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Small-molecule antioxidants in different diseases

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Abstract: Reactive oxidants play a crucial role in the inflammatory response and cytokine outbreak, such as during virus infections, diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases. Therefore, antioxidant is an important medicine to reactive oxidants-related diseases. An antioxidant can be defined as a substance that can prevent oxidative stress by Scavenging reactive oxidants and also delays oxidation of oxidizable substance. The present study mainly deals with different types of small-molecules antioxidants in different pathogenesis.

Keywords: Antioxidant, Diabetes, Cardiovascular diseases, Neurodegenerative diseases, Gastropathy, inflammation.

1. INTRODUCTION

Antioxidants are very much effective in different diseases where reactive oxidants and oxidative stress play an important role . A variety of antioxidants are produced within cells to prevent harmful reactive oxidants. Reactive oxidants like hydrogen peroxide (H_2O_2), hydroxyl radical (OH) and superoxide radical ($O_2^{\bullet-}$) are generated during normal aerobic cellular metabolism in the coral host during photosynthesis in the endosymbiotic algae present within the coral tissue [1-2].The antioxidant compounds can be recycled in the cell or are irreversibly damaged, but their oxidation products are less harmful or can be further converted to harmless substances [3].

At the cellular and organism level, the antioxidant protection is provided by numerous enzymes and endogenous small molecular weight antioxidants such as ascorbic acid, uric acid, GSH, tocopherols and several others. Many compounds contain antioxidant activity in addition to their specialized physiological function, and their importance as antioxidants *in vivo* is sometimes ambiguous [4].

The major restrictions with some of the chemically synthesized antioxidants are their solubility in physiological conditions, and cell membrane permeability. The antioxidant activity of plant secondary metabolites has been widely established in *in vitro* systems and involves several of the above mentioned mechanisms of action. In this section various antioxidants in different pathologies such as diabetes, cardiovascular diseases, neurodegenerative diseases, gastropathy or ulcer and inflammation have been discussed. These diseases were selected because these diseases are the major problems in all over the world.

1.1. **Anti-diabetic activity**

Diabetes is a major worldwide health problem which increased cardiovascular mortality and serious morbidity. Diabetes mellitus is characterized by abnormal insulin secretion, derangement in carbohydrate and lipid metabolism, and is diagnosed by presence of hyperglycemia [5]. Several mechanisms seem to be involved in the genesis of oxidative stress in both diabetic patients and diabetic experimental animals like glucose autooxidation, protein glycation, formation of advanced glycation products and the polyol pathway [6].

There is also evidence that higher glucose concentration causes a depression on natural antioxidant defence agents such as glutathione or vitamin C [7].

The increase in the levels of reactive oxidants and free radicals cause damage in the biological structures such as cell wall, genetic material and enzymes. Several antioxidants have been reported such as monascin [8], trilobatin [9], probucol [10],α-tocopherol [11], hydroxycinnamic acid [12], β-sitosterol [13], dipyridamole [14], curcumin [15], chlorogenic acid [15], glibenclamide [16], metformin [17], cycloart-23-ene-3 [18], oleanolic acid [19], hydroxytyrosol [20], 1α,25 dihydroxy vitamin D3 [21], and 2,5-Dihydroxy-4,3'-Di(-D-Glucopyranosyloxy)- trans-Stilbene [22] (Fig. 1) are effective against diabetes.

Monascin-treated rats show higher serum insulin level, lower reactive oxidants production and higher activities of GPx, SOD, and CAT in the pancreas compared to diabetic rats. Monascin significantly induces the hepatic mRNA levels of FOXO3a, FOXO1, MnSOD, and CAT in streptozotocin (STZ) -induced diabetic rats. Monascin-treated *C. elegans* show an increased survival rate during oxidative stress compared to untreated controls. Moreover, monascin increases the life span under high-glucose conditions and enhanced expression of small heat shock protein (sHSP-16.2), SOD-3, and glutathione S-transferase (GST-4) in *C. elegans*. Mechanistic studies in rats and *C. elegans* suggest that, monascin shows protective effects through the regulation of the FOXO/DAF-16-dependent insulin signaling pathway. By inducing the expression of stress response/antioxidant genes, monascin enhances oxidative stress resistance [8].

Trilobatin shows anti-diabetic activity by inhibiting α-glucosidase in non-competitive manner. Concentration (IC_{50}) for DPPH scavenging activity of trilobatin is 0.57 mg/mL, which indicates that trilobatin has a moderate antioxidant potential [9].

Probucol, a lipid-lowering agent with

a potent anti-oxidant action, protects diabetic pancreatic islets. Thioredoxin-interacting protein (TXNIP), an endogenous inhibitor of the ubiquitous thiol oxidoreductase thioredoxin (TRX), has been associated with oxidative stress in diabetic rat islets. Probucol decreases TXNIP expression and increases TRX expression, which may alleviate hypoinsulinemia by reducing oxidative stress [10].

By increasing plasma adiponectin and triglyceride contents of liver tissue, α-tocopherol plays anti-diabetic role in rats. β-Sitosterol increases serum insulin levels in diabetic patients. Furthermore, treatment with β-Sitosterol increases pancreatic antioxidant levels, with a concomitant decrease in thiobarbituric acid-reactive substances. β-Sitosterol has promising anti-diabetic as well as antioxidant effects and may be considered in clinical studies for drug development [13].

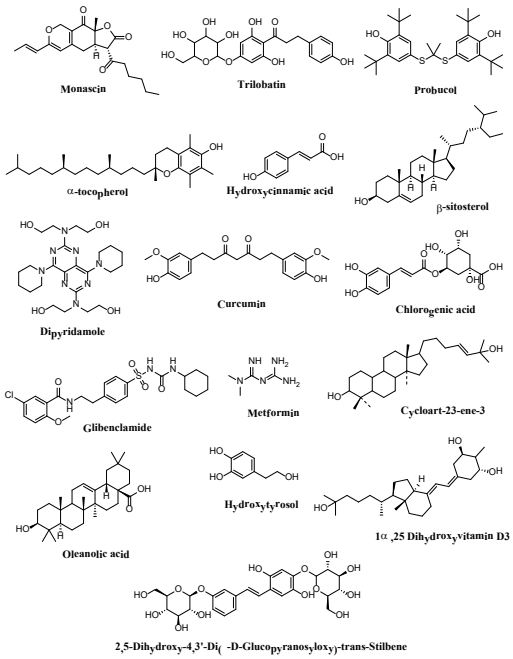

FIGURE 1. Structure of antioxidants having anti-diabetic activity.

In diabetic animals dipyridamole therapy quickly rectifies ischemic hind-limb blood flow to near preligation levels within 3 days of the start of therapy. Dipyridamole significantly increases total nitric oxide metabolite levels in tissue, which are not associated with changes in endothelial NO synthase expression or phosphorylation. Interestingly, dipyridamole therapy significantly decreases ischemic tissue $O_2^{\bullet-}$ and protein carbonyl levels, identifying a dominant antioxidant mechanistic response.

Dipyridamole therapy also moderately reduces diabetic hyperglycemia and attenuates development of dyslipidemia over time. Therefore, dipyridamole therapy is an effective modality for the treatment of chronic tissue ischemia during diabetes [14].

In diabetic rats, fasting plasma glucose, glycosylated Hb (HbA1C), thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxides (LOOH) are significantly increased, whereas insulin, total Hb, non-enzymic antioxidants (reduced GSH), vitamin C, vitamin E, and ceruloplasmin are decreased significantly. The combined treatment with curcumin and chlorogenic normalize all the above-mentioned biochemical parameters in STZ-induced diabetic rats [15].

Glibenclamide decreases hepatic and renal lipid peroxidation with a concomitant increase in total ascorbic acid (TAA), SOD, reduced GSH, GPx, and FRAP levels in the in fluoride (F) intoxicated diabetic rats. Therefore, glibenclamide may be useful for treatment of diabetes in F endemic areas [16].

Metformin plays anti-diabetic role by reducing fasting blood serum levels of glucose, insulin, renal LPO, renal somatic index (RSI), and daily rate of water consumption and increasing renal SOD, CAT, and GSH in diabetic animals [17]. Cycloart-23-ene-3β, (B2) isolated from stem bark of *Pongamia pinnata*, shows anti-diabetic activity in STZ-nicotinamide induced diabetic mice. In diabetic mice, glycosylated Hb, serum cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, globulin, bilirubin, lactate dehydrogenase, urea and uric acid are decreased significantly after B2 treatment. B2 decreases liver malondialdehyde (MDA) as well as increases SOD and reduces GSH in STZ-induced diabetic mice [18].

Oleanolic acid (OA) from Ligustrum Lucidum Ait (LLA), in the alloxan-induced diabetic rats shows significant hypoglycemic activity by lowering blood glucose at doses of 60 and 100 mg/kg for 40 days. The levels of serum total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol in the OA-treated diabetic rats are lower, and the high-density lipoprotein (HDL) cholesterol level was higher than in the diabetic rats. OA significantly reduces the serum level of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in diabetic rats. Furthermore, OA treatment decreases the MDA level, but increases SOD and GPx activities of the liver and kidney in diabetic rats [19].

Anti-diabetic effect of hydroxytyrosol is due to its antioxidant activities restraining the oxidative stress which are widely associated with diabetes pathologies and complications [20].

Administration of 1α,25 dihydroxyvitamin D3 in diabetic rats increases the plasmatic insulin level, favours the normal blood glucose levels and normalizes the hepatic glycogen concentration. 1α,25 dihydroxyvitamin D3 enhances SOD, CAT and GPX by 20, 52 and 72% respectively compared to diabetic rats. It also reduces lipid peroxidation and the indexes of toxicity in liver as well as kidneys by significantly decreasing ALP, AST, ALT activities, total bilirubin, triglycerides (TG), cholesterol, creatinine, urea, and iron levels in diabetic rats. Moreover, the plasmatic non-enzymic antioxidant level of HDL-cholesterol, magnesium, calcium and copper increases after 1α,25 dihydroxyvitamin D3 administration. 1α,25 dihydroxyvitamin D3 protects against alloxan-induced histological changes in pancreas [21].

At a dose of 200-800 mg/kg, 2,5-dihydroxy-4,3-di(β-D-glucopyranosyloxy)-trans-stilbene (DGTS) improves hyperglycemia in the rats. The histological observation shows that DGTS prevents atrophy of pancreatic β-cells and vascular degenerative changes in the islets. DGTS decreases the levels of cytochrome P 450 2E1 mRNA in the livers in diabetic rats. Therefore, DGTS might be beneficial in the treatment of type 1 diabetes [22].

1.2. **Cardioprotective activity**

Cardiovascular events represent a major health burden for Canada and other modern societies and myocardial infarction (MI) accounts for a large percentage of them. MI is a very lethal

disease with near 30% of deaths, among which near half occurs before arriving to hospital [23].

The prognosis of this clinical event depends on the patient's acknowledgement of his clinical symptoms and the decision to seek for medical care; on the delay between the first symptoms and the arrival to hospital (onset-to-door); on the emergency care team rapidity of response, and on the swiftness and suitability of the treatment received during hospitalization [24-25], but also after discharge. Several antioxidants such as resveratrol [26], rosiglitazone [27], naringin [28], KR-31378 [29], carvedilol [30], amlodipine [31], dexrazoxane [32] , apomorphine [33], atorvastatin [34], acetaminophen [35], isonicotinoyl hydrazone [36], ellagic acid [37], oestrogen [38], vitamin C [39], benidipine [40], estrogen [41], phytoestrogens [38], and ursolic acid [42]

(Fig. 2) show excellent cardioprotective activity.

Trans-resveratrol is a nutraceutical with known antioxidant and cardioprotective properties. Resveratrol significantly decreases Fe^{2+}/ascorbate oxidant system-induced lipid peroxide levels, preserves physiological levels of GSH, and increases NO levels in mitochondria. During calcium-mediated stress, resveratrol prevents the increment of NO levels, and a mild decoupling in the mitochondrial respiratory chain. These results provide a mechanism for and support the beneficial effects of resveratrol under pathological conditions induced by oxidative stress and calcium overload. These findings underscore the usefulness of resveratrol in the prevention of cardiovascular diseases [26].

Rosiglitazone, a peroxisome proliferator activated receptor-γ agonist, prevents hyperhomocysteinemia-induced cardiac hypertrophy in rats. It is reported that, rosiglitazone provides benefit in hyperhomocysteinemia-induced cardiac hypertrophy and fibrosis in a dose-dependent manner and its protective action is independent of change in mean arterial blood pressure and serum homocysteine levels in rats [27].

In case of isoproterenol (ISO)-induced rats, naringin at a dose of 40mg/kg, significantly decreases the levels of lipid peroxidative products and improves the antioxidant status by increasing the activities of antioxidant enzymes and nonenzymic antioxidants [28].

KR-31378 [(E)-1-((2S,3S,4R)-6-amino-2-(dimethoxymethyl)-3-hydroxy-2-methylchroman-4-yl)-3-benzyl-2-cyanoguanidine] prevents butionine sulfoximine (BSO) induced release of LDH and the reactive oxidants elevation in H9c2 cells. These protective effect and antioxidant effect of KR-31378 appears to be independent on KATP channel opening. Cells exposed to BSO shows an early reduction in mitochondrial membrane potential (MMP), and this reduction in MMP is significantly reversed by treatment with KR-31378. Caspase-3 activity in BSO treated H9c2 cells are remarkably increased, and this increased caspase-3 activity is significantly reversed by KR-31378. Therefore, KR-31378 can produce cardioprotective effect against oxidative stress-induced cell death through antioxidant mechanism [29].

Carvedilol, a beta-blocking agent with alpha-blocking properties, is widely used for the treatment of heart failure. Carvedilol shows cardioprotective activity by reducing hypoxia-induced creatine kinase release [30].

Amlodipine has been reported to improve endothelial function in patients with arterial hypertension and to significantly limit the progression of carotid atherosclerosis. Amlodipine has also intrinsic antioxidant activity with both anti-hydroxyl and anti-peroxyl radical activity [31].

Hydrolyzed dexrazoxane metabolites prevent site-specific iron-based oxygen radical damage by displacing iron from doxorubicin and chelating free and loosely bound iron. Dexrazoxane also attenuates doxorubicin-induced oxidation of intracellular dichlorofluorescin. Dexrazoxane protects cardiac myocytes against doxorubicin by preventing iron-based oxidative damage [32].

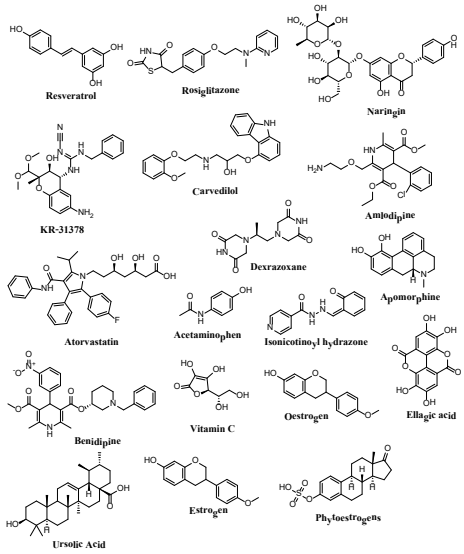

FIGURE 2. Structure of antioxidants having cardioprotective activity.

Iron and copper ions (mediators in formation of oxygen-derived free radicals) are released during myocardial reperfusion. Apomorphine forms stable complexes with copper and iron, and inhibits the copper-induced ascorbate oxidation. Therefore, apomorphine plays an essential role in post-ischemic cardioprotection [33].

Benidipine (hydrochloride), a calcium antagonist, prevents H_2O_2-induced injury in Langendorff-perfused rat hearts. Benidipine (1 nmol L^{-1}) decreases the myocardial contractility and perfusion pressure to a similar degree in the hearts under normal conditions [40].

Acetaminophen plays cardioprotective role by attenuating release of $^{\bullet}OH$ and peroxynitrite during ischemia and reperfusion [35].

Isonicotinoyl hydrazone provides a very powerful and very fast protection against the oxidative stress exerted by H_2O_2 presumably via the iron-mediated Fenton reaction producing $^{\bullet}OH$ in adult cardiomyocytes [36].

HDL is susceptible to oxidation, which affects their cardioprotective properties. Vitamin C plays cardioprotective role by protecting HDL from oxidation [39].

1.3. **Neuroprotective activity**

Neurodegenerative diseases comprise a condition in which nerve cells from brain and spinal cord are lost leading to either functional loss (ataxia) or sensory dysfunction (dementia). Mitochondrial dysfunctions, excitotoxicity and finally apoptosis have been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease,

Multiple Sclerosis and amyolotrophic lateral sclerosis. Neurodegeneration have been speculated to be interplay of a number of factors including environmental and genetic predisposition but redox metal abuse occupies central role as most of symptoms stems out from abnormal metal metabolism [43].

Oxidative stress and free radical generation catalyzed by redox metals have been shown to play pivotal role in regulating redox reactions *in vivo* contributing RNS and reactive oxidants, main culprits in neurodegeneration [44-45].

Several antioxidants are reported such as caffeic acid [46], quercetin [47], morroniside [48], genistein [49], curcumin [50], propofol [51], Z-ligustilide [52], sesamin [53], trolox [54], lipoic acid [55], glabridin [56], pinusolide [57], FLZ [58], tert-butylhydroquinone [59], afzelechin [60], catechin [60], dipyrrolidinylpyrimidine [61], ergothioneine [62], 8-amino-1,4-benzoxazine derivatives [63], 6,7-dihydroxy-2-methoxy-1,4-phenanthrenedione [64], and cannabidiol [65]

(Fig. 3) have shown neuroprotective activity.

Oxidative stress has an important role in the pathogenesis of cerebral ischemia/ reperfusion (I/R) damage. Caffeic acid significantly decreases I/R damage in rats. Caffeic acid decreases total oxidant status (TOS) and oxidative stress index (OSI) levels and increases total antioxidant status (TAS) in I/R damaged rats [46].

Quercetin, one of the plant flavonoids, prevents H_2O_2-induced apoptosis in human neuronal SH-SY5Y cells. It also prevents H_2O_2-mediated cytotoxicity and lactate dehydrogenase release in a concentration dependent manner. In addition, quercetin represses the expression of the pro-apoptotic *Bax* gene and enhances that of the anti-apoptotic *Bcl-2* gene in SH-SY5Y cells. Moreover, quercetin effectively inhibits the activation of the caspase cascade that leads to DNA fragmentation, a key feature of apoptosis, and subsequent cell death [47].

Morroniside protects I/R-induced brain injury by minimizing oxidative stress and apoptosis. Morroniside (30, 90 and 270 mg/kg) significantly decreases the level of malondialdehyde (MDA) and caspase-3 activity in ischemic cortex tissues. Morroniside (270 mg/kg) also significantly increases the content of GSH, enhances the activity of SOD in ischemic cortex tissues [48]. Curcumin prevents homocysteine (*Hcy*) neurotoxicity in a dose dependent manner. Curcumin prevents *Hcy* induced lipid peroxidation in rats' brain. Curcumin has the ability to improve the memory deficits by protecting the nervous system against oxidative stress [50].

Genistein (GEN), a principal component of soybean isoflavones, possesses the neuroprotective role through its antioxidant activity. GEN can alleviate the oxidative stress caused by Aβ25-35 treatment and maintain redox balance in PC12 cells, which may be associated with the regulation of Nrf2/HO-1 signal pathway [49].

Sesamin attenuates the ischemic cell death and plays a crucial role as a neuroprotectant in regulating levels of

reactive oxidants in the rat brain. Thus, sesamin may be a potential compound in stroke therapy [53]. Protocol decreases the neuronal behavioral scores, brain water content, activity of SOD, and content of MDA in brain tissue during intracerebral hemorrhage (ICH) in rats. Propofol also inhibits caspase- 3 expression in dose-dependent manner. Brain damages caused by ICH in rats can be alleviated by propofol, and its mechanism may be attributed to its antioxidant activity [51].

It has been reported that neuroprotective effects of trolox is associated with its ability to block the mitochondrial pore openings in the neurons under exploration, and this is the way to prevent apoptotic death [54].

FLZ [N-[2-(4-hydroxy-phenyl)-ethyl]-2-(2,5-dimethoxy-phenyl)-3-(3-methoxy-4-hydroxy-phenyl)-acrylamide] attenuates the Aβ25-35-induced apoptotic cell ratio, regulates the apoptotic gene (*Bcl-2* and *Bax*) expression, and decreases the cytochrome c release from mitochondria.

FLZ also significantly inhibits the generation of reactive oxidants and the depletion of GSH induced by Aβ25-35 in SH-SY5Y cells. FLZ has protective action against Aβ25-35-induced toxicity in SH-SY5Y cells, which may be mediated through its antioxidant property [58].

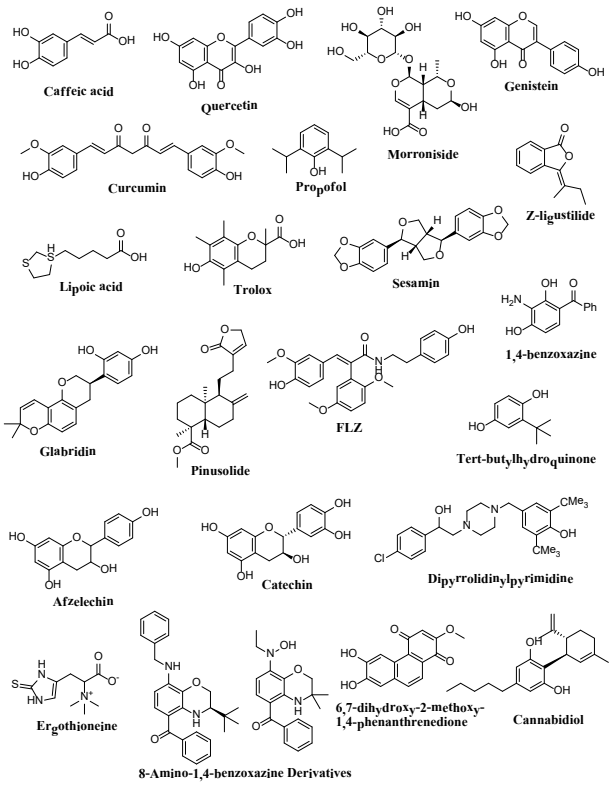

FIGURE 3. Structures of antioxidants having neuroprotective activity.

Glabridin, a major flavonoid of Glycyrrhiza glabra (licorice), possesses multiple pharmacological activities. Glabridin significantly attenuates the level of brain MDA in middle cerebral artery occlusion (MCAO) rats, while it elevates the level of two endogenous antioxidants in the brain, i.e. SOD and reduced GSH. Glabridin significantly inhibits the staurosporine-induced cytotoxicity and apoptosis of cultured rat cortical neurons in a concentration dependent manner. Consistently, glabridin significantly reduces the DNA laddering caused by staurosporine. Glabridin suppresses the elevated Bax protein and caspase-3 proenzyme and decreases bcl-2 induced by staurosporine in cultured rat cortical neurons. Glabridin also inhibits

staurosporine (STS)-induced $O_2^{\bullet-}$ production in cultured cortical neurons. These findings indicate that glabridin has a neuroprotective effect via modulation of multiple pathways associated with apoptosis [56].

Pinusolide protects neuronal cells from STS -induced apoptosis by preventing the increase in Ca^{2+} concentration and cellular oxidation caused by STS. Which indicates it can be used to treat neurodegenerative diseases [57].

Z-ligustilide (LIG) protects I/R-induced brain injury by minimizing oxidative stress and apoptosis. LIG treatment significantly decreases the level of MDA and increases the activities of the antioxidant enzyme GPx and SOD in the ischemic brain tissues. In addition LIG provides a great increase in Bcl-2 expression as well as a significant decrease in Bax and caspase-3 immunoreactivities in the ischemic cortex [52].

Tert-Butylhydroquinone (tBHQ) is known as a strong inducer of phase II detoxification enzymes, which have antioxidative functions. Neuroprotective effect of tBHQ has been investigated against 6-hydroxydopamine (6-OHDA)-induced cell death using human neuroblastoma SH-SY5Y cells. The pretreatment of SH-SY5Y cells with tBHQ significantly reduces 6-OHDA-induced generation of reactive oxidants, the phosphorylation of c-Jun N-terminal kinase (JNK), and subsequent cell death. In addition, tBHQ dose-dependently activates the antioxidant responsive element (ARE), which plays a key role in the transcriptional activation of phase II detoxification enzymes including NAD(P)H:quinone oxidoreductase (NQO1) [59]. A series of new 8-amino-1,4-benzoxazine derivatives have been synthesized and examined for their intrinsic cytotoxicity and their capacity to inhibit oxidative stress-mediated neuronal degeneration in neuronal cell cultures. 3-alkyl substituents have been seemed to be essential for efficient neuroprotective activity. Furthermore, within the sub-series of substituted 3-alkyl benzoxazines, the most active derivatives are those bearing an 8-benzylamino substituent [63].

The neuroprotective action of cannabidiol has been examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate and the results show that is a good neuroprotective agent. Cannabidiol prevents H_2O_2-induced oxidative damage in neuronal cells. Cannabidiol is more protective against glutamate neurotoxicity than either ascorbate or α-tocopherol, which indicates it is a potent antioxidant [65].

1.4. **Anti-ulcer activity**

Gastroduodenal ulcer is a prevailing disorder of gastrointestinal system and a very common global human health problem today [66-68].

Previously, gastric acid was considered to be solely responsible for development of peptic ulcers, hence the dictum “no acid no ulcer” has been proposed. But later on extensive studies have established that acid has fewer roles in the development of peptic ulcer. Generally gastric ulcer patients show normal or reduced level of acid secretion, it is the duodenal ulcer patients who usually secrete more acid. About 30% of duodenal ulcer patients

show hyperchlorohydria and a very few of gastric ulcer patients exhibit such incidence. Therefore, the dictum "no acid no ulcer" may be true only for duodenal ulcer [69-70].

Besides, acid itself does not have sufficient ability to induce ulcer formation. Rather, the corrosive and peptic actions of acid actually aggravate the ulcer, already formed by other factors or make mucosa susceptible to injury [66, 70].

The pathogenesis of gastric ulcer is now considered as a multifactorial process, which is often associated with inflammation, acid-induced necrosis, oxidative damage, apoptosis and loss of gastroprotection [71-82].

Among various mechanisms involved in the formation of gastric lesions, oxidative injury induced by reactive oxidants [83, 76, 84-86], which develop due to neutrophil infiltration [87-89], deranged antioxidant system [89, 76-77] and ischaemia [90] caused by mucosal microvascular damage and decreased blood flow [91-93] are considered to be one of the major causative factors for the gastric lesions. Several antioxidants having anti-ulcer activity are presents in the literature like nicotinamide [94], fucoidan [95], alendronate [96], fluvoxamine [97], IAC [98], probucol [99], eugenol [100], mangiferin [101], polaprezinc [99], rebamipide [102], cinitapride [103], dantrolene sodium [104], gallic acid [105], lansoprazole [106], melatonin [107], and omeprazole [70] (Fig. 4).

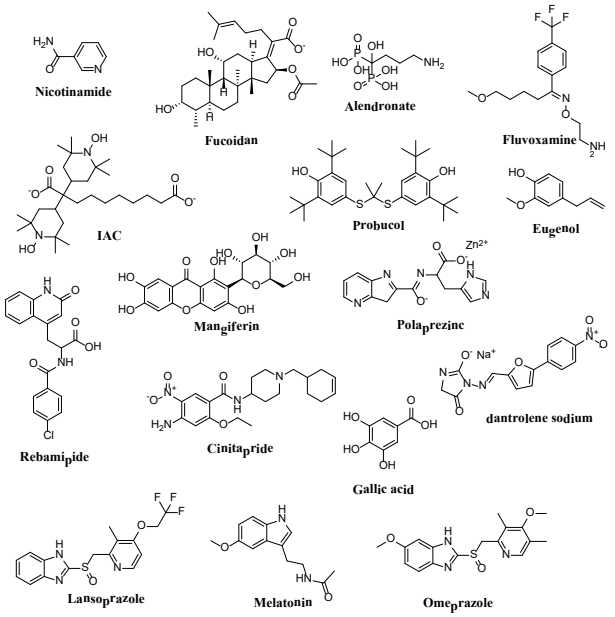

FIGURE 4. Structures of antioxidants having anti-ulcer activity

Nicotinamide, a precursor of NAD (NAD+), is an essential nutrient for cell growth that participates in DNA repair and energy production. Nicotinamide markedly decreases the severity of indomethacin (NSIAD)-induced gastric lesions. Gastroprotective effect of nicotinamide is mediated by conservation of gastric mucus, as well as nitric oxide contents, enhanced gastric microvascular permeability, and its antioxidant properties [94].

Fucoidan shows considerable protection against ulceration by inhibiting the acute alterations of AST, ALT, cytokines, and stomach glycogen. Anti-ulcer property of fucoidan may contribute in protecting the inflammatory cytokine-mediated oxidative damage to gastric mucosa [95].

Rebamipide dose-dependently suppresses the ulcerogenic response to

alendronate, with a concomitant reversal of the increased vascular permeability, MPO activity and lipid peroxidation as well as the reduced SOD activity and GSH content. Rebamipide prevents the antral ulcers, probably due to its antioxidative as well as anti-inflammatory actions [102].

It has been reported that fluvoxamine show anti-ulcer effects by activating antioxidant parameters and inhibiting of some toxic oxidant parameters [97].

Bis(1-hydroxy-2,2,6,6-tetramethyl-4-piperidinyl)-decandioate (IAC), prevents indometacin-induced gastric ulceration [98]. Probucol accelerates the ulcer healing and inhibits the increase in the TBA-reactive substance content in the ulcerated region. Probucol promotes the ulcer healing by their potent antioxidant activities in rats [98].

Anti-ulcer effect of eugenol is mediated by opening of ATP-sensitive potassium channels, scavenging free radicals, decreasing acid-pepsin secretion, increasing mucin production, and preventing the deleterious rise in nitric oxide level [100].

Mangiferin shows gastroprotective activity through its antisecretory and antioxidant mechanisms of action [101]. Polaprezinc inhibits the development of H. pylori-induced gastritis through its scavenging action against monochloramine [99].

Dantrolene sodium prevents ethanol-induced gastric mucosal lesion by reducing lipid peroxidation and increasing the activity of antioxidant enzymes SOD and GPx [104]. Rebamipide offers a potential for protection against reactive oxidants and activated neutrophil-associated gastric mucosal injury by scavenging $^{\bullet}OH$ and inhibiting neutrophil activation or lipid peroxidation [102].

Cinitapride, a novel prokinetic benzamide-stimulating gastrointestinal motility agent, shows anti-ulcer effect by decreasing myeloperoxidase activity (MPO) and the GPx levels in the injured mucosa [103].

Omeprazole, a proton pump inhibitor, blocks stress-induced increased generation of $^{\bullet}OH$ and associated lipid peroxidation and protein oxidation, indicating that its antioxidant role plays a major part in preventing oxidative damage. Omeprazole also prevents stress-induced DNA fragmentation, suggesting its antiapoptotic role to block cell death during ulceration [70].

Melatonin prevents the development of mitochondrial oxidative stress and activation of mitochondrial pathway of apoptosis induced by indomethacin in the gastric mucosa. Melatonin inhibits the important steps of indomethacin-induced activation of mitochondrial pathway of apoptosis such as upregulation of the expression of *Bax* and *Bak*, and the downregulation of *Bcl-2* and *BclxL*. Melatonin also protects indomethacin-induced mitochondrial translocation of *Bax* and prevents the collapse of mitochondrial membrane potential. Moreover, melatonin reduces indomethacin-mediated activation of caspase-9 and caspase-3 by blocking the release of cytochrome c and finally rescues gastric mucosal cells from indomethacin-induced apoptosis. Thus, melatonin has significant anti-apoptotic

effects to protect gastric mucosa from NSAID-induced apoptosis and gastropathy, which makes its use as potential therapy against gastric damage during NSAID treatment [107].

Lansoprazole, another proton pump inhibitor, prevents indomethacin-induced gastric damage by blocking activation of mitochondrial and Fas pathways of apoptosis. Lansoprazole prevents indomethacin-induced up-regulation of proapoptotic Bax and Bak and down-regulation of antiapoptotic Bcl-2 and Bcl(xL) to maintain the normal proapoptotic/antiapoptotic ratio and thereby arrests indomethacin-induced mitochondrial translocation of Bax and collapse of mitochondrial membrane potential followed by cytochrome c release and caspase-9 activation. Lansoprazole also inhibits indomethacin-induced Fas-mediated mucosal cell death by down-regulating Fas or FasL expression and inhibiting caspase-8 activation. Lansoprazole favours mucosal cell renewal simultaneously by stimulating gene expression of prosurvival proliferating cell nuclear antigen, survivin, epidermal growth factor, and basic fibroblast growth factor. The up-regulation of Flt-1 further indicates that lansoprazole activates vascular epidermal growth factor-mediated controlled angiogenesis to repair gastric mucosa. Lansoprazole also stimulates the healing of already formed ulcers induced by indomethacin. These antiapoptotic and prosurvival effects of lansoprazole offers gastroprotection against indomethacin-induced gastropathy [106].

1.5.**Anti-inflammatory activity**

Today it is believed that inflammation is part of the non-specific immune response that occurs in reaction to any type of bodily injury. Cardinal signs of inflammation can be explained by increased blood flow, elevated cellular metabolism, vasodilatation, release of soluble mediators, extravasation of fluids and cellular influx [108].

Zhang, yi-chun *et al.* [109] have synthesized some new conjugates of indomethacin with natural phenolic antioxidants (Fig.5), which show excellent antioxidant as well as anti-inflammatory activities. Indomethacin has no significant antioxidant activity.

However, all the synthetic conjugates offeres remarkable protection against *in vitro* lipid peroxidation and some of them possessed very significant capacity to interact with DPPH. These conjugates of indomethacin are examined for their inhibitory activities against the croton oil induced mouse ear swelling.

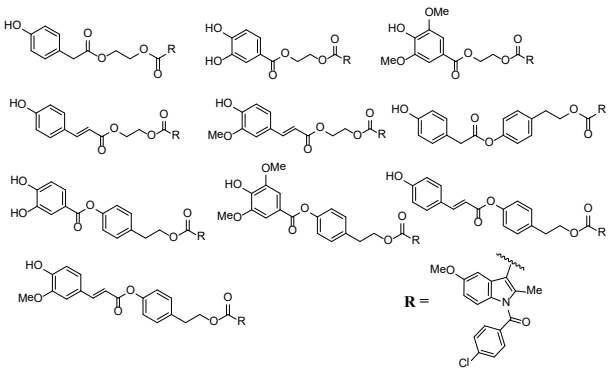

FIGURE 5. Structure of antioxidants having antiinflammatory activity.

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2. CONCLUSIONS AND FUTURE DIRECTIONS

From the above studies it is evident that

antioxidants are very much effective in different diseases originated due to reactive oxidants and oxidative stress.

There are so many reported molecules having antioxidant activity; however, not all of these are therapeutically viable drug-like molecules due to various limitations such as toxicity, low bioavailability and rapid inactivation under *in vivo* conditions. Thus, synthesis of new molecules by cutting down the toxophore part of active antioxidant molecules and simultaneously adding valuable moieties/scaffold to them with a view to overcome the above-mentioned limitations might be fruitful for developing novel antioxidants for a future generation. Furthermore, studies on drug synergism should receive special attention, which can open new avenues to improve the efficacy of antioxidants in combination with others. Medicinal plants are important source of indigenous medical systems in many parts of the world and these resources will be useful for the development of antioxidants. I have tried to incorporate the maximum number of known antioxidants, but the number of reported lead molecules may be much higher than incorporated in this report. It can be anticipated that effective research in the near future capitalizing antioxidants will open new avenues for the development of drugs against different pathologies.

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