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OXIDATIVE STRESS RELATED PATHOLOGICAL CONDITIONS AND HERBS CONTRIBUTING AGAINST OXIDATIVE STRESS: A REVIEW

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ABSTRACT

Oxidative stress is one of the pathogenesis of lifestyle-related diseases related to humans which includes cancer, diabetes mellitus, cardiovascular diseases and neuro-degenerative disease disorders. The apt definition of oxidative stress is "A state where oxidative forces exceed the antioxidant systems due to imbalance between them". Oxidative stress is largely induced by the modern lifestyle, which includes eating processed food, being exposed to a variety of pollutants, and not exercising. The use of medicinal plants with antioxidant properties has been used to treat or prevent various human pathological conditions. Herbal medicines are being explored as alternative agents for oxidative stress and its related pathological conditions. These natural compounds have been found to be safe, inexpensive, highly tolerated, and improve patient convenience. Plants have been crucial in healthcare since ancient times, particularly in treating diseases and discovering new drug molecules. However, the active constituents of plant extracts are complex due to their numerous ingredients. Many herbal folk medicines for oxidative stress have not been thoroughly studied, making them an alternative to synthetic sources. Future research should focus on determining the pharmacological activities of these herbal medicines and developing effective formulations. This review summarizes the herbs that are useful in reduction of pathological conditions due to oxidation of tissues. Furthermore the morphology, the active constituents, their mechanism of action against oxidative stress and their therapeutic activities are being discussed.

KEYWORDS: Anti-oxidants, ROS, cancer, cardiovascular diseases, diabetes, neuro-degenerative disorder.

INTRODUCTION

In recent years, oxidative stress and diseases linked to a sedentary lifestyle have developed a strong correlation. Free radicals and antioxidants in your body are not balanced, which causes oxidative stress[1]. Organs and tissues may be harmed as a result, leading to numerous disorders. By leading a healthy lifestyle, you can assist your body in keeping its equilibrium. It not only brings about dangerous occurrences like lipid peroxidation and oxidative DNA damage[2], but also physiological adaption phenomena and control of intracellular signal transduction[3]. Oxidative stress is largely induced by the modern lifestyle, which includes eating processed food, being exposed to a variety of pollutants, and not exercising. Condition in which oxidation outpaces the body's antioxidant systems as a result of the loss of their delicate equilibrium. The use of medicinal plants with antioxidant properties has been exploited for their ability to treat or prevent several human pathological conditions, in which oxidative stress is seems to be one of the causes[4]. As a result of several side effects associated with current drug compounds, there is a continuous search especially natural source for alternative agents for oxidative stress and its related pathological conditions. Several herbal medicines constitute towards a potentially important avenue leading to novel therapeutics for oxidative stress that may be safe, relatively inexpensive, highly tolerated and improves patient convenience. This review aims to provide an overview of oxidative stress related pathological conditions and the possible naturally derivable antioxidant compounds with their mechanisms of antioxidant defences that can help in the prevention of such related diseases.

Free radicals

Free radicals are atoms and molecules that contain unpaired electrons. Due to the unpaired electrons' propensity to form pairs with other electrons, free radicals are typically unstable and extremely reactive. When an oxygen molecule oxygen molecule is metabolized in vivo, it goes through a four-electron reduction. Reactive oxygen metabolites are produced during this process by the secondary excitation of electrons caused by the addition of energy or by interaction with transition elements. Thus, the formed reactive oxygen metabolites are known as active oxygen species and are more intensely reactive than the initial oxygen molecule. Active oxygen species in the strict sense include singlet oxygen, superoxide, hydrogen peroxide, hydroxyl radicals, and hydrogen peroxide[1,5]. Some externally and internally generated sources of free radicals are given below, (Table 1)

Table 1 – Various sources of free radicals[5]

External source	Internal source
Cigarette smoke	Mitochondria
Environmental pollutants	Xanthine oxidase
Radiation	Peroxisomes
Certain drugs	Inflammation
Pesticides	Phagocytosis
Industrial solvents	Arachidonate pathways
Ozone	Exercise
	Ischemia/reperfusion injury

Anti-oxidants

An antioxidant is a molecule that is stable enough to give an electron to an out-of-control free radical and neutralize it, so lowering the radical's potential for harm. These antioxidants' ability to scavenge free radicals is primarily responsible for delaying or inhibiting cellular damage. These antioxidants having low molecular weight can interact with free radicals to terminate the chain reaction before important molecules are harmed. Some of these antioxidants, such glutathione, ubiquinol, and uric acid, are created by the body's regular metabolic processes[6]. The diet also contains some softer antioxidants. Although the body contains many enzymes that scavenge free radicals, vitamin E (α-tocopherol), vitamin C (ascorbic acid), and beta-carotene are the main micronutrient antioxidants[7]. These micronutrients must be given in the food because the body cannot produce them on its own[1].

Mechanism of action

The following pictorial representation depicts both the Enzymatic and Non-enzymatic mechanism that controls free radicals formation and therefore the effect of free radicals on these both mechanisms that causes imbalance leading to oxidative stress and its related pathological conditions.

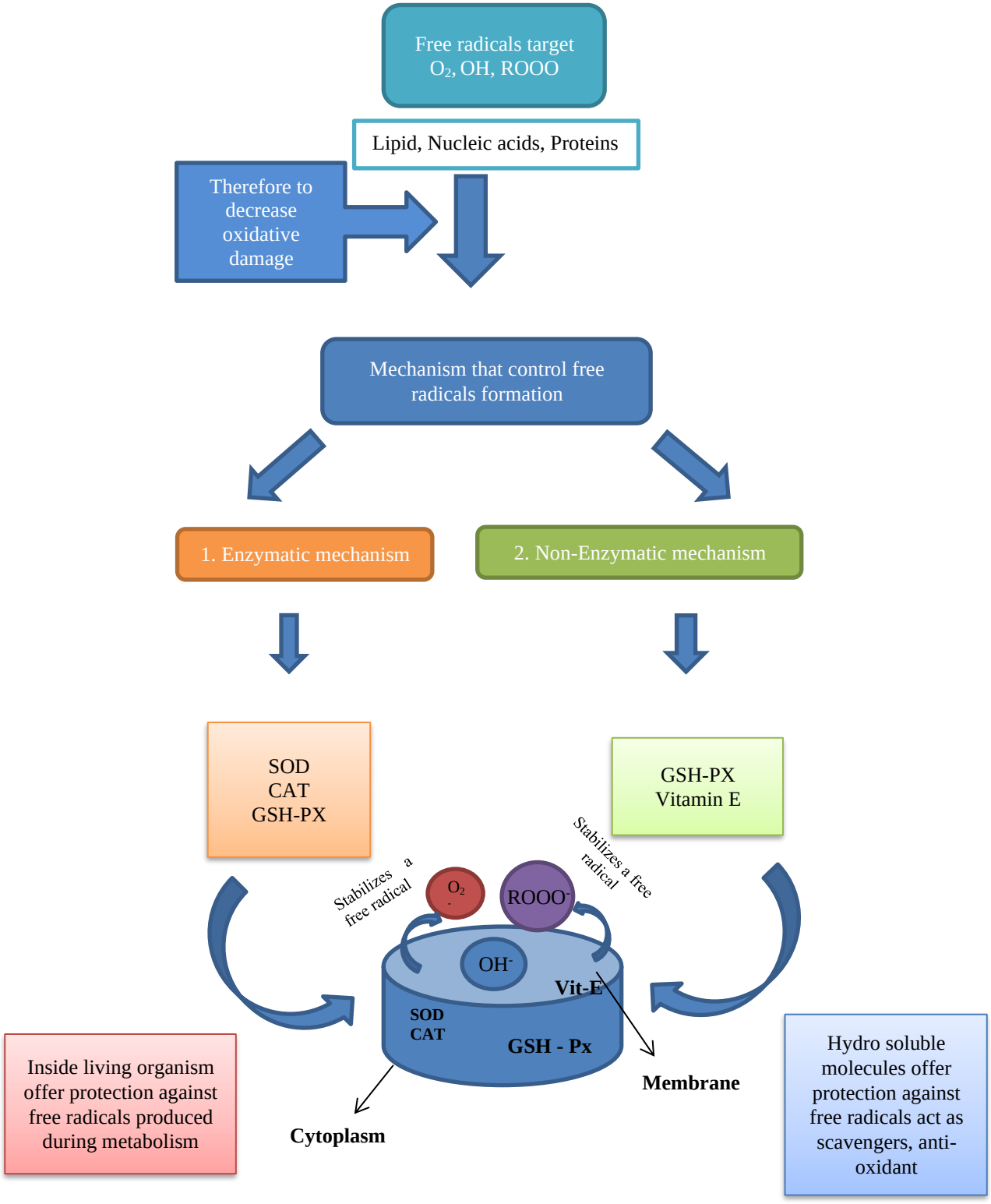


Figure 1. Mechanism of action of oxidative stress

Rapid metabolism introduces additional free radicals that produces an imbalance between reactive oxidative species generation and the antioxidant system. Such free radical species lead to oxidative damage to cells like lipids, proteins, or nucleic acids. The first-line defence antioxidants basically include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase(GPx)[8]. Several antioxidants have been exploited from the herbal phytomolecules in recent years for their actual or supposed beneficial effects against oxidative stress. The following table shows the herbs containing chemical constituents contributing towards oxidative stress induced diseases.

Herbs contributing against oxidative stress induced diseases

A. Cancer

Cancer in humans is caused by both cellular and molecular alterations that are mediated by endogenous and/or exogenous stressors. It is widely known that oxidative DNA damage is one of the factors that contribute to the emergence of cancer. Oxidative stress-induced chromosomal abnormalities and oncogene activation can drive and/or promote cancer[9]. Many medicinal herbs containing phytoconstituents are used to treat cancer induced by oxidative stress; some of them are discussed in the above table.

Table 2. Herbs contributing against cancer

Herbs	Isolated Phytoconstituents	Therapeutic uses	Reference
1. *Moringa peregrine* **(Moringaceaea)** 	Carvacrol, Geijereme, Linalool, Caryophyllene-Oxide, N-Hexadecane.	Antioxidant, Antibacterial, Anti-Diabetic, Anti-Spasmodic, Hypertension, Hepatotoxic, Lipid-Lowering Action, Anti-Inflammatory, Anticancer, and Memory Disorders.	[10-13]
2. *Curcuma longa* **(Zingiberaceae)** 	Curcumin, Zingerone,Curcuminoid,	Anti-oxidant, Anti-cancer, Anti-inflammatory, Anti-bacterial, Anti-fungal, Anti-viral, Anti-diabetic, Anti-ageing and lipid lowering effect.	[14-17]

3. *Phyllanthus acidus* **(Phyllanthaceae)** 	Catechin, Gallic acid, Mallic acid, Rutin, Quercetin, β sitosterol, lupeol	Purgative, Cure Sciatica, Lumbago, and Rheumatism, Treat Stomach Ailments, Blood Enhancer, Strong Immune System.	[18-22]
4. *Flemingia vestita* **(Fabaceae)** 	Genistein, Diadzein, Formononetin and Pseudobaptigenin.	Stomach Ailments, Menstrual Problems, Antioxidant and Treat Nemtodes.	[23-25]

1. Moringa peregrine *(Hyperanthera aptera (Gaertn.) Steud*

Moringa peregrine (Forssk.) Fiori belonging to the family Moringaceaea. It consists of Carvacrol (figure 2), geijerene, linalool (figure 3), caryophyllene-oxide and n-hexadecane as some of the active constituents. Carvacrol improves glutathione (GSH) levels. Carvacrol maintains GSH levels by the removal of ROS, through its radical elimination effects and also it prevents lipid peroxidation by inducing SOD, GPx, glutathione reductase (GR), and CAT. Carvacrol effectively eliminates free radicals, such as peroxyl radicals, superoxide radicals, hydrogen peroxide, and NO[10]. The Parts of M. peregrine were examined for a variety of medicinal and pharmacological properties, including antioxidant, antibacterial, anti-diabetic, anti-spasmodic, hypertension, hepatotoxic, lipid-lowering action, anti-inflammatory, anticancer, and memory disorders[11,12,13].

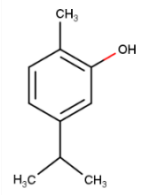


Figure 2. Carvacrol

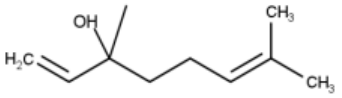


Figure 3. Linalool

2. Turmeric *(Curcuma domestica* Valeton)

Curcuma longa belonging to the family Zingiberaceae. Turmeric constitutes of curcumin (figure 4), curcuminoid, zingerone (figure 5) and many other chemical constituents as their active constituents. Curcumin reduces the level of malondialdehyde (MDA) in serum and has potential to raise the total anti-oxidant potential (TAC). The action of curcumin on markers of oxidative stress is associated with its properties towards the removal of reactive oxygen and nitrogen, metal chelation, and regulation of numerous enzymes[14]. Curcuma longa serves as an anti-oxidant, anti-cancer, anti-inflammatory, anti-bacterial, anti-fungal, anti-viral, anti-diabetic, and anti-ageing and also shows lipid lowering effect[15-17].

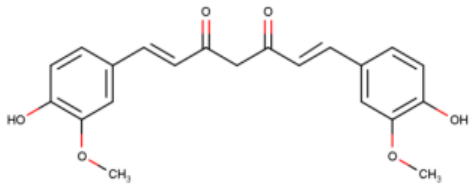


Figure 4. Curcumin

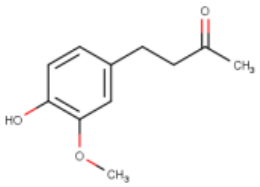


Figure 5. Zingerone

3. Phyllanthus acidus *(Averrhoa acida L)*

Phyllanthus acidus(L.) Skeels belonging to the family Phyllanthaceae**.** Catechin (figure 6) is the chief active constituent, that are reactive oxygen species (ROS), scavengers and metal ion chelators and indirectly comprises induction of antioxidant enzymes, inhibition of pro-oxidant enzymes and production of the phase 2 detoxification enzymes and antioxidant enzymes[18,19]. While the seeds are used as a cathartic and the root, when properly prepared, as a purgative, the peppered leaves are used to produce a poultice to cure sciatica, lumbago, and rheumatism (but have been shown to cause low blood pressure when mixed with nitrates). It plays an important role in Ayurveda, an Indian system of medicine, and is used to treat jaundice, gastropathy, diarrhoea, dysentery, fevers, menorrhagia, scabies, bronchitis, asthma, genital infections, ulcers, and wounds[20-22].

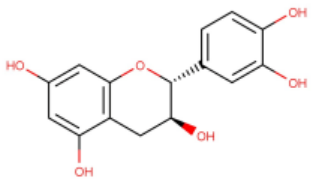


Figure 6. Catechin

4. Flemingia vestita (Moghania procumbens (Roxb.) Mukerjee)

Flemingia vestita belongs to the family **Fabaceae.** It is rich in bioactive isoflavones, such as genistein (figure 7), diadzein (figure 8), formononetin and pseudobaptigenin[23]. Genistein shows a strong inhibitory effect on oxidative stress through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)-heme oxygenase-1 (HO-1)/NAD(P)H dehydrogenase (quinone) 1 (NQO1) pathway. Because genistein is able to activate the Nrf2/NQO1 pathway, after phosphorylation, Nrf2 activates antioxidant response element (ARE) and increases transcription of Nrf2-regulated genes including NQO-1, HO-1, and glutathione S-transferase(GST) [24]. Flemingia vestita is used in the treatment of stomach ailments, menstrual problems, antioxidant, treatment of soft bodied intestinal worms ant to treat nematodes [23-25].

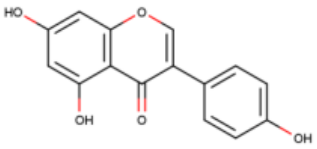


Figure 7. Genistein

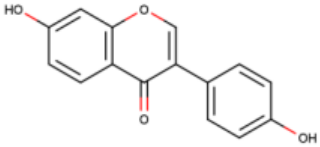


Figure 8. Diadzein

B. Cardiovascular diseases

Cardiovascular illnesses are clinical conditions having a complex origin. They are typically brought on by a wide range of risk factors, the most well-known of which include hypercholesterolemia, hypertension, smoking, diabetes, an imbalanced diet, stress and sedentary lifestyle[9]. Recent research findings indicated that oxidative stress should be regarded as either the major or secondary cause of many CVDs. Atherosclerosis is mostly brought on by oxidative stress. It is generally recognized that early endothelial inflammation, which in turn triggers the recruitment of in-situ macrophages to produce ROS, is the cause of atheromatous plaque development. Reactive oxygen species subsequently oxidize the circulating LDL, causing foam cells to develop and fat build up. An atherosclerotic plaque develops as a result of these circumstances. Both in vivo and ex vivo studies provided evidences supporting the role of oxidative stress in atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy, and congestive heart failure[26]. The phyto-metabolites present in the following plants are used to treat the cardiovascular diseases.

Table-3: Herbs contributing against cardiovascular disease

Herbs	Active constituents	Therapeutic uses	Reference
1.*Centella asiatica* **(Apiaceae)** 	Asiaticoside, Brahmoside, Asiatic acid, Brahmic acid Centellose, Centelloside, and Madecassoside	Insomnia, Asthma, Gastrointestinal Diseases, Fever, and Is Anti-Leprosy, Diuretic and Stomachic.	[27-29]
2.*Convallaria majalis* **(Asparagaceae)** 	Convallarin, Convallamarin, Neoconvallоside, Glucoconvalloside, Majaloside, Convallatoxon, Corglycon.	Heart Tonic	[15,30,31]
3.*Fraxinus excelsior* **(Oleaceae)** 	Nuzhenide, G13, G15, ligstroside, oleoside 11-methyl ester, excelsides B, oleoside dimethyl ester, coumarins.	Hypotensive Agent	[32-35]
4. *Digitalis purpurea* **(Scrophulariaceae)** 	Digitoxin, Gitoxin, Gitaloxin, Purpurea glycoside A & B, Inositol, luteolin, digitoflavon, digitonin.	Cardiac Stimulant, Diuretic And Heart Tonic	[36-38]

1. Centella asiatica (*Hydrocotyle asiatica L.*)

Centella asiatica (L.) belongs to the family **Apiaceae.** It constitutes of triterpenoids, which include asiaticoside, brahmoside, asiatic acid (figure 9), and brahmic acid (figure 10) (also known as madecassic acid), are found in leaves and make up roughly 1.0% of the leaves. Centellose, centelloside, and madecassoside are some of the additional components[27]. Asiatic acid is a most efficient chain breaking antioxidant. This operates against species of

reactive oxygen (ROS). Asiatic acid attenuates the stimulation of myeloperoxidases and prevents lipid peroxidation by enhancing the concentrations of enzymatic and non-enzymatic antioxidants[28]. The entire plant offers medicinal benefits. It is used as a nervine tonic to treat mental illnesses and to improve memory. It is useful for insomnia, asthma, gastrointestinal diseases, fever, and is anti-leprosy, diuretic, and stomachic. Leprosy is treated using a decoction of the plant[29].

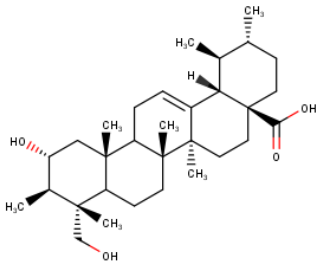


Figure 9. Asiatic acid

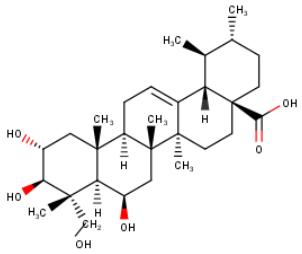


Figure 10. Madecassic acid (Brahmic Acid)

2. Convallaria majalis (*May bells)*

Convallaria majalis L. belongs to the family Asparagaceae. Cardiac glycosides (cardenolides) occur in the plant, convallatoxin(figure 11), convallarin, convallamarin(figure 12), neoconvalloside, glucoconvalloside, majaloside, convallatoxin[15] and corglycon are some of the active constituents present in Convallaria majalis. Cardenolides in general are proven to be stronger DPPH radical scavenger[30]. The Convallaria Majalis, a Strong homoeopathic medicine known as Mother Tincture is suggested for treating heart conditions and is regarded as a heart tonic. When the ventricles are enlarged and dialation starts, it is helpful[31].

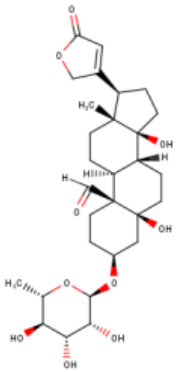
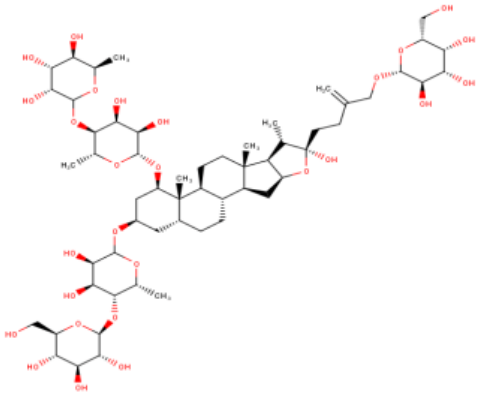


Figure 11. Convallatoxin



`Figure 12. Convallamarin

3. Fraxinus excelsior (*European ash)*

Fraxinus excelsior L. belongs to the family Oleaceae. Nuzhenide, G13, G15, ligstroside(figure 14), oleoside 11-methyl ester, excelsides B, oleoside dimethyl ester, coumarins(figure 13) are some of the active constituents present in the herb[32]. Coumarins serve as scavengers for DPPH radicals and therefore inhibit oxidation[33,34]. Fraxinus excelsior extract induces diuresis, according to a study on herbal remedies, and may therefore be utilized as a hypotensive agent[35].

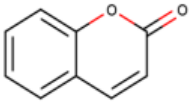


Figure 13. Coumarins

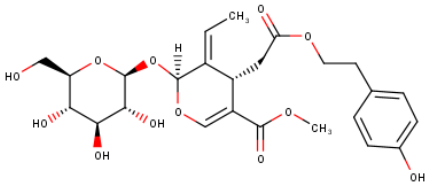


Figure 14. Ligsrtoside

4. Digitalis purpurea (*Foxglove)*

Digitalis purpurea belonging to the family Scrophulariaceae. Some of the active constituents reported are digitoxin(figure 15), gitoxin, gitaloxin, purpurea glycoside A(figure 16) & B, luteolin, digitoflavon and digitonin. However, a recent study has shown that Digitalis purpurea contains various antioxidant enzymes such as superoxide dismutase (SOD), peroxidase (POD), and catalase (CAT). These enzymes are responsible for protecting the biological system against the harmful effects of reactive oxygen species (ROS) [36]. Digitalis purpurea serves as cardiac stimulant, diuretic and heart tonic[37,38].

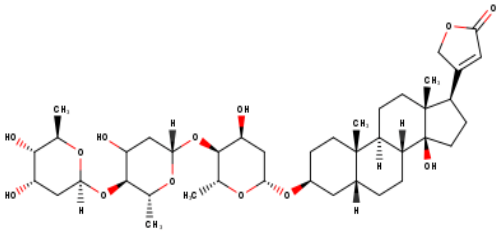


Figure 15. Digitoxin

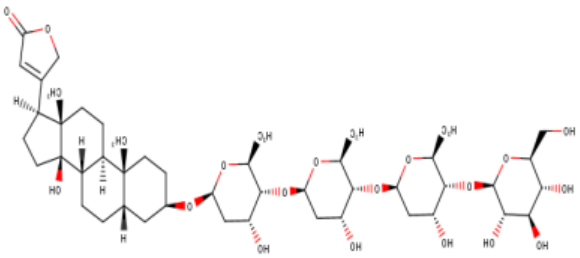


Figure 16. Purpurea Glycoside A

B. Diabetes

Table-4: Herbs contributing against diabetes

Herbs	Active constituents	Therapeutic uses	Reference
1. *Grevia asiatica* **(Malvaceae)** 	3,5-Diglucoside, Naringenin-7-O-B-D-Glucoside, Quercetin, Quercetin 3-O-B-D-Glucoside, Tannins, Catechins, And Cyanidin-3-Glucoside, Catechins, Cyanidin-3-Glucoside, Grewinol, Naringenin, 3,21,24-Trimethyl-5, 7-Dihydroxy-Hentriacontanoic Acid Δ Lactone, Betulin, Lupeol, Lupenone, Friedelin	Antifertility, Antioxidant, Antipyretic, Analgesic, Antibacterial, Antibiotic	[18,39,40]
2. *Zingiber officinale* **(Zingiberaceae)** 	Gingerols, Shogaols And Paradols	Carminative, Positive Inotropic, Spasmolytic, Aromatic Stimulant, And Antiemetic	[41,42]
3.*Nigella sativa* **(Ranunculaceae)** 	Thymoquinone, Dithymoquinone, Carvacrol, Longifolene, Dihydrocarvone, Piperitone, Anethole.	Treats Worms, Skin Eruptions,Indigestion, Lack Of Appetite, Diarrhoea, Dropsy, Amenorrhoea, And Dysmenorrhoea.	[43-47]

1. Grewia asiatica (*Grewia hainesiana Hole*)

Phalsa is its biological source and it belongs to the family Malvaceae. Grewia Asiatica contains pelargonidin 3,5-diglucoside, naringenin-7-O-β-D-glucoside, quercetin, quercetin 3-O-β-D-glucoside, tannins, catechins(figure 17), cyanidin-3-glucoside, Grewinol, Naringenin, 3,21,24-trimethyl-5, 7-dihydroxy-hentriacontanoic acid δ lactone, Betulin, Lupeol, lupenone, Friedelin as its active constituents[39]. Catechins are reactive oxygen

species (ROS), scavengers and metal ion chelators and indirectly comprises induction of antioxidant enzymes, inhibition of pro-oxidant enzymes and production of the phase 2 detoxification enzymes and antioxidant enzymes[18]. Grewia asiatica have reached wide spread acceptability as therapeutic agent for diabetic, antifertility, antioxidant, antipyretic, analgesic, antibacterial and antibiotic[40].

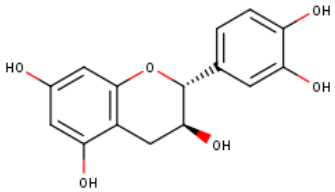


Figure 17. Catechin

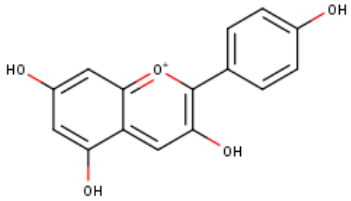


Figure 18. Pelargonidin

2. Ginger *(Ginger Officinale)*

Ginger consists of the dried rhizomes of the Zingiber officinale Roscoe of Zingiberaceae family. Ginger contains various active constituents, such as phenolic and terpene compounds. The phenolic compounds include gingerols (figure 18), shogaols (figure 19), and paradols. In fresh ginger, gingerols are the major polyphenols, such as 6-gingerol, 8-gingerol, and 10-gingerol[41]. Gingerol decreases the levels Hydrogen peroxide, Malondialdehyde, Nitrogen monoxide, Tumour necrosis factor-α and caspase-3 and increases enzymes such as catalase, SOD, GPx and GSH[42]. Ginger is used as a carminative, condiment, positive inotropic, spasmolytic, aromatic stimulant, and antiemetic. In addition, it is used for dyspepsia, flatulent colic, vomiting spasms, painful stomach afflictions, cold cough, and asthma[42].

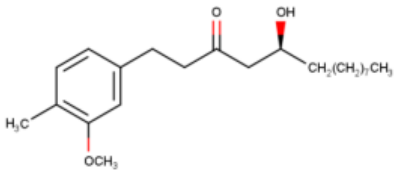


Figure 18. Gingerol

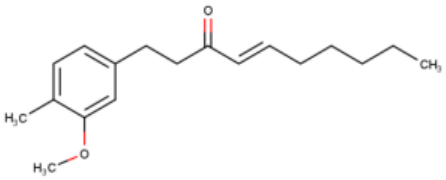


Figure 19. 6-shogaol

3. Nigella Sativa *(Nigella cretica Mill.)*

Black cumin is its biological source that belongs to the family Ranunculaceae. Thymoquinone(figure 21), dithymoquinone, Carvacrol(figure 20), longifolene, dihydrocarvone, α and β pinene, piperitone and anethole(figure 22) are some of the reported chemical constituents in N.Sativa[43]. Carvacrol improves glutathione (GSH) levels. The

maintenance of GSH levels by carvacrol occurs mainly by the removal of ROS, through the effects of its radical elimination. Carvacrol prevents lipid peroxidation by inducing SOD, GPx, glutathione reductase (GR), and CAT[44]. Carvacrol truly eliminates free radicals, such as peroxyl and superoxide radicals, nitrogen monoxide and hydrogen peroxide [45,46]. Nigella sativa is also proven to be anti-bacterial, anti-fungal, anti-microbial, anti-parasite, anti-schistosoma and anti-viral[47].

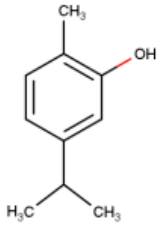


Figure 20. Carvacrol

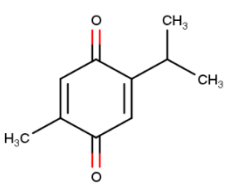


Figure 21. Thymoquinone

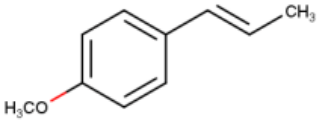


Figure 22. Anethole

C. Neuro-degenerative disorder:

Table-5: Herbs contributing against neuro-degenerative disorder

Herbs	Active constituents	Therapeutic uses	Reference
1.*Ginkgo biloba* **(Ginkgoaceae)** 	Ginkgolides A, B, C, J and bilobalide, many flavonol glycosides, biflavones, proanthocyanidins, quercetin, kaempferol	Treats blood disorders and memory issues, antioxidant, reduces inflammation	[48-50]
2.*Panax ginseng* **(Arialiaceae)** 	Protapanaxatriol, dammarane, protopanaxadiol, ginsenoside	Treats unclear thinking, diabetes, and erectile dysfunction	[51-53]

1. Ginkgo biloba (*Maiden hair tree)*

Ginkgo biloba belongs to the family Ginkgoaceae. Ginko biloba constitutes of Ginkgolides A, B, C, J and bilobalide (figure 23), many flavonol glycosides, biflavones, proanthocyanidins, quercetin and kaempferol are some of its active constituents[48]. Ginkgolides and Bilobalide improve the levels of antioxidant proteins through mediating the Akt/Nrf2 signalling pathway which protects the neurons from injury due to oxidative stress[49]. Ginkgo leaf and seeds are used in treating blood disorders and memory issues, antioxidant and reduces inflammation[50].

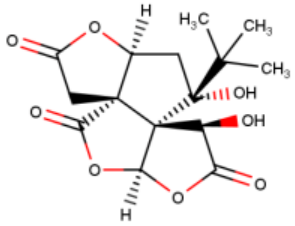


Figure 23. Bilobalide

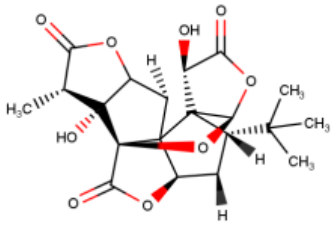


Figure 24. Ginkgolide

2. Panax ginseng (*Asian ginseng)*

Panax ginseng belongs to the family Arialiaceae. Protapanaxatriol(figure 26), dammarane, protopanaxadiol and ginsenoside(figure 25) are some of its chief active constituents[51]. Ginsenoside Rb1 reduced lipid peroxidation in the brain, removed oxygen free radicals and increased the activities of CAT and GPx[52]. It is a proven Anti-diabetic, anti-inflammatory, anti-sterility, anti-cancer, anti-proliferative and aid to menopausal women's health[53].

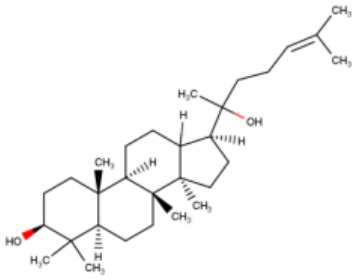


Figure 25. Ginsenoside

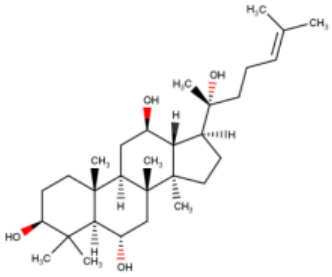


Figure 26. Protapanaxatriol

DISCUSSION

Plants have played a vital role in health care since the ancient period. Traditional herbal medicines still exert a great importance to the living population in developing

countries and also lead to the discovery of new drug moieties. Despite the diversity of herbal medicines against various diseases, active constituents of the most plant extracts have not been elucidated thoroughly because of the complexity in mixtures containing hundreds of ingredients. However, still many herbal folk medicines for oxidative stress have not undergone through scientific investigations and careful assessment of their adverse and toxic effects[54].

CONCLUSION

As discussed above, oxidative stress is one of the principal reasons for various diseased conditions. Despite various synthetic sources, natural sources can be a great alternative to facilitate the therapeutic activities towards oxidative stress induced disorders and other pathological conditions. In this review, the pharmacological profiles of various herbs and their contribution to oxidative stress have been discussed. Hence, in future it is a need of time to consider all such folk herbal medicines for determination of their pharmacological activities, isolation of the single drug enitity responsible for eliminating the effect of oxidative stress and developing suitable formulation, beneficial against oxidative stress.

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