serum concentrations are regulated by the liver, which preferentially releases α-tocopherol again. Antioxidants effectively protect from the oxidative damage caused by free radicals, which can cause cell damage and may play a role in the development of other severe disorders. Vitamin E is being studied to see if it can help prevent or delay chronic diseases due to free radicals by limiting free-radical production and possibly through other mechanisms [25].

Case studies (liver cirrhosis)

Case 1

This research examined the effectiveness of using antioxidants such as vitamin E and bicyclol to treat NAFLD (Non-alcoholic fatty liver disease) [26]. After 24 weeks of treatment, steatosis, inflammation, hepatocellular ballooning, and NAS (neonatal abstinence syndrome) were reduced. Bicyclol was also shown to reduce hepatic inflammation and NAS. Metformin was found to improve glucose metabolism when used in combination with bicyclol or vitamin E. A combination of drug therapies is critical in the treatment of NAFLD with IFG (impaired fasting glucose) [27].

Case 2

One article was published in 2013, which explains the effects of vitamin E probiotics on patients with liver cirrhosis [28]. 34 patients were given placebo tablets and 33 received vitamin E. After a year, the serum level of alpha-tocopherol had grown significantly, but there was no effect on rates of death. When cirrhotic patients were compared to alcoholics with liver disorders, serum levels were found to be lower. Vitamin E supplementation raised plasma concentration and the vitamin E: cholesterol ratio, but still had no impact on the patients' liver function. The data indicates that these techniques work, but measures should be taken from the starting to prevent extreme circumstances.

Case 3

TPGS (Tocopherol polyethylene glycol succinate) micelles are loaded with resveratrol, a natural polymer with antioxidant and anti-inflammatory properties, for reverse spinocerebellar degeneration and lipid peroxidation. Infrared spectroscopy, differential scanning calorimetry and loading capacity testing showed that TPGS improves water solubility and lessens cytotoxic effects [29].

Parkinson's Disease (PD)

Parkinson's a type of neurodegenerative disorder, invades pre-eminently dopamine-producing neurons which are present in a specific area of the midbrain called substantia nigra [30]. Earlier research study shows that antioxidant can't cure the PD completely but they delay the process by reducing the oxidative stress.

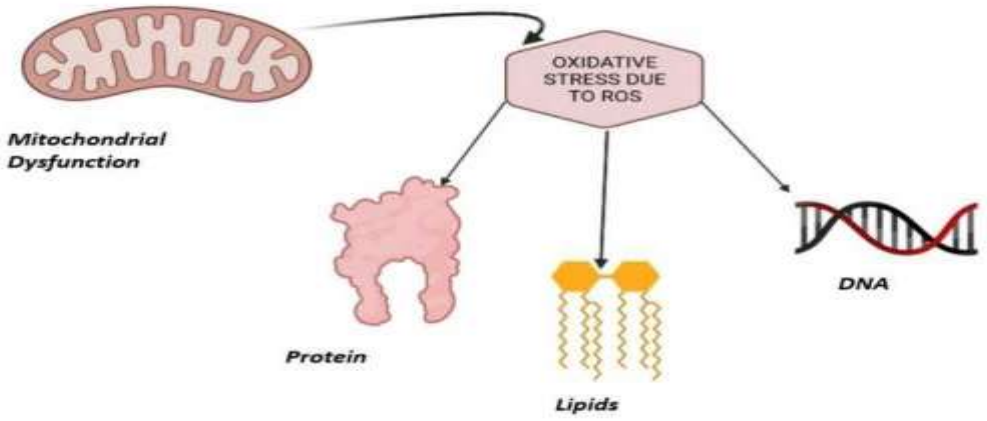
Role of antioxidants against Parkinson's Disease (PD)

PD is a neurological disorder characterized by loss of nerve cells in the substantia nigra of midbrain, leading to reduced dopamine production and abnormal movements. Oxidative stress is involved in the process of

Section: Research Paper
ISSN 2063-5346

neurodegeneration. Glutathione reduces oxidative stress. The predominant ROS, O_2^- (superoxide anion) is produced in ETC chain by complex I and complex III (Figure 6)

Figure 6: Biomarkers of oxidative stress.



Ginseng is a popular herbal medicine used as a treatment for PD, with two types: Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*, L.) (Table 6) [31].

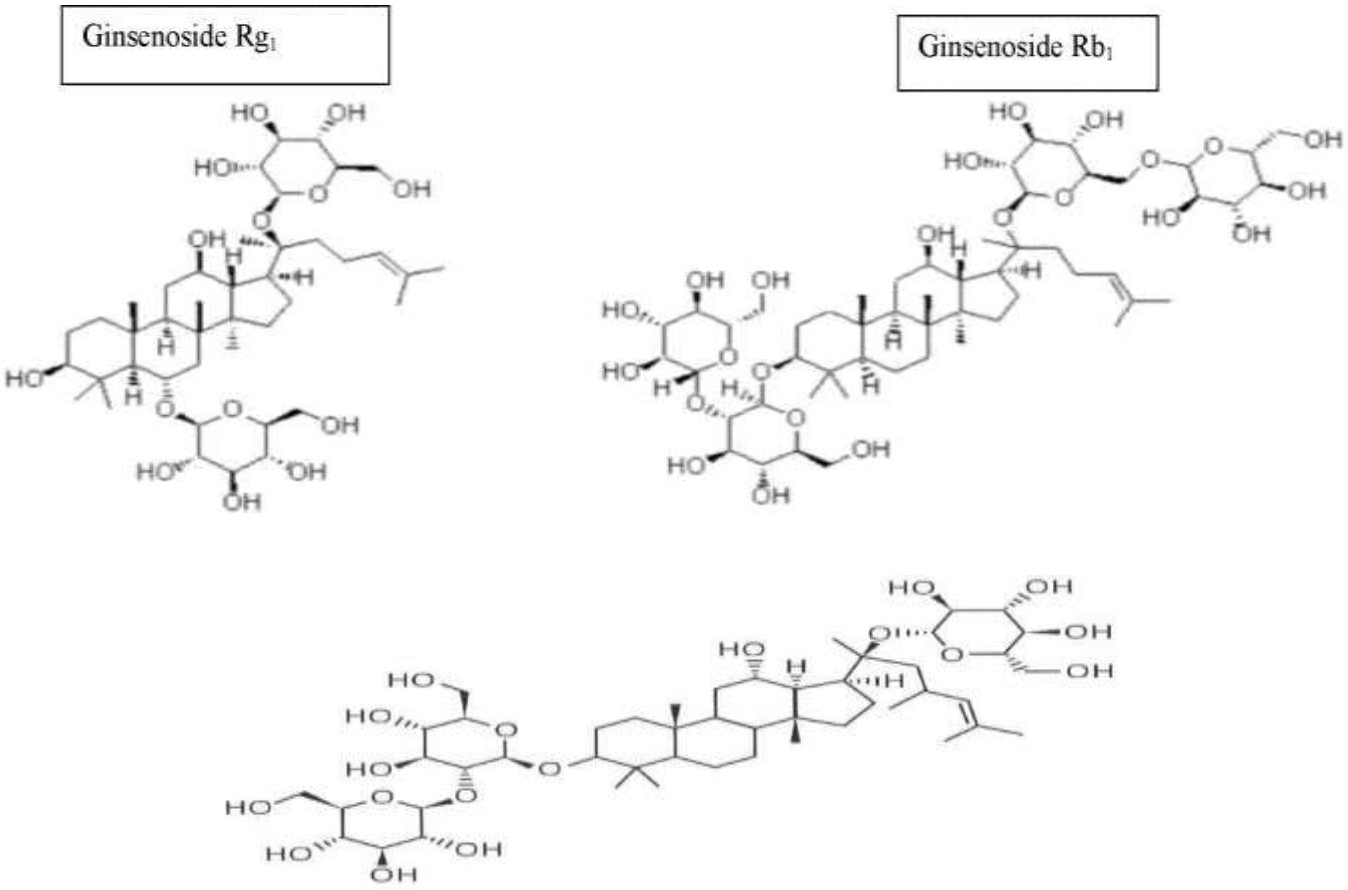
Table 6: Types of *Panax* species [31]

Panax species	**Habitat**
Panax ginseng	China, Japan and Korea
Panax quinquefolius	US, Northern China and South Canada
Panax notoginseng	China
Panax pseudoginseng	Eastern Himalayas and Nepal

From red ginseng over 100 ginsenosides are isolated they are Rb_1, Rb_2, Rb_3, Rc, Rd, Re, Rf, Rg_1, Rg_2, Rg_3 , Rh_1, Rh_2, Ro *etc* (Figure 7).

Section: Research Paper
ISSN 2063-5346

Figure 7: Chemical structure of ginsenoside Rgi, Rbi, Rd



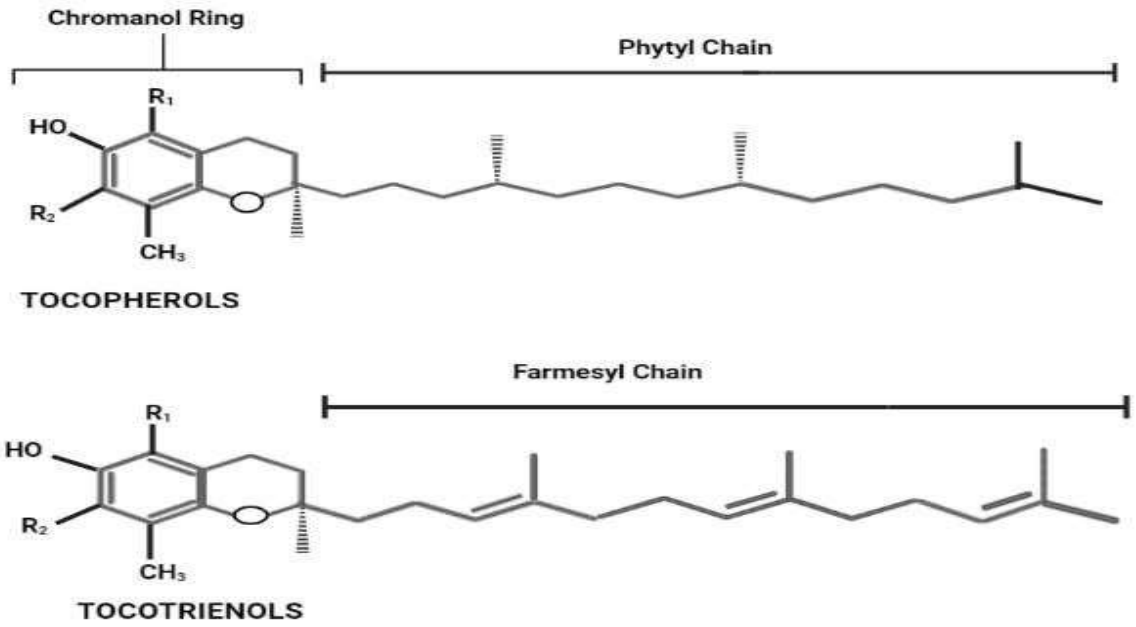
The sequence of scavenging effects of red ginsenosides are Rc> Rb2> Rg2> Rh2> Rh1> Rf> Rg3> Rg1> Rb1> Re> Rd. Among them Rb1, Rd and Rg1 have most frequently studied in Parkinson's disease (PD) [31].

Rb1 and Rg1 are ginsenosides used to treat PD, which is caused by glutamatergic transmission and excitotoxicity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine rodent model [32]. Rg1 has both *in vitro* and *in vivo* effects on dopaminergic cells, relieving oxidative stress and decreasing cell apoptosis [33]. It also increases the secretion of NGF (nerve growth factor) and BDNF (Brain derived neurotrophic factor) and diminishes the function of antiapoptotic proteins Bax (Bcl-2-associated X protein) and Bcl-2 (B-cell leukemia/lymphoma 2 protein).

Vitamin C acts as an antioxidant to neutralize free radicals, but its role in PD is controversial [34]. Melatonin reduces oxidative stress and protects mitochondria and neurons, delaying PD progression [35].
Vitamin E is a lipid soluble vitamin composed of tocopherol and tocotrienols, which are different due to the presence of different positions and number of methyl groups in the aromatic ring (Figure 8) [36].

Section: Research Paper
ISSN 2063-5346

Figure 8: The Structure of Tocopherols and Tocotrienols [36]



Tocopherol / Tocotrienol	**R_1**	**R_2**
α-	CH3	CH3
β-	CH3	H
γ-	H	CH3
δ-	H	H

Effect of vitamin E in nervous system

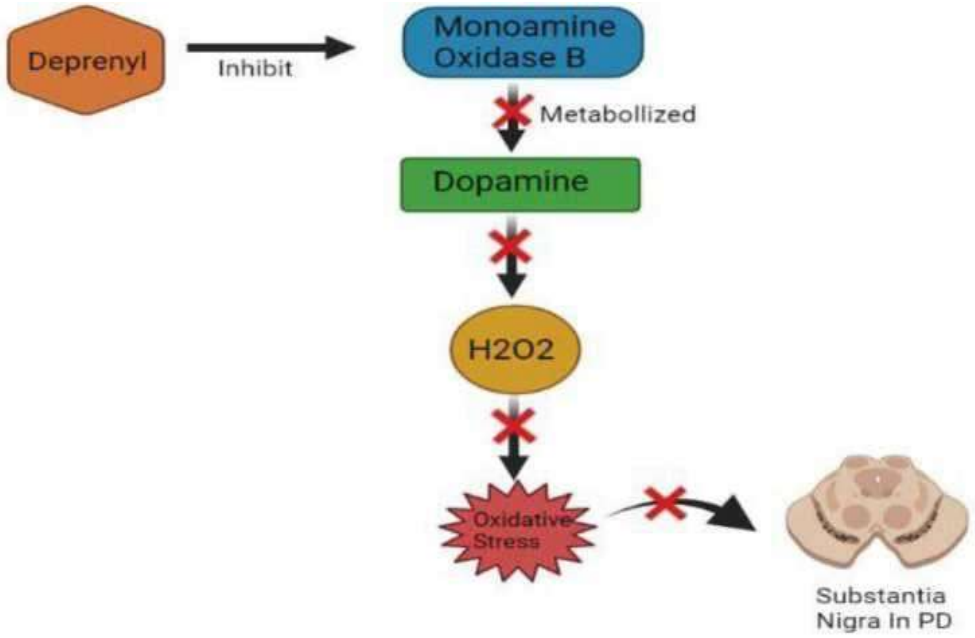
Vitamin E deficiency causes neuropathological changes in the nervous system, such as cystic fibrosis, chronic cholestatic hepatobiliary diseases, short-bowel syndrome, and a beta lipoproteinemia [37]. Deficiency of vitamin E is depleted faster in cerebellum than other parts of the brain, resulting in changes such as reduced activity of Cytosolic phospholipase A2, decreased production of prostaglandin E2, and reduced synapses in cerebellar glomeruli [38].

Section: Research Paper
ISSN 2063-5346

Effect of vitamin E in PD

Vitamin E may be used as a therapeutic agent to protect against the development of Parkinson's disease by inhibiting protein kinase C by α-tocopherol [39]. Deprenyl inhibits mono amine oxidase B, preventing oxidative stress in Parkinson's disease patients. Thus, deprenyl can reduce oxidative stress and delay the application of levodopa [40] (Figure 9).

Figure 9: Parkinson's disease is prevented by Deprenyl



Vitamin E can increase the concentration of α-tocopherol in spinal fluid and act as an antioxidant in neuro degenerative diseases, but its protective effect is unclear [41-45].

CONCLUSIONS

Hyperglycaemic condition in the body leads to an increase in the number of ROS and RNS, which oxidize the important free radical macromolecules of the body. The source of antioxidant taken from the diet is found to be the most beneficial form of antioxidant which helps on preventing and curing diabetes mellitus. Dietary supplements like vitamin E, vitamin C, carotene and polyphenols can reduce the oxidative radicals in atherosclerosis, melatonin can delay the PD, HuMSC can cure liver cirrhosis, and green tea and jujube honey can also be used to save livers.

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Section: Research Paper
ISSN 2063-5346

Conflict of interest

Theauthorshavenorelevantaffiliationsorfinancialinvolvementwithanyorganizationorentitywithafinancialinterest in or financial conflict with the subject matter or materials discussed int he manuscript.

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Section: Research Paper
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