Antioxidant rich medicinal plants as a potential candidate to treat gastric ulcer

Abstract: Oxidative stress is a key cause of gastrointestinal disorders, primarily stomach ulcers. Multiple intrinsic and extrinsic mechanisms caused the body to produce reactive oxygen species (ROS). The body's antioxidant defense system protects against these reactive species. When the degree of ROS production exceeds the normal range, the body's natural defense system fails to neutralize these dangerous free radicals, necessitating need for an exogenous source of natural antioxidants. Natural herbal remedies have been widely employed as antioxidants to relieve oxidative stress in gastric ulcers. Polyphenols, tannins, essential oils, flavonoids, notably quercetin, carotenoids, vitamin C, vitamin A, and minerals are among the molecules of immense interest in bioassays due to their significant antioxidant effects. In the present review, several natural anti-ulcer medicinal plants along with their antioxidative mechanism have been reported. Electronic databases including PubMed, Google Scholar and Scopus were explored to identify the antioxidant and gastroprotective potential of all the plants.

Keywords: Botanicals; Antioxidants; Ulcer; Gastroprotective; Natural products

Resumen: El estrés oxidativo es una causa clave de trastornos gastrointestinales, principalmente úlceras estomacales. Múltiples mecanismos intrínsecos y extrínsecos hacen que el cuerpo produzca especies reactivas de oxígeno (ROS). El sistema de defensa antioxidante del cuerpo protege contra estas especies reactivas. Cuando el grado de producción de ROS excede el rango normal, el sistema de defensa natural del cuerpo no logra neutralizar estos peligrosos radicales libres, lo que requiere de una fuente exógena de antioxidantes naturales. Los remedios herederos naturales se han empleado ampliamente como antioxidantes para aliviar el estrés oxidativo en las úlceras gástricas. Los polifenoles, taninos, aceites esenciales, flavonoides, especialmente quer cetina, carotenoides, vitamina C, vitamina A, y minerales son algunos de los compuestos de interés para los ensayos biológicos debido a sus efectos antioxidantes. En la presente revisión se han reportado varias plantas medicinales naturales antiuclerosas junto con su mecanismo antioxidante. Se exploraron bases de datos electrónicas como PubMed, Google Scholar y Scopus para identificar el potencial antioxidante y gastroprotector de todas las plantas.

Palabras clave: Botánicos; Antioxidantes; Úlcera; Gastroprotector; Productos naturales
INTRODUCTION
Reactive oxygen species (ROS) are byproducts of the normal biological metabolic reactions. The formation of a limited amount of ROS has beneficial impacts on several physiological functions like pathogen clearance, wound healing, and cell regeneration. ROS are key signaling molecules. Yet, excessive generation of ROS disrupts the body’s homeostasis, resulting in oxidative damage to tissues (Checa & Aran, 2020). ROS are produced as a result of alcohol consumption, ultraviolet (UV) radiation, cigarette smoking, nonsteroidal anti-inflammatory drugs (NSAIDs), and a range of other environmental variables (Bhattacharyya et al., 2014). Infections and cardiac injury can also increase ROS levels. The primary source of ROS generation is the gastrointestinal (GI) system. Consumption of materials and pathogens may result in the production of cytokines and other inflammatory mediators, resulting in oxidative stress. Oxidative stress can cause peptic ulcers and other GI pathogenic diseases (Suzuki et al., 2012). ROS can be generated by a number of intracellular compartments, including mitochondria, peroxisomes, the endoplasmic reticulum, the cytosol, plasma membranes, nuclei, and extracellular spaces (Balaban et al., 2005; Forrester et al., 2018). The electron transport chain of mitochondria is the primary location for ROS generation in mammalian cells (Zhao et al., 2019). Enzymes involved in catalysis of ROS-producing chemical reactions are peroxidases, NADPH oxidase, xanthine oxidase (XO), glucose oxidase, lipoxygenases (LOXs), cyclooxygenases (COXs), nitric oxide synthase and myeloperoxidase (MPO) (Bhattacharyya et al., 2014). The equations for these enzymes’ operations that produce free radicals are depicted in Figure No. 1.

Numerous environmental factors are contributing of oxidative stress. Pollutants in the air, radiations such as x-rays or neutrons, cigarette smoke, medicines, foods, and xenobiotics can all cause oxidative stress (Mena et al., 2009; Poljšak & Fink, 2014). In addition, chemical agents including quinones, organic solvents; heavy metals and pesticides are common exogenous sources of ROS (Chung et al., 2006; Phaniendra et al., 2015). Figure No. 2 illustrates a variety of endogenous and exogenous sources, with an emphasis on the references most relevant to the GI tract.

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**Figure No. 1**
The equations of the enzymes involved in catalysis of ROS-generating chemical reactions

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**Figure No. 2**
A variety of endogenous and exogenous sources of ROS, with an emphasis on the references most relevant to the GI tract.
Defensive system against Reactive Oxygen Species
The ability of human and other living organisms to carry out oxidation reactions during metabolic activities is critical. Several ROS are generated during the oxidation processes, which are then inactivated by antioxidants to keep their levels within a certain range in the body. The excessive generation of ROS is extremely harmful to biological molecules (Di Meo & Venditti, 2020; Yang & Lian, 2020). Because antioxidants guard against the detrimental effects of ROS and restore the redox antioxidant balance, the live body can only withstand a limited amount of oxidative stress (Abdel-Saeed & Salem, 2019; Abdoon et al., 2020; Elghobashy et al., 2020; Hussain et al., 2021a; Liu et al., 2021; Mushtaq et al., 2021; Sayyar et al., 2021).

The antioxidative defense system, which comprises both enzymatic and non-enzymatic antioxidants, is made up of several defensive antioxidants molecules. However, this antioxidative defense mechanism has a low capabilities to eliminate ROS. If the ROS level surpasses an unacceptable threshold, the antioxidative defence system will be unable to eliminate all ROS, resulting in oxidative stress and oxidative deterioration of important biological components in cells such as DNA, proteins, and lipids presented in Figure No. 2 (Surai et al., 2019). External antioxidant substances can also aid in the removal of free radicals from the body. Natural medicinal plants contain antioxidant properties such as vitamin A, vitamin E, flavonoids, carotenoids, phenols, and tannins (Lobo et al., 2010).

Endogenous antioxidants
These antioxidants are of two forms enzymatic and non-enzymatic antioxidants.

Enzymatic antioxidants
These include glutathione peroxidase, superoxide reductase, catalase, glutathione-reductase, and superoxide dismutase. Among these antioxidants superoxide dismutase, glutathione peroxidase (GPX) and catalase (CAT) are considered as first-line antioxidants against ROS (Ighodaro & Akinloye, 2018).

Superoxide dismutase (SOD)
SOD are enzymes requiring metal ion cofactor. Human body is composed of three isoforms of SOD: manganese-requiring mitochondrial enzyme (Mn-SOD), copper and zinc-containing enzyme (Cu-Zn-SOD) and Cu-Zn containing SOD (EC-SOD)
Melatonin's anti-inflammatory effects are reduced by it including ROS, lipid peroxidation and HOCl, sulfur radicals, O₃, RNS. As a result, it is known as a deadly or suicide antioxidant (Moniruzzaman et al., 2018; Tan et al., 2000). Melatonin's anti-inflammatory benefits in animal research and limited human studies show that supplemental melatonin may be beneficial in colitis (Terry et al., 2009; Zhao et al., 2021).

**Glutathione peroxidase (GPX)**

The enzyme oxidizes glutathione (GSH) into glutathione (also called glutathione disulfide, GSSG) and simultaneously reduces H₂O₂ to H₂O and lipid hydroperoxides (ROOH) to respective alcohols. The GPX reaction is coupled to glutathione reductase (GSSG-R), which maintains reduced glutathione (GSH) levels (De Oliveira-Silva et al., 2019).

**Glutathione reductase (GSR or GR)**

This enzyme is responsible for the reversible oxidation of glutathione disulfide (GSSG) to glutathione (GSH). GR protects haemoglobin and cellular membranes from oxidative stress by generating GSH (Couto et al., 2016).

**Heme oxygenase (HO)**

Heme oxygenase (HO) enzyme is involved in the breakdown of heme and generates biliverdin, carbon monoxide and iron. There are two isoforms, HO-1 and HO-2. HO-2 is constitutively expressed, and HO-1 is inducible (Chen et al., 2019). HO-1 does not involve directly in antioxidant enzymatic function, against oxidative stress (Vanella et al., 2012).

**Non-enzymatic antioxidants**

**Glutathione (GSH)**

It is mainly found in reduced form. In gastric mucosa, it performs the function of antioxidant barrier. The level of GSH is much higher in the gastric tissues providing additional protection against effects of gastric acid (Kwon et al., 2019). The *H. pylori* infection-induced inflammation further enhance the production of ROS. However, mucosal damage by free radicals is prevented by local glutathione (Matthews & Butler, 2005).

**Melatonin**

Melatonin is a hormone that is secreted by the pineal gland but is also found in lymphocytes, bone marrow, the GI system, and the retina (Tordjman et al., 2017). It can also be present in yeast, oats, and other plants. It deactivates the hydroxyl and peroxy radicals. This hormone has been irreversibly oxidised and cannot be returned to its original state. As a result, it is known as a deadly or suicide antioxidant (Moniruzzaman et al., 2018; Tan et al., 2000). Melatonin's anti-inflammatory benefits in animal research and limited human studies show that supplemental melatonin may be beneficial in colitis (Terry et al., 2009; Zhao et al., 2021).

**Thioredoxin (Trx)**

The thioredoxin complex system is composed of thioredoxin (Trx) and thioredoxin reductases (TrxR). Trx is an oxireductase containing disulphide group and is involved in regulating redox-sensitive transcription factors activity. Thioredoxin binding protein-2 (TBP-2) is also considered as a regulator of Trx and involved in the negative regulation of Trx. The TBP-2 also performs regulatory functions in cellular redox reactions (Ghareeb & Metanis, 2020).

**Exogenous antioxidants**

**Vitamin C**

Vitamin C or ascorbic acid is obtained from fresh vegetables and fruits. Vitamin C prevents the oxidation by donating electrons to free radicals and several species are reduced by it including ROS, HOCl, sulfur radicals, O₃, RNS (Kaźmierczak-Barańska et al., 2020; Namratha et al., 2021).

**Carotenoids**

Food-derived vitamin A is known as provitamin A or carotenoid. Fruits and vegetables with green leaves are potential sources of carotenoids (Larsson et al., 2007). Beta-carotene has been found in mouse studies to reduce lipid peroxidation (Hosseini et al., 2010; Toti et al., 2018).

**Vitamin E**

It is an ubiquitous and vital antioxidant that prevents lipid peroxidation and so protects cell membranes (Ni & Eng, 2012). Alpha tocopherol is the most physiologically active form of vitamin E (Huang et al., 2002). Vitamin E inhibits lipid peroxidase activity by destroying lipid peroxy radicals (LOO) (Ni & Eng, 2012). As a pro-oxidant, vitamin E is also implicated in the reduction of Fe or Cu (Floridi et al., 2009).

**Minerals**

Manganese (Mn), iron (Fe), copper (Cu), selenium (Se) and Zinc (Zn) are essential components of
antioxidant enzymes and are known to be antioxidant micronutrients. Among these minerals Mn, Cu and Zn are essentially considered as ionic cofactors of superoxide dismutase (Cu/Zn-SOD) (Wolencje et al., 2016).

**Antioxidants medicinal plants**
In recent years, medicinal plants have gained special attention of scientific community in treating various diseases and disorders of both humans and animals (Al-Sarraj, 2021; Ashraf et al., 2021; Hussain et al., 2021b; Majeed et al., 2021; Moryani et al., 2021; Murtaza et al., 2021; Rafay et al., 2021; Rehman et al., 2021; Wajiha & Qureshi, 2021; Aidy et al., 2022; Doudach et al., 2022; Naseer et al., 2022; Saif et al., 2022). The extracts of medicinal plants comprising of standardized contents of flavonoids, tannins, polyphenols, vitamins and minerals have been investigated for their total antioxidant activity and these medicinal plants have also been reported for the treatment of gastric ulcer by ameliorating the oxidative stress in the body (Table No. 1). The potential therapeutic candidates have also been described below along with their antioxidant mechanism of action against peptic ulcer.

**Mimosa pudica**
*Mimosa pudica* belongs to the family, Fabaceae. The English name of this plant is ‘touch me not’. It belongs to tropical countries and several subtropical regions. The phytochemical constituents of *M. pudica* are quercitin, saponins, flavonoids, tannins, mucilage, naringin. For the treatment of intestinal ulcers, the decoction of the seeds and leaves is consumed. The fresh leaves of *M. pudica* have been indicated to have gastroprotective, anti- ulcer and antioxidant activity of extracts of the leaf may assist in treating the ulcer. Alkaloid mimosine is considered as the active constituent of the plant (Vinnothapoooshan & Sundar, 2010). In another research study, the antioxidant activity of aqueous extract and ethanolic extract of *M. pudica* leaves was evaluated in ethanol-induced and pylorus ligation induced gastric ulcers. The results indicate that ethanolic extract significantly increased gastrointestinal pH and antioxidant enzymes such as CAT, SOD and decrease the lipid peroxidation indicated by reduced content of MDA with respect to control (Momin et al., 2011).

**Zingiber officinalis and Zingiber zerumbet**
*Zingiber officinalis* and *Zingiber zerumbet* belong to the family, Zingiberaceae and the English name is Ginger. The main pungent compound is 6-gingerol, which shows various pharmacological activities. The extract of *Z. officinalis* also contains gingerols which inhibit prostaglandin E2 (Banerjee et al., 2011). The active phenolic compounds, including zingerone and gingerol, inhibiting parietal cell H+, K+-ATPase, play an important role in proton pump inhibition and decrease gastric acid secretion. *Z. officinalis* plays a protective role against *Helicobacter pylori* induced ulcers (Siddaraju & Dharmesh, 2007).

It also acts as a natural antioxidant against gastric ulcers (Jiang et al., 2008). Moreover, extract also recovered the 2.6 fold increased level of thiobutyric acid reactive substance (TBARS) levels indicating the decrease in lipid peroxidation or damage to ulcerous tissue (Dharmesh et al., 2011)

Moreover, Sidahmed et al. (2015), indicated that *Z. zerumbet* played an important role as a gastroprotective agent in an ethanol-induced gastric ulcer rat model. It was demonstrated that prophylactic treatment with omeprazole or zerum bone in rats decreased ulcer area significantly in comparison to the ulcer control group.

**Camellia sinensis**
*Camellia sinensis* belongs to the family, Theaceae and the English name is Tea plant. *Camellia sinensis* is the most common beverage used. Among several green tea constituents, epigallocatechin gallate and polyphenol suppress the expression of tumor necrosis factor-alpha gene (Fujiki et al., 2002). An investigation on *Camellia sinensis* extract indicated that the extract assists in treating *H. pylori*-related peptic ulcers by inhibiting the urease enzyme of the bacterium, hence inhibiting bacterial colonization (Matsubara et al., 2003). Several other in-vivo studies inferred the inhibiting effect of plant extract on ulcer formation by enhancing cell vacuolation by vacuolating cytotoxin A and urea conduction in *H. pylori* infection and prevent gastric ulcer (Ruggiero et al., 2007).

Rao et al. (2008), demonstrated the protective activity against gastric ulcers of *Ficus glomerata* fruit in gastric ulcer rat models. The fruit was given per mouth at a dose of 50, 100, and 200 mg/kg body weight, twice daily for five days for prevention against ulcer formation by alcohol and cold stress. The study reported a dose-dependent reduction of ulcer and prevention from the oxidative damage of gastric mucosa as antioxidant agent. The study results indicated that *F. glomerate* has gastroprotective potential contributed by gastric defense factors (Rao
et al., 2008).

In another study, hydroalcoholic extract of green tea (Camellia sinensis L.) was observed on chronic gastric ulcers of rats. It was found that extract prevented the reduction of the level of glutathione (GSH) and reduced the content of lipid hydroperoxide (LOOH). Moreover, the extract administration restored the SOD activity as compared to control group (Borato et al., 2016).

**Aloe barbadensis**

Abarbadosis belongs to the family, Liliaceae and its English name is “aloe vera”. The constituents of the plant are isobarbaloin, aloin and emodin whereas the active chemical constituents include isobarbalin, sponins and barbalin. The aloe gel extracted from the leaves was used to treat ulcerative colitis in rats. The aloe vera gel treated the acetic acid-induced ulcerative colitis in rat models and produce anti-inflammatory, antioxidant and wound healing effects. Moreover, the gel also boosts the immune system of animals (Subramanian et al., 2007).

Aloe vera was compared to omeprazole and cimetidine, to determine the most potent therapeutic drug. The anti-ulcer effect was observed by administering the drugs to ulcerative model in rats and it was inferred that aloe vera showed greater healing potential than cimetidine and omeprazole as no traces of ulcer were noticed in the stomach of animals after 7 days of treatment (Sai et al., 2011). The antiulcer and antioxidant activity of Aloe vera juice was determined in ethanol-induced ulcerated rat models. The administration of plant gel decreased ulcer index and acid secretion and increased activity of oxidative enzymes including reduced glutathione and superoxide dismutase. In addition, Plant also reduced the activity of alkaline phosphatase and lipid peroxidase enzyme treatment. The results of the study showed that the gel has good efficiency to treat gastric ulcer (Subramanian et al., 2007).

**Curcuma longa**

Curcuma longa belongs to the family, Zingiberaceae with English name turmeric. The plant possesses anti-inflammatory and antioxidant potential and is involved in down regulation of proteins encoding genes, which play an important role in acute inflammation. The phytochemical constituents are involved in reducing gastric acid secretion and inhibiting the pro-inflammatory cytokines like tumor necrotic factor-alpha (TNF-a) (Salehi et al., 2017). Mahattanadul et al. (2006), reported in their study that C. longa rhizome protected the formation of acid reflux esophagitis.

On the other hand, when used in combination with dimethyl sulfoxide, it reduced the esophagitis ulcer index to almost that of lansoprazole drug (Mahattanadul et al., 2006). Herbal drugs can be useful for suppressing and preventing H. pylori-related ulcerative infection. Therefore, C. longa plant products have revealed as strong antioxidants bearing potential to treat gastric diseases (Langmead & Rampton, 2001; Amalraj et al., 2017).

**Asparagus racemosus**

Asparagus racemosus belongs to the family, Asparagaceae and the English or common name is 'curer of hundred diseases'. The habitat of A. racemosus is tropical and subtropical dry and deciduous forests. Significant parts of the plant used for the extraction of chemical constituents are tuberous roots and shoots. The major phytochemical constituents having healing potential are steroidal saponins like Shatavarin (Alok et al., 2013).

The roots of the plant contain four types of shatavarin, including Shatavarin I–IV. Additionally, quercurtin-3-glucorinide, rutin, stigmasterol, sitosterol and several unidentifed saponins are also present (Goyal & Sairam, 2021). The plant's tubers are used as an aphrodisiac, cooling agents, diuretic, tonic and demulcent and are applied for the synthesis of various medicated oils. The mixture of fresh juice of the plant roots with honey is also given to treat gastrointestinal disorders. The powder of roots is employed to enhance the strength and vigour and as an antiulcerogenic agent (Mazumder et al., 2008). The antioxidant effect of the plant was evaluated in swim (restraint) stress and indomethacin (NSAID) induced ulcerous model of rats. The administration of plant improved the antioxidant defense system by increasing the level of catalase, superoxide dismutase and ascorbic acid and by decreasing lipid peroxidation (Bhatnagar et al., 2005; Sabiu et al., 2016).

**Annona squamosa**

Annona squamosa belongs to the family, Annonaceae and the English name is sugar apple tree. A. squamosa is a deciduous tree growing at an altitude of 5-10 m. It is located throughout the Philippines and Americas. The tree is commonly growing in secondary forests at low and medium altitudes. The barks of the tree hold a large quantity of tannic acid. The pulp of the fruit contains extractive matters, gum,
ash and sugar. Bark also contains a principle constituent similar to 'cathartin'. The parts mostly used for the pharmacological purpose are seeds, bark, fruit and leaves. The bark powder is used to treat mouth ulcers. The juice of bark is added to coconut milk and is given to boot out colicky pains. These barks are also brushed to strengthen the teeth. Leaves are used for treating headache gastric pain and gastric ulcer. The stem-bark extract is applied for an antidiarrheal purpose with cathartin (Suleiman et al., 2008).

The aqueous extracts of A. squamosa were investigated for antiulcer activity in aspirin 7801 plus pyloric ligation induced gastric ulcer models of rats. The antioxidant activity of plant extracts was determined by in vitro assays such as nitric oxide scavenging activity and lipid peroxidase inhibiting assay. The extract showed the potential to significantly scavenge nitric oxide and inhibited the lipid peroxidation (Dos Santos & Sant’na, 2001)

**Azadirachta indica**

*Azadirachta indica* belongs to the family Meliaceae with English name neem. It is an evergreen medicinal plant and grown throughout India and in several countries of Africa. It is typically grown in tropical and semi-tropical regions of the world. It is a native tree of India and is studied to be part of India's genetic biodiversity. Nowadays, the tree is also cultivated in the western hemisphere's tropical areas and several countries of Asia. The tree exhibits furrowed, short, dark brown to grey bark and pinnate leaves. The main chemical constituent of neem with pharmacological properties is 'azadirachtin'. It is used to prepare a neem-based pesticide that is natural, biodegradable, environment friendly and safe at the farmer's level. Many other chemical compounds found in the neem tree, including nimbin, nimbidol, nimbidin, quercetin and sodium niminate. However, nimbin provides antioxidant, antihistamine, antipyretic, antifungal and anti-inflammatory properties. Neem seed oil is composed of a large percentage of active compounds combined with several fatty acids including stearic acid, palmitic acid, oleic acid, linoleic acid and so on. Whereas, less amount is also present in bark and leaves of neem tree. Nimbidin contains anti-ulcer, antifungal, analgesic, antibacterial and antiarrhythmic properties. Nimbidol shows antipyretic, antitubercular and antiprotozoal properties. Sodium niminate exhibits spermicidal, antiarthritic and diuretic properties. At the same time, quercetin contains antioxidant, antiprotozoal, antibacterial and anti-inflammatory properties (Nathan et al., 2005; Veitch et al., 2007; Alzohairy, 2016). The plant protects against oxidative damage of gastric mucosa by inhibiting lipid peroxidation and by removing the endogenous hydroxyl radical, a major factor for causing ulcer. Moreover, the in-vitro study indicated that bark extract of the plant also protected the gastric mucosal DNA from harmful effect of hydroxyl radical (Bandyopadhyay et al., 2002).

**Alstonia spp.**

*Alstonia* spp. belongs to the family Apocynaceae and the English name is devil tree. *Alstonia* spp. comprises 40-60 species and grows mostly in the Malaysian region native to the tropical and subtropical areas. The trees can grow quite long, as A. pneumatophore may grow to 60 m in height. *Alstonia longifolia* species is mostly located in Central America. The active constituents include coumarins, phlobotannins, reducing sugars, alkaloids, simple phenolic, steroids, flavonoids, and saponins. The percentage of lipids and saponins are more significant than other agents. Several compounds are found in *A. scholaris* which may make the plant pharmacologically valuable for the cure of various diseases. It was reported that the antioxidant potential of *A. scholaris* was because of the presence of phenolic compounds. Flavonoids are polyphenolic compounds that are involved in scavenging of free-radical, hydrolytic enzyme inhibition and anti-inflammatory activity. The plants' flavonoids and saponins are used in treating peptic ulcers and dysentery (Antony et al., 2011). The antioxidant activity of the plant was evaluated by determining lipid peroxidation. The extract of *A. scholaris* leaves in ethanol, showed significant antioxidant activity by reducing lipid peroxidation (Vanita & Deepali, 2019).

**Moringa oleifera**

*Moringa oleifera* belongs to the family Moringaceae and the English name is horseradish tree. The plant grows naturally in the Western and sub-Himalayan regions and countries like Pakistan, Arabia, Africa, Asia Minor and India. The plant's principal chemical constituents are saponins, tannins, kaempferol, flavonoids, alkaloids, zeatin, quercetin, and terpenoids (Subitha et al., 2011). The principal constituents of the plant are beta carotene, beta sitosterol and quercetin. In folklore medicine, this plant has high pharmacological importance. The leaves of *M. oleifera* are consumed to treat peptic
ulcers, especially by Indian people. Flower buds of the plant are extensively used in Pakistan and indicated to prevent peptic ulcer formation (Subitha et al., 2011).

The antioxidant activity of *M. oleifera* was determined. It was found that oxidative stress markers (MDA) increased significantly and the antioxidant biomarkers (GST, SOD and GPX) decreased significantly as compared to control group. It was inferred that *M. oleifera* leaves extract has good antioxidant and antiulcer activities and the extract has the potential to scavenge free radicals and protect against gastric ulceration (Almuzafar, 2018).

**Myrtus communis**

*Myrtus communis* belongs to the family Myrtaceae and the English or common name is Myrtle. It is cultivated in tropical, subtropical, mediterranean and temperate regions of the world. The plant's chemical constituents are present in ripe berries composed of Myrtle's oil (essential oil), citric acid, resin, tannin, sugar and malic acid. Powdered leaves are useful to cure ulcers and wounds. The fruit, Myrtle berry, is considered as carminative and administered for treatment of internal ulceration (Sisay & Gashaw, 2009). A topical dosage form of *M. communis* was applied for wound healing activity in rat excision wounds (Rezaie et al., 2012). *M. communis* fruits were used to prevent peptic ulcers associated to indomethacin, ethanol and pylorus ligation in rat model via suppression of gastric acid and other secretions. The main active constituent considered for antiulcer activity is oil of Myrtle (Sumbul et al., 2010).

*In vitro* study indicated that myrtle berry seed extract was rich in total polyphenols and anthocyanins hence, showing antioxidant activity. *In vivo* study on the plant showed antioxidant activity by increasing hydrogen peroxide (H$_2$O$_2$) and free iron levels. Moreover, myrtle berry seed extract also regulates other intracellular mediators (Sebai et al., 2014).

**Psidium guajava**

*Psidium guajava* belongs to the family Myrtaceae and the English name is Guava. This tree is grown throughout India and Bengal. It’s tree is native to central America and is present in tropical and subtropical regions throughout the world. The chemical constituents present in the plant are crystals of calcium oxalate, resin and tannins. Leaves are composed of fat, resin, tannin, volatile oil, mineral salts, chlorophyll and cellulose. The active constituents of *P. guajava* include guajaverin, galactose-specific lecithins, quercetin and flavonoids. The decoction of the leaves of the plant is employed to treat ulcers and is an effective gargle for mouth ulcers and swollen gums. Methanol leaf extract was administered orally to rats for 10 days to treat ethanol-related peptic ulcers. The extract significantly reduced ulcer symptoms when compared to the control group (Uduak et al., 2012).

The free radical scavenging potential of extract of *P. guajava* in ethanol was investigated by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and nitric oxide radical inhibition assays. It was concluded from results that the plant has significant free radical scavenging property because of the presence of flavonoids. As the bioflavonoid mostly show the potential of the gastric protection through inhibition of free radicals (Jayakumari et al., 2012).

**Sesbania grandiflora**

*Sesbania grandiflora* belongs to family Fabaceae. It is a decorative plant and is grown at Western Himalayas plains and Sri Lanka. The chemical constituents of the plant include tannins, saponins and triterpenes. Active constituents include saponins and tannins. The leaves of the plant are employed to prepare soup and taken orally in several countries especially in India for healing peptic ulcer. The decoction of leaves is administered orally as vermifuge. The leaves are taken and boiled in the milk of cow and then administered orally in Kikuku village of Tanzania, for healing gastric ulcers. Moreover, the leaves are first boiled in water and then administered by mouth to cure ulcer by Paliyar tribes of India (Alahakoon & Ganegoda, 2019).

An ethanol extract of *S. grandiflora* leaves was given orally to rats to cure aspirin, ethanol, and indomethacin-related peptic ulcers (400 mg per kilogramme body weight). The extract stopped gastric mucosal layer damage and dramatically lowered stomach acid output (Bhalke et al., 2010).

Antioxidant effect of the hydroalcoholic extract of the plant was evaluated against the acetic acid induced ulcerative colitis mice. The extract containing polyphenols and flavonoids showed potent antioxidant activity by restoring the normal levels of MDA GSH, SOD, MPO, and NO. Hence the plant showed a potent protective effect against ulcerative colitis (Gupta et al., 2018).  

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Shorea robusta

*Shorea robusta* belongs to the family Dipterocarpaceae and the English name is Sal tree. It is commonly grown at sub-Himalayan sections and the Western Bengal forests. The chemical constituents of the plant include trihydroxy ursenoic acid and tetrahydroxy ursenoic acid, alpha amyrin, asiatic acid, beta amyrin, ursolic acid, mangiferonic acid and uvaol. The active constituents of *S. robusta* are amyrin and ursolic acid. The ointment of a mixture of *S. robusta*, cinnabar, calamus draco, ghee and mastiche employed for foetid ulcers (Singh & Kumar, 2018). In a study, *S. robusta* extract was administered orally to pylorus ligated induced and the ethanol-induced ulcerative rats. It was found that the extract provided significant protection against gastric ulcer (Santhoshkumar et al., 2012).

*S. robusta* includes natural resins that are efficient therapeutic components for ulcer therapy. The gastroprotective activity of *S. robusta* resin was tested in two doses on rats suffering pyloric ligation and ethanol-induced gastric ulcers. The results indicated that pretreatment with the resin of the plant prevented gastric mucosal damage and normalize the antioxidant markers (catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), lipid peroxidation (LPO) and superoxide dismutase (SOD) in ethanol-induced model (Santhoshkumar et al., 2012).

Solanum nigrum

*Solanum nigrum* belongs to the family Solanaceae and the English name is black nightshade berries. The plant is found all over India. The principal active constituents are saponins, phytosterol, flavonoids, and alkaloids. The fresh leaves are used for the cure of intestinal ulcer by Paliyar tribals of the Indian region (Mayilsamy & Rajendran, 2013). *S. nigrum* leaf extract in water was given to rats to protect them from pylorus ligation, which causes peptic ulcers (Shree et al., 2012).

In another study, the *S. nigrum* extracts were evaluated for determining gastro-protective and antioxidant activity in indomethacin-induced and pylorus ligated induced gastric ulcerative models of rats. *S. nigrum* pretreatments significantly elevate SOD activity and GSH as well as NO contents as compared to gastric ulcerative control group. Moreover, the extract significantly reduce MDA content as compared to gastric ulcerative control group. Hence, it was inferred from results that *S. nigrum* protected against gastric-ulceration (Zaghoool et al., 2019).

Tamarindus indica

*Tamarindus indica* belongs to the family Caesalpiniaceae and the English name is Tamarind tree. It is an evergreen tree, native to South India and is grown in Burma, Pakistan and India. The plant is composed of malic acid, tartaric acid, acetic acid and citric acid, invert sugar, pectin and gum. Seeds are composed of fat, albuminoids, fibre whereas, the fruit contains traces of oxalic acid and tannins. The tannins in the plant are considered to be active constituents in this plant. The decoction of the plant leaves is consumed as a wash against indolent ulcers and enhances the ulcer healing activity. In a study, the extract of seed in methanol considerably decreases the secretion of gastric juice in the ulcer model of rats compared to control (Kalra et al., 2011). A study examined at the antioxidant capabilities of plant extracts derived from the stem, bark, and roots. Plant extracts were examined for phosphor molybdenum (PM), hydrogen peroxide, and PPH radical scavenging to determine their antioxidant activity. According to the findings, the antioxidant potential of both plant extracts was similar. As a result, both extracts exhibited high antioxidant activity (Borquaye et al., 2020).

Terminalia chebula

*Terminalia chebula*, sometimes known as myrobalan, is a combretaceae plant. It grows in the Northern Indian and Bengal woods. The chemical components of the plant include lucilage, a colourant (brownish yellow), tannic acid, gallic acid, and chebulinic acid. Chebulinic acid, tannins, sorbitol, and gallic acid are among the bioactive ingredients of *T. chebula*. *Triphala* ash is applied in powder form on syphilitic ulcers to remove the ulcer exudates. Fine powder is mixed with dry *T. chebula* catechu and myrobalans, and then rubbed into a thick paste with blending oil or ghee to make ointment for wounds with chronic wounds and ulcers (Jantraprion et al., 2021). *T. chebula* methanolic solution was given orally to patients with gastric ulcers at dose rates of 250 and 500 mg per kilogramme body weight, and it cured and reduced the ulcer's symptoms (Raju et al., 2009). *T. chebula* fruit extract had substantial in vitro ferric-reducing antioxidant activity, and an in vivo examination of the extract revealed that administration with the plant's extract reduced oxidative stress indicators such as glutathione disulfide level and lipid peroxidation. As a result,
plants have a high potential for preventing oxidative damage (Saha & Verma, 2016).

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Extract/part used</th>
<th>Active constituent</th>
<th>Animal model</th>
<th>Antioxidative mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alliaceae</strong></td>
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<tr>
<td><em>Allium sativum</em></td>
<td>Fresh juice and dried powder of garlic bulbs</td>
<td>Allicin, diallyl disulfide, Diallyl trisulfide</td>
<td>Indomethacin-induced gastric ulcer in rats</td>
<td>Elevated SOD and CAT activity, lowered MDA conc.</td>
<td>Azamthulla et al., 2009; Tope et al., 2014; Martins et al., 2016</td>
</tr>
<tr>
<td><strong>Anacardiaceae</strong></td>
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<tr>
<td><em>Mangifera indica</em></td>
<td>Ethanolic extract of seed and kernel powder</td>
<td>Anthocyanins and flavonoids</td>
<td>Acid alcohol-induced ulcer in rats</td>
<td>Reduced LPO activity, increased GSH and SOD activity</td>
<td>Prabhu &amp; Rajan, 2015</td>
</tr>
<tr>
<td><strong>Asteraceae</strong></td>
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<tr>
<td><em>Artemisia campestris</em></td>
<td>Aqueous extract</td>
<td>Limonene, myrcene, β-phellandrene, α-pinene</td>
<td>Aspirin induced gastric ulcer in rats</td>
<td>Increase SOD, CAT and GPX activity and decrease H₂O₂ and free iron levels</td>
<td>Sebai et al., 2014</td>
</tr>
<tr>
<td><em>Matricaria chamomilla</em></td>
<td>Hydroalcoholic extract</td>
<td>α-Bisabolol chamazulene</td>
<td>Ethanol-induced gastric mucosal injury</td>
<td>Significantly decreased the content of MDA, and increased GSH, Serum β-carotene and retinol levels at 200 mg/kg dose of extract</td>
<td>Cemek et al., 2010; Singh et al., 2011</td>
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<tr>
<td><strong>Apiaceae</strong></td>
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<tr>
<td><em>Foeniculum vulgare</em></td>
<td>Aqueous extract</td>
<td>anethole and d-fenchone</td>
<td>Ulcer induced in rats</td>
<td>Significantly reduce MDA concentration, and β-carotene, nitrate, retinol, GSH, and ascorbic acid, levels increased.</td>
<td>Birdane et al., 2007</td>
</tr>
<tr>
<td><strong>Basellaceae</strong></td>
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<tr>
<td><em>Basella alba</em></td>
<td>Ethyl acetate extract of leaves</td>
<td>Kaempferol</td>
<td>Ulcerated rats</td>
<td>Reduce antioxidant enzymes level such as lipid peroxidase and SOD, whereas increase CAT and GPX level</td>
<td>Jaiswal &amp; Rao, 2016</td>
</tr>
<tr>
<td><strong>Brassicaceae</strong></td>
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<tr>
<td><em>Brassica oleracea</em></td>
<td>Broccoli extract</td>
<td>Sulforaphane</td>
<td>Acetylsalicylic acid-induced gastric ulcer in rats</td>
<td>Increased SOD activity, GSH-PX activity, total antioxidant status, total thiolnic oxide levels, endothelial nitric oxide synthase.</td>
<td>Zeren et al., 2016</td>
</tr>
<tr>
<td>Burseraceae</td>
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<tr>
<td><em>Protium heptaphyllum</em></td>
<td>Burseraceae</td>
<td>α-pinene, terpinolene, α-phellandrene, limonene, sesquiterpenes</td>
<td>ethanol, nonsteroidal anti-inflammatory drugs and acetic acid induced ulcer in male wistar rats</td>
<td>increase the GSH and GR levels and maintained the same levels of SOD and GPX</td>
<td>Araujo <em>et al.</em>, 2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caricaceae</th>
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</thead>
<tbody>
<tr>
<td><em>Carica papaya</em></td>
<td>Caricaceae</td>
<td>Alcoholic extract of dried fruits</td>
<td>Vit. C, vit, B, flavonoids, folate, pantothenic acids</td>
<td>Pylorus-ligated and aspirin-induced ulcer in rats</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Euphorbiaceae</th>
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</thead>
<tbody>
<tr>
<td><em>Croton macrostachyus</em></td>
<td>Euphorbiaceae</td>
<td>Methanol extract</td>
<td>Flavonoids phenolic compounds</td>
<td>Induced ulcer in odents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fabaceae</th>
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</thead>
<tbody>
<tr>
<td><em>Libidibia ferrea</em></td>
<td>Fabaceae</td>
<td>Dry extract of pods</td>
<td>Galloylquinic acid</td>
<td>acetic acid-induced chronic ulcer model.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamiaceae</th>
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</thead>
<tbody>
<tr>
<td><em>Mentha piperita Mentha haplocalyx</em></td>
<td>Lamiaceae</td>
<td>menthol</td>
<td>Menthol</td>
<td>ethanol-induced gastric ulcers in rats.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mimosaceae</th>
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</thead>
<tbody>
<tr>
<td><em>Acacia catechu</em></td>
<td>Mimosaceae</td>
<td>Aqueous or 95% ethanolic extracts of heartwood and roots</td>
<td>Flavonoids (catechin) and tannins</td>
<td>Aspirin + pylorus-ligated model, absolute alcohol-induced models in rats</td>
</tr>
</tbody>
</table>
### Malvaceae

**Althaea officinalis**
- Aqueous extract of flowers
- Flavonoids and mucilage
- Pyloric-ligation and indomethacin-induced gastric-ulcer model in rats
- Antioxidant activity, pretreatment expressed a significant increase in GSH, and NO levels and SOD activity reduce pro-inflammatory cytokines formation like TNF-α and IL-1β
- Zaghloul *et al.*, 2019

**Abelmoschus esculentus**
- Aerial parts
- Flavonoids (quercetin) and carotenoids
- Ethanol-induced gastric ulcer in Wistar rats
- Pylorus ligated and ethanol induced ulcer
- Scavenging activity toward hydroxyl and peroxyl radicals and superoxide anions
- NO inhibition and superoxide scavenging
- Abourehab *et al.*, 2015

**Abutilon indicum**
- Leaves
- Quercetin, alkaloids, saponins and tannins, starch, glycosides and flavonoids
- Pylorus ligated and ethanol induced ulcer
- NO inhibition and superoxide scavenging
- Chakraborty, 2009

### Myrtaceae

**Corymbia citriodora**
- Ellagitannin rich fraction obtained from dry leaves
- Ellagitannin
- Ethanol-induced gastric ulceration in rats.
- Increase GSH and SOD levels in a dose-dependent manner
- Al-Sayed & El-Naga, 2015

### Phyllanthaceae

**Phyllanthus emblica**
- Butanol extract of fruit
- Polyphenols (ellagic acid, chebulinic acid, gallic acid, quercetin)
- Indomethacin induced model of ulcerous rat
- SOD level remained unaltered while significantly decrease MDA content
- Bandyopadhy *et al.*, 2000

### Piperaceae

**Piper betel**
- Ethanol extract
- Allylpyrocatechol
- Indomethacin induced ulcer in male Sprague-Dawley rats
- Antioxidant activity (Decreases ROS, as well as inhibits ROS/NF-κB dependent pathway within gastric tissue)
- Bhattacharya *et al.*, 2007

### Plumbaginaceae

**Plumbago auriculata**
- Ethanol extract
- Flavonoids
- Ulcerative model of animal
- *In vitro* antioxidant activity assays including DPPH assay, Lipid peroxidase inhibition assay indicated positive results.
- Ittiyavirah & Paul, 2016
| **Polygonaceae** |
|------------------|------------------|------------------|------------------|------------------|
| *Rumex patientia* | Aqueous extract  | Rutin            | Ethanol-induced ulcer in rat model | Antioxidant action reduce ethanol-induced ulcer zone | Süleyman *et al.*, 2002 |
| *Punica granatum* | Ethanol extract of dried peel | punicalagins and ellagitannin | Ulcer model of rats | Decrease free radicals lipid peroxidation (LPO and nitric oxide NO) and antioxidant enzymes SOD whereas, increase CAT and GSH | Chauhan *et al.*, 2017 |

| **Rutaceae** |
|------------------|------------------|------------------|------------------|------------------|
| *Citrus decumana* | ethyl acetate extract | Naringin Naringenin | Ulcerative model in rats | Reduce TBARS and ulcer index and increase GSH, SOD and CAT in the blood and tissue samples | Sood *et al.*, 2010 |
| *Aegle marmelos* | methanolic extract of unripe fruit | mucilage and marmelosin | Helicobacter pylori-Lipopolysaccharide (HP-LPS) induced gastric ulcer in Sprague Dawley (SD) rats | Antioxidant action prevented the reduction of antioxidant enzymes (SOD, CAT GSH-PX, GSR and glutathione transferase (GST)) and non-enzymatic antioxidants (reduced glutathione, vitamin C and vitamin E) | Ramakrishna *et al.*, 2015 |

| **Vitaceae** |
|------------------|------------------|------------------|------------------|------------------|
| *Cissus quadrangularis* | Methanol extract of dried stem | Amino acids, carbohydrates, steroids, glycosides, saponins, phytosterols, tannins, polyphenols, triterpenoids | Aspirin-induced gastric ulcer in rats | Antioxidant activity by lowering TNF-α, IL-1β, reduced activity of NOS-2. Increased activity of SOD, CAT and GSH, lowered activity of LPO in mitochondria | Jainu & Devi, 2006 Srinivas *et al.*, 2013 |

**CONCLUSION**
A wide variety of medicinal plants have been reported for possessing antioxidant activity to treat peptic ulcer. In this review, the scientific evidences proving the therapeutic potential of natural plants were explored from electronic databases. The specific plants have their effectiveness against peptic ulcer through antioxidant mechanism of action including enhancement of antioxidant enzymes (SOD, GSH, CAT etc) level and reduction of MDA level and inhibition of ROS/NF-κB dependent pathway. Studies on the antiulcer activity of the
investigated plants revealed that their extract possess significant antioxidant activity by scavenging free radicals and by restoring and maintaining the oxidative balance of the body.

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