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THE GASTROPROTECTIVE EFFECT OF TADALAFIL ON STRESS-INDUCED ULCER IN WISTAR RAT MODEL

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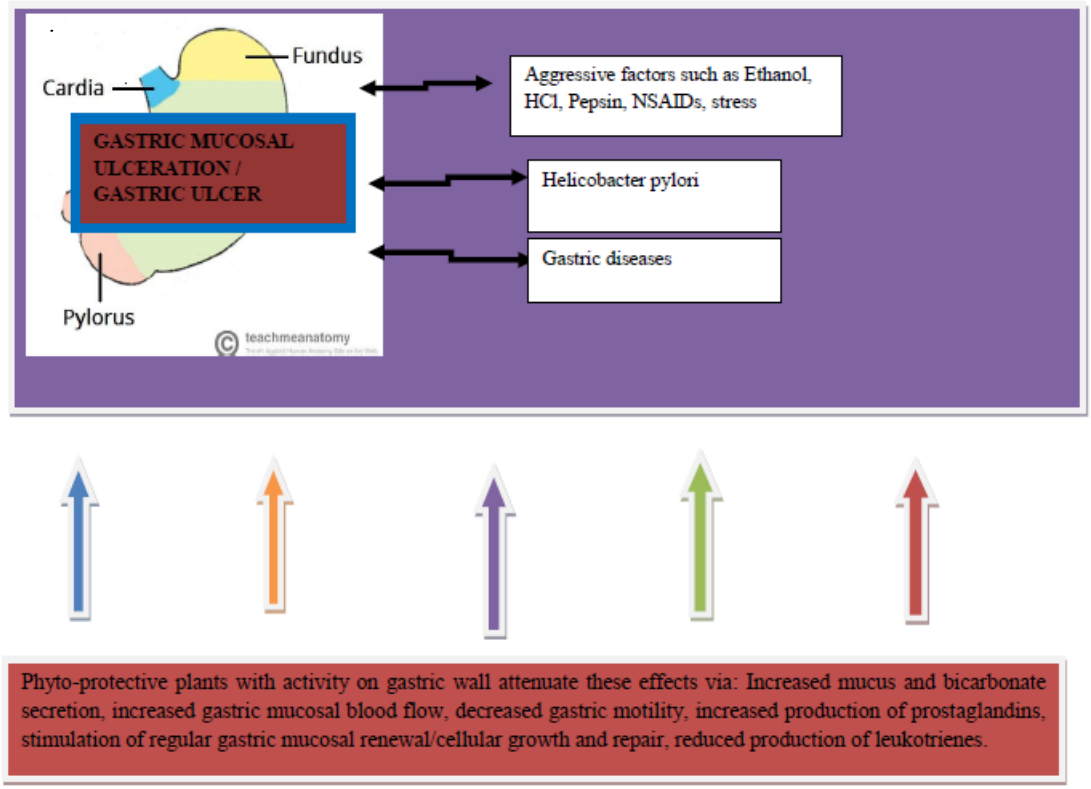
ABSTRACT

Gastric lesions and ulcerations are predominantly induced by aggressive factors such as stress, alcohol consumption, and Helicobacter pylori infection due to the use of non-steroidal anti-inflammatory drugs. The use of phyto-therapy in management of gastric ulcerations and lesions dates back centuries ago. So many plant-derived compounds are employed clinically to manage diseases and they were also the basis of drug discovery. Plant products with gastro-protective and cyto-protective properties are widely employed globally due to their natural source and minimal adverse effects. Secondary metabolites found in these plants can be utilized for the management of various ailments. Some examples of plant bioactive compounds are alkaloids, flavonoids, carnitine, choline, phenolic acids, saponin, glycosides, polyphenols and taurine. However, vitamins and minerals elicit pharmacological activity and are categorized as bioactive agents. Some of these bioactive compounds/ secondary metabolites are found in food.

KEYWORDS: Plants, Secondary metabolites, Gastric ulcer, Cyto-protection.



INTRODUCTION

The massive utilization of medicinal plants in Africa is associated with both cultural and economic purposes. For this reason, WHO supports African member states to enhance and incorporate traditional medicine practice in their health system.[1] Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants or other plant materials as active ingredients. While 80% population in Africa use herbal remedies for their primary healthcare.[2] Medicinal plants are the most easily accessible health resource available to the community. In addition, they are most often the preferred option for the patient. Africa is blessed with enormous biodiversity resources and it is estimated to contain between 40 and 45,000 species of plant with a potential for development and out of which 5,000 species are used medicinally. This is not surprising since Africa is located within the tropical and subtropical climate and it is a known fact that plants accumulate important secondary metabolites through evolution as a natural means of surviving in a hostile environment.[3] Before the development and civilization by the British in Nigeria, medicinal plants are believed traditionally to be a therapeutic agent for the treatment of diseases such as typhoid, cholera, measles, and gonorrhea. The importance of medicinal plants cannot be underestimated in Nigeria.[4]

The epidemiological report shows that Peptic ulcer disease (PUD) is on increase in West African countries due to poor diet, increase in H. pylori infection and stress and poor diet Gastric ulcer is precipitated by acid imbalance and low mucosal defense to bring about inflammation. This manifests as hyper secretion of hydrochloric acid and pepsin and creates an imbalance between gastric luminal factors and breakdown in the protective effect of the gastric mucosal barrier such as mucus, secretion of bicarbonate, mucosal blood flow and epithelial cell defense. The influx of acid and pepsin into a weakened section of the mucosal barrier triggers the release of histamine. Histamine activates parietal cells to produce more acids.[5] The cycle continues giving rise to erosions to form ulcers.[5] Currently, antacids give symptomatic relief without suppressing gastric secretion or enhancing healing. The H_2 receptor blockers and proton pump inhibitors reduce acid secretion to promote healing but are usually associated with relapse and reoccurrence. Acid rebound occurs at the end of therapy with long term adverse effects which limit their use.

Phyto-products are employed for cyto-protection due to presence of flavonoids, saponins, phenol, proanthocyanins and alkaloids. Vitamins and minerals are also important components of these plants that enable them elicit cytoprotection. Therefore, plants are among the most useful source of new drugs with promising results in Peptic ulcer disease management.

Abbreviations: cAMP, CAT, catalase, cyclic Adenosine mono phosphate, CO_2, carbon dioxide, CO, carbon monoxide, COX, cycloxygenase, EP_4, prostaglandin receptor, EGFR, epidermal growth factor receptor, G6PD, glucose-6-phosphate dehydrogenase, GSH, glutathione, GST, glutathione-s-transferase, H. pylori, helicobacter pylori, HCl, hydrochloric acid, HCO_3-, bicarbonate ion, H_2S, hydrogen sulfide, H^+K^+-ATPase, hydrogen potassium pump, IL-1α, interleukin-1alpha, IL-1β, interleukin-1beta, LPO, lactoperoxidase, LTC_4, leukotriene-C_4, LTD_4, leukotriene- D_4, NO, nitric oxide, NMDA, N-nitroso dimethylamine, PAF, platelet activating factor, PGE_2, prostaglandin- E_2, PGI_2, prostaglandin -I_2, PUD, peptic ulcer disease, ROS, reactive oxygen species, SOD, sodium dismutase enzyme, TGF-α, transforming growth factor-alpha, TNF-α, tumor necrosis factor-α.

MATERIALS AND METHODS

Relevant information was retrieved from Pub Med, and Google Scholar. They were used to collect data and references, searching by the following keywords. Cross references by Pub Med functions, hand searching and also experts recommendations without time restrictions.

The review was carried out investigating articles that involves cyto-protective compounds of plant origin. The following keywords were employed: "gastric ulcer", "plant products", "natural plants", "cyto-protective products of plant origin", "gastro-protective plants ", "gastro-protective compounds of plant origin", "cyto-protective plants in Nigeria", "cyto-protective plants in West Africa", "cyto-protective plants in sub-Saharan Africa". Suitable articles were sifted, compiled and chosen by the authors. Some terminologies were also used to obtain information for this systematic review such as; ''Persia americana" and "Asparagus racemosus", ''Cassia siberiana", "Psidium guajava", "Azadirachta indica" and "Moringa oleifera plants'

RESULT AND DISCUSSION

Gastric ulcer disease

Gastric ulcer involves the erosion of the lining of the stomach or duodenum principally by disruption of the gastric mucosal defense and repair systems.[6] Gastric ulcer occurs in the stomach. Gastric ulcer disorders commonly occur due to regular intake of NSAIDs. It is also established that gastroduodenal ulcer is affected by aggressive and defensive factors such as acid-pepsin secretion, parietal cell, mucosal barrier, mucus secretion, blood flow, cellular proliferation and internal protective factors (prostaglandin and epidermal growth factors).[7]

Previous studies have shown that factors such as bad dietary habits, excessive consumption of NSAIDs, stress, hereditary makeup and H. pylori infection also account for more than 70% of cases of gastric ulcer.[8] Oxidative destruction is known to be implicated in the development of ulceration. Gastric mucosal damage due to ethanol, Indomethacin, paracetamol and cold-resistant stress-mediated system triggers the production of free radicals.[9] NSAIDs bring about the blockade of the cyclooxygenase (COX) pathway hence, moving the arachidonic acid metabolism to the 5-lipooxygenase pathway thereby enhancing the synthesis of leukotriene (LTC4 and LTD4), giving rise to glandular modification, ulceration and bleeding.[10] It also reduces mucus and bicarbonate secretion, diminishes mucosal blood flow, and distorts platelet aggregation, microvascular structures leading to epithelial damage, angiogenesis and elevated leukocytes adherence.[10] NSAIDs with acidic components destroy the epithelial cells via osmotic lyses subsequently uncoupling of oxidation phosphorylation. They reduce the mucus bicarbonate secretion thus decreasing the activity of pH gradient in shielding the epithelium. NSAIDs facilitate ROS effect in gastric mucosa; giving rise to lipid per oxidation.[11] The production of free reactive oxygen species (ROS) elevates lipid per

oxidation, neutrophil infiltration, mucosal hydrogen peroxide and hydroxyl ion levels, which induces oxidative mucosal destruction. Ethanol (alcohol) is a risk factor for inducing gastric ulcers. It diffuses across the gastric mucosa by its solubilizing property via protective mucous layer hence revealing the mucosa to the proteolytic and hydrolytic effects of hydrochloric acid and pepsin and damaging the membrane. Ethanol (alcohol) triggers acid secretion, diminish mucosal blood flow, disrupt micro vascular endothelium and enhance vascular permeability. It activates the release of superoxide anion and hydroperoxy free radicals thereby increasing oxidative stress in the tissues which are usually seen with elevated levels of malondialdehyde, a marker of elevated lipid per oxidation.[12] The ugly consequence of ethanol is seen via the generation of reactive metabolites, including free radical species that react with cell components, changing their structure and functions or promoting oxidative damage.[13] Ethanol also generates necrotic lesions in the gastric mucosa via reduction in bicarbonate and gastric mucus production, cell membrane damage to enhance the permeability of the plasma membrane to sodium and water hence, inducing gastric mucosal injury. This could result in apoptosis and exfoliation in the surface epithelium.[14]

Other drugs that can induce gastric ulcers aside from NSAIDs include diethyldithiocarbamate, reserpine and ferrous-iron-plus ascorbic acid (Fe/As). The diethyldithiocarbamate is reported to generate antral lesions via the release of superoxide radicals and hydroxyl radicals. The superoxide radical and hydroxyl radicals contribute largely to the induction of gastric ulcers.[15] Helicobacter pylori (H. pylori) live within gastric mucus leading to gastric modifications. It inhabits the human stomach for a long time.[16] Acidic PH (<2) is a biological barrier to bacterial infection. The mucus covering the gastric epithelial cells consists of a PH gradient ranging from about pH 2 at the luminal surface to between 5 and 6 at the epithelial surface. To escape the bactericidal effect of acid, H. pylori generates systolic and cell-surface associated Urease. Urease is an enzyme found in the H. pylori strain and buffers the acidic environment by converting urea to ammonia and carbon dioxide. This is one strategy employed by H. pylori to reduce exposure to low pH in the gastric lumen. So it is domicile in the gastric lumen within the mucus close to the epithelial surface with neutral pH. The spiral shape of H.pylori enables and facilitates movement within the viscous mucus layer and promotes colonization.[17] Cytoprotection describes the remarkable ability of substances like prostaglandins and gastric mucosal blood flow at sub-antisecretory doses; to reduce the damage to the stomach induced by necrotizing agents.

Cytoprotective plants possess components that shield the gastric mucosal epithelial surface from mucosal injury by inhabiting or neutralization of gastric acid.[18]

Medicinal plants from sub-sahara Africa have become the mainstay for the management of peptic ulcer due to failure of orthodox drugs, emergence of resistance to conventional drugs and development of ugly adverse effect associated with orthodox medicine. Plants utilized for cyto-protection include Cassia siberiana, Ficus asperifolia, Asparagus racemosus, Zingiber officinale, Solanum nigrum, Azadirachta indica, Carica papaya, Moringa oleifera, Bidens pilosa etc. Studies have shown that plants are richly studded with polyphones and different natural polyphenolics.[19] possess anti-inflammatory and anti-ulcer properties via the suppression of reactive oxygen species.[20] These plants also exhibit gastric mucosal protective effect by reason of the presence of secondary metabolites richly found in them. Alkaloids, flavonoids, saponins, steroids, terpenoids and tannins enable these plants to perform this function. These secondary metabolites increase mucosal protective factors such as mucin secretion, stimulate prostaglandin synthesis, increase bicarbonate level and inhibit oxidative stress on gastric mucosal surfaces.

Mechanisms involved in cyto-protection

Mucosal defense is the major cyto protective mechanism involved in maintaining gastric mucosal integrity. Mucosal defense describes the different factors and components implicated in sustaining mucosa integrity despite exposure to a wide range of temperature, pH and cyto-toxic elements.[21] Ideally, gastric mucosa is not impervious to destruction by these agents; in fact, mucosal damage occurs frequently but doesn't lead to disruption of gastric mucosa barriers properties of the tissue. The following factors enhance gastric mucosa protection via strengthening of gastric mucosal barrier: Increased mucus and bicarbonate secretion increased gastric mucosal blood flow, decreased gastric motility, increased production of prostaglandins, stimulation of regular gastric mucosal renewal/cellular growth and repair, reduced production of leukotrienes.[18] Some of the plants commonly used for cyto-protection produce one or more of these effects.

Increased production of prostaglandins

Prostaglandins are products of fatty acid that work as chemical messengers near the site of synthesis. Prostaglandin greatly dominates the gastric mucosa and gastric juice. Exogenous prostaglandins suppress the secretion of acid, stimulate mucus and bicarbonate production, enhance blood flow and ultimately provide cytoprotection.[21] Prostaglandin, PGE2 promotes

the release of viscous mucus that coats the gastric mucosal layer and also permits the formation of bicarbonate via EP3 and EP4 receptors mediated by cAMP and Ca^{2+} signaling.[22,23] These alkaline components support the neutralization of the acidic stomach content on the gastric walls. PGE_2 and PGI_2 are obtained from cyclooxygenases (COX 1 and 2) enzymes on arachidonic acid hence; they decrease acid secretion and produce vasodilatation in blood vessels of the gastric mucosa. These two substances play an active role in maintaining gastric mucosal integrity.[23] PGE_2 analogue (misoprostol) act on the intestinal mucosa to promote mucus and bicarbonate production and mucosal mass.[24] Misoprostol triggers mucosal DNA mass synthesis and proliferation. Studies have shown that the mucus bicarbonate barrier is rich enough to shield the gastric mucosa against luminal acid and pepsin attack.[22] Prostaglandins activate the epithelial cells to discharge more bicarbonate and mucus to minimize permeability of the epithelium to acid back diffusion.[25] Plants like Opuntia ficus-indica cladodes promote mucus bicarbonate production.[26]

Prostaglandins especially PGE_2 and PGI_2 act through EP_3 and EP_4 receptors enhance mucosal defense, stimulate mucus and bicarbonate secretion in the stomach and maintain pH gradient at the mucosal surface.[27] Prostaglandins may also promote the surface-active phospholipids on the mucosal surface. Analogues of PGE_2 elevate the volume of some sub-cellular organelles that act as storage sites for gastric surfactants. Prostaglandins also suppress NSAID-induced gastric injury largely via inhibiting gastric acid secretion.[28] It also reduces epithelial permeability to acid.[25] Additionally, prostaglandins down-regulate the release of some inflammatory mediators implicated in mucosal injury.[29] For instance, PGE_2 is a potent inhibitor of the release of histamine, tumor necrosis factor-α (TNF-α) and platelet-activating factor (PAF) from mast cells.[30] Report also reveals that it inhibits the release of interleukin-1 from macrophages, and suppresses the release of leukotriene-B_4 and Interleukin-8 from neutrophils.[31] These inflammatory mediators are involved in the susceptibility of the stomach to injury induced by NSAIDs or other irritants to initiate mucosal injury that occurs during hemorrhagic shock.[32] Prostaglandin is an active inhibitor of leukocyte adherence to vascular endothelium. Therefore, prostaglandins are established to increase the resistance of the gastric mucosa to injury by their capacity to diminish inflammatory responses.

Increased Mucus and Bicarbonate secretion

The mucous epithelium is known for the internal protection of the organs with the external environment.[33] In the stomach, the mucus bicarbonate layer, made up of gelling property forms a physical barrier against acid and pepsin and ensures appropriate cyto protection. The mucus possesses antioxidant and protective properties on epithelial surfaces against stress and infection.[34] which contributes to the protection of the gastric mucosa in host defense against pathogens and gastric irritants.[35] Again, the mucus display permeability to hydrogen (H+) ion and bicarbonate (HCO3-) produced by epithelial cells from mixing with acid hence, keeping the pH neutral.[36] The pH gradient is almost neutral due to the retention of bicarbonate HCO3-[37] The bicarbonate (HCO3-) is an inorganic alkaline salt that neutralizes excess gastric acidity. The conversion of CO_2 to HCO_3^- is catalyzed by carbonic anhydrase (metalloenzymes) at low pH and by hypoxia in the gastric mucosa. The synthesis of mucus can be triggered by nitric oxide (NO) and hydrogen sulfide (H2S) donors that react to generate mucus.[38] Meanwhile, mucus is produced from mucin molecules. Mucins are glycoprotein that acts as a filter to block the movement of deleterious harmful molecules and pathogens. Destruction of mucus production and mucin layer exposes to infection such as H. pylori.[35]

Stomach lumen PH < 2

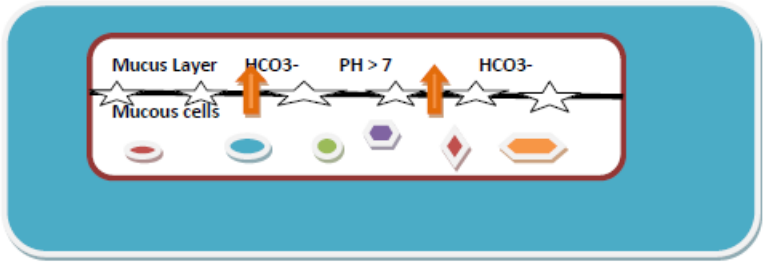


Fig 1: Gastric mucus at the epithelium. The production of mucus occurs at the epithelial cells and foveolar cells of the mucosal surface and bicarbonate components of the mucus enables an elevated PH of the epithelial cells shielding them from acid attack. Bicarbonate formed from (CO_2 and H_20) are pumped into the mucus layer.

Increased gastric mucosal blood flow

This is another mechanism of strengthening the gastric mucosal barrier and optimizing cytoprotection. Sufficient gastric blood flow is required for the optimal maintenance of mucosal integrity.[38] Diseases that induce stress on the gastric mucosa layer bring about a

compromise of mucosal defense via gastrointestinal hypo-perfusion and ischemia.[39] For instance, ethanol induces oxidative stress to induce gastric damage, promote hypoxia via the generation of ROS, the release of inflammatory mediators and also inhibit the activity of antioxidant enzymes resulting in decreased microcirculation sub-mucosal edema, and development of hemorrhagic gastritis.[40] However, according to literature searches, to reparate gastric injury, substances such as angiotensin, NO, H2S or carbon monoxide (CO) and ghrelin contribute to promoting an increase in gastric microcirculation.[41] An increase in the endogenous production of prostaglandin, CO and H2S may promote the recovery of damaged gastric mucosa and gastric blood flow. The interaction of NO and H2S gaso-transmitter is pivotal to the maintenance of gastric blood flow.[38]

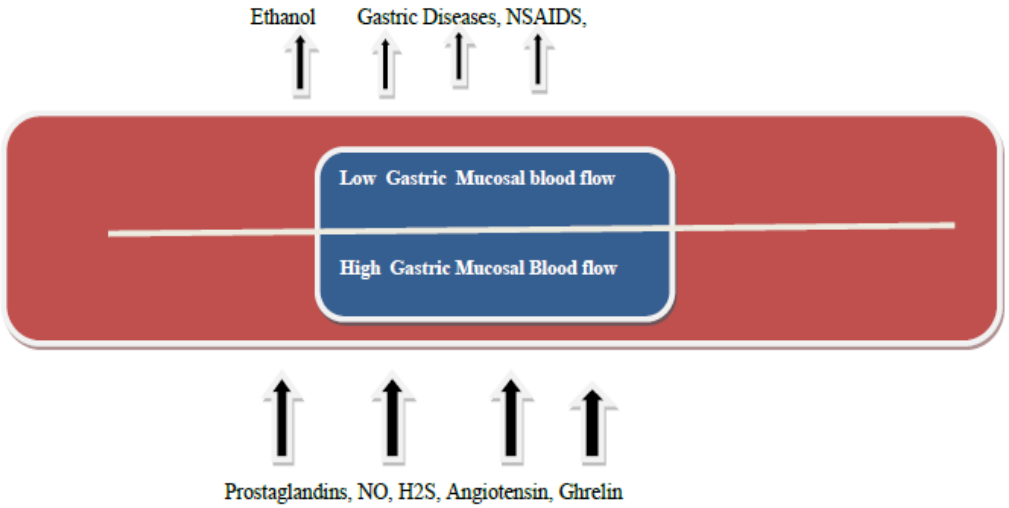


Fig. 2: Factors that triggers low or high gastric mucosal blood flow.Optimal/high gastric mucosal blood flow is paramount to avoid pH drops which may trigger the formation of hemorrhagic lesions. This system of enhanced vascular perfusion provides an immediate mucosal defence system especially during mucosal damage which may progress to epithelial destruction and necrosis of the mucosal layer.

Stimulation of regular gastric mucosal renewal/cellular growth and repair

It is known that gastric mucosal surface epithelium participates in cyto-protection and shield the stomach lumen from acid, pepsin and other irritants-NSAIDs, ethanol and stress. Studies have shown that gastric mucosa can rapidly restore its epithelium after minor/moderate damage.[42] The immediate restitution of mucosal surfaces preserves the underlying submucosa from digestion by acid and proteases. The slower process involves the replacement of lost cells by cell division. Some growth factors including bFGF, intestinal

trefoil factor, EGF and TGF-α all participate in gastric cell mucosa renewal and repair[43] and play a role in mucosal restitution and cytoprotection. TGF-α activates intrinsic tyrosine kinase while reduced activation of EGF-R-tyrosine kinase precipitates poor mucosal reparation. Activation of mucosal cell proliferation occurs after mucosal repair. Furthermore, a report has stated that EGF and TGE-α also activate gastric mucosal cell proliferation[44] and speed up mucosal repair[45] Polyamines and trefoil peptides participate actively to surface mucosal repair and proliferation.[45]

Reduced production of leukotrienes

Prostaglandins, leukotrienes and thromboxanes are together called eicosanoids.[46] Leukotrienes trigger pepsin production, impair mucosal blood flow and inhibit gastric emptying. Studies have shown that leukotrienes damage gastric mucosal integrity.[47] The release of leukotriene B engages leukocytes and macrophages that phagocytes necrotic tissue and release pro-inflammatory cytokines, e.g., TNFα, IL-lα, and IL-lβ. They in turn stimulate local fibroblasts, endothelial cells, and epithelial cells. Literature has disclosed that leukotrienes participate in gastric mucosal injury via enhancing tissue ischemia and inflammation.[48] Consequently, drugs and plants that have leukotriene inhibiting properties may be useful cyto-protective agents.[49]

Gastric Emptying and Motility

The previous study has shown that abnormal gastric motility and delayed gastric emptying play a major role in the development of gastric ulcers.[50]

The antioxidant property of plants is cyto-protective

Free radicals generate the oxygen that is cytotoxic and facilitates tissue breakdown whereas radical scavengers activate the healing of refractory peptic ulcers.[51] Thus, the antioxidant property of medicinal plants can be used to promote cytoprotection and antiulcer property. Some plants such as Ocimum suave possess cytoprotection. The cyto-protective and ulcer healing effects of Ocimum suave extract are attributed to enhanced mucus production and antioxidant properties which may likely be associated with the high presence of flavonoids and polyphenols.[52] Kolaviron, a natural antioxidant from the seed of Garcinia kola, displayed gastro-protective and cyto-protective activity which may be linked to its intrinsic antioxidant properties.[53]

Medicinal plants with cyto-protective Properties

In our world today, plants have been the mainstay for the treatment of many illnesses including gastric ulcers. Due to the level of resistance recorded with the use of orthodox drugs for gastric ulcer management, there has been a need to seek other modes of therapy. Recently, it has been discovered that peptic ulcers can be resistant to conventional anti-ulcer therapy or reappear after initial treatment. The previous study has reported an increase in the rate of resistance to proton pump inhibitors.[54] Europen Medicines Agency and Ministry of Health in Nigeria has banned all Histamine-2 receptor antagonists based on the report issued by the US Food and Drug Administration after discovering that the popular heartburn medication Zantac (Ranitidine) contains low levels of the nitrosamine impurity (N-nitrosodimethyl amine, NMDA) impurity.[55] Meanwhile, the alarming rate of antibiotic resistance to H. pylori strains, particularly clarithromycin and metronidazole is weakening the efficacy of gastric ulcer treatment regimen.[56] But the relative safety and availability of plants and plants products with minimal costs in comparison with orthodox drugs gives rise to the potential for their use in the management of gastric ulcers.[57] Examples of medicinal plants studied include Spondias mombin, Momordica charantia, Persea americana, Paullinia pinnata, Psidium guajava, Cnestis ferruguinea, Vernonia amygdalina, Trema orientalis Latana carmara, Morinda lucida, Citrus aurantifolia, Bidens Pilosa, Maytenus senegalensis, Carapa procera, Trichilia monadelpha, Spathodia campunalata and Cassia siebieriana.

Persia americana

This plant belongs to Lauraceae family, commonly found in Nigeria and Kenya. It is used for management of anemia, gastritis, hypercholesterolemia, stomach ache, bronchitis, diarrhea, diabetes, exhaustion, hypertension and peptic ulcers. Persea americana extract has been studied to possess cyto-protective property by suppression of gastric acid secretion via blockade of H histamine receptors competitively. Persia Americana reduced secretion of gastric acid and demonstrated protective property against the creation of gastric mucosal lesions. It also prevents histamine-stimulated gastric acid secretion and suppresses acid-induced gastric lesions.[58]

Asparagus racemosus

Asparagus racemosus belong to Liliaceae family and commonly used as diuretic, aphrodisiac, antispasmodic and nervine tonic agent. It is used for treatment of diarrhea, dysentery, peptic ulcer, neurodegenerative disorders, rheumatism and nervous breakdown. The root extract of

A. racemosus enhance cyto-protection via mucosal protective factors thus, mucus secretion, cell life span, cellular mucus enrichment and also display antioxidant property.[59]

Cassia siberiana

Cassia siberiana of the family of caesalpiniaceae has a widespread distribution in Senegal, Nigeria and other sub-sahara Africa countries. It is basically utilized for the management of fever, jaundice, aches, gonorrhea, pile, ulcer, debility and rheumatism. The root of this plant is used as a phyto-therapeutic agent to manage stomach disorder including indigestion, gastric ulcer and stomach pain. C. siberiana root display gastric cyto-protection by suppressing oxidative activity and myeloperoxidase levels which suggests that the antioxidant potential may be a component of antiulcer mechanism.[60]

Ficus asperifolia

This plant belongs to moraceae family and commonly used to treat arthritis, fever, malaria and diabetes. It has a wide distribution in West African countries such as - Sierra Leone, Nigeria Ghana and Ethiopia. It elevates the mucus content of the epithelial surface of the gastric mucosa.[61] The cyto-protective effect is due to presence of alkaloids, carbohydrates, tannins, phenols, cardenolides and saponins.

Guiera senegalensis

It belongs to combretaceae family and is widespread in West Africa.[62] The plant is utilized for GI disorders, respiratory infections (cough and pneumonia), and rheumatism and anti malarial agent. A study has shown that the root and leaves of G. senegalensis are applied for healing GI disorders such as diarrhea and ulcer in animals.[63] The mucosal protective effect of this plant is due to activation of prostaglandin production. Prostaglandins play a role in gastro-cytoprotection. The plant also elevates gastric mucus o or leukotriene antagonism.[63]

Moringa olefera

M.olefera of the family of moringaceae is distributed in so many tropical and sub-tropical regions. It is highly medicinal and rich in nutritious value. Traditionally, it is employed for analgesic, anti-inflammatory and anti-infertility activities. It possess a wide range of pharmacological properties such as antitumor, antioxidant, antipyretic, local anesthetic, anti-nociceptive, antispasmodic, diuretic, anti-urolithiatic, antiulcer, hypotensive, cardio-protective, anti-helmentic, hypolipidemic, anti-atherosclerotic, hepatoprotective, wound healing, antifungal, antibacterial, anti-trypanosomal, hypoglycemic, and anti-AIDS outcomes.

A study has shown that the ethanol extract of the root bark is effective for treatment of ethanol-induced and pylorus –gated-induced gastric ulceration in albino rats due to its anti secretory, mucus membrane protective property and cyto-protective effects of the alkaloids content (Moringine and Moringinine), Triterpenoids, Saponins and Tannins.[64]

Zingiber officinale

Zingiber officinale or ginger of the family of Zingiberacae is widely used in food and drink and for management of a broad collection of unrelated disorders such as arthritis, muscular aches, rheumatism, pain, sprains, sore throat, constipation, cramp, stomach upset, indigestion, nausea, diarrhea, vomiting, dementia, hypertension, infectious diseases, fever, and helminthiasis. Additionally, some constituents in ginger have potent antioxidant, anticancer, anti-inflammatory, antimicrobial, antiviral, anti-platelet, cholagog, antitumor, and immunomodulatory effects.[65] Rhizome of Zingiber officinale is used for GI disorders. The healing and antiulcer properties of ginger may be due to its powerful thromboxane synthetase property, Inhibition of gastric H+, K+ -ATPase, and H. pylori growth via phenolic antioxidants.[66]

Table 1: Medicinal plants with cytoprotective property in west africa sub-region.

Plant	Phytochemical constituents	Isolates with antiulcer activity	Traditional Medicinal Uses	Native/ Local /country	Antiulcer Activity Model	Antiulcer mechanisms	Reference
Morinda Lucinda L (Rubiaceae).	tannins, saponins, flavonoids, alkaloids, anthraquinone, triterpenes	molucidin, a tetracyclic iridoid, rubiadin, purpuroxanthin, lucidin, nordamnacanthal and soranjidol, which are all anthraquinones	Diabetes, hypertension, leprosy and ulcers	Nigeria Brimstone tree (leave)	Indomethacin and acetic acid-induced, Acetylsalicylic acid-induced gastric ulcer	=Increase in prostaglandins which play a role as a cyto-protective agent in the stomach =stimulation of the secretion of mucus and bicarbonate ions which preserves the gastric membrane may be responsible for the antiulcer activity =enhanced intestinal motility and gastric emptying time	[66]
Cnestis ferruginea (Connaraceae)	Alkaloids, tannins, saponins, tannins, reducing sugars, flavonoids, cardiac glycosides, terpenes, phytosterol,	Stigmasterol-3-O-^a-D glucopyranoside, stigmasterol, oleanolic acid, betulinic and ursolic acid	Fever, gonorrhoea, wounds, gum pain, dysmenorrhea, whooping-cough,	Senegal to West Cameroons (root)	Stress model	reduction in stress-induced gastric mucosal lesion and ischemia to enhance gastric blood flow	[67]

	oxalate, steroid, cyanogenic glycoside and anthocyanin		tuberculosis, headache and arthritis				
Momordica charantia (Cucurbitaceae)	Bitter glycosides flavonoids, saponins and sterols, alkaloids,	charantin, momordicilin, momordenol and momordin	Wound healing, infections, malaria, fevers and parasitic infections, ulcer	Africa (Fruits)	pylorus ligation and stress-induced ulcer	gastric cytoprotective effect by preventing the growth of H. pylori enhanced secretion of mucus, and reduction in the production of acid	[66] [68]
Vernonia amygdalina (Asteraceae)	flavonoids, alkaloids, saponins, tannins, terpenoid, steroids Cyanogenic glycosides, anthraquinones, coumarins, xanthones, sesqui-terpenes, edotides and phenolic compounds	neo-phytadiene, triacontane, squalene, heptacosane and phytol, luteolin-7-Oglucuronide, luteolin 7-O-glucoside, sesquiterpenes [43, 44], 4,15-dihydrovernodalin, vernodalin, vernolide, 11,13-dihydrovernorodeline , vernomenin [45, 46] 4α-Hydroxy-n-	Infections, gastrointestinal disturbances and parasitic infections	Nigeria, Cameroon and Zimbabwe (Bitterleaf)	Aspirin-induced ulcer model	=H. Pylori eradication in the treatment of PUD =possess antacid and carminative properties =acid neutralizing and carminative characteristics = beneficial in the remedy of hyperacidity	[69] [70] [71]

		pentadecanoic acid,				associated with gastric and duodenal ulcers. = decrease in the gastric content, pepsin activity, malondialdehyde , free and total acidity =H2 receptor antagonism and antioxidation	
Lantana camara (Verbanaceae)	saponins, tannins, flavonoids, steroids, anthocyanins , alkaloids, terpenoids , glycosides, quinones, cardiac glycosides, caumarins, phlobatannins, anthraquinones and phenols	oleane-12-en-3β-ol-28-oic acid 3β-D-glucopyranoside (OAG),	malaria, influenza, stomachache, fevers, ulcers, epilepsy, chickenpox and eczemas	Kenya, Tanzania and Uganda	aspirin induced model	=prevention of gastric acid release leading to prevention of gastric membrane destruction. =The added improvement in prostaglandin E2 content = decrease in ulcer index	[72]
Psidium guajava Myrtaceae	annins, phe-nols, triterpenes, flavonoids, saponins alkaloids, glycosides	Guaijaverin,pedunculagin and (þ)-gallo-catechin, α-pinene, β-copanene, limonene, gallocatechin, Quercetin and ursolic	stomach ddiseases including peptic ulcer	Kenya, Tazania, Uganda, Nigeria	aspirin-induced model	=reduction of ulcer lesions to enhance mucosal blood flow	[73]

		acid					
Zingiber officinale Zingiberacae	saponins, tannins, flavonoids, steroids, anthocyanins , alkaloids,		malaria, pain, ulcer,	Ghana, Senegal, Nigeria, Cameroun	NSAID-induced, Stress-induced model	Inhibition of gastric H+, K+ -ATPase, and H. pylori growth via phenolic antioxidants.	(65)
Trema orientalis (Ulmaceae)	saponins, alkaloids, cardiac glycosides, steroids, terpenoids, tannins, coumarins, flavonoids and phenolics	trematol; scopoletin; p-hydroxybenzoic acid; phytosterols, 2α, 3ß-dihydroxyurs-12-en-28-oic acid and ethylswertianin	diarrhea, fever, asthma, jaundice, malaria, pain, ulcer, hypertension, diabetes mellitus	Ethiopia, Kenya, Tazania, Uganda	ethanol-induced ulcer model	= gastroprotective activity = cytoprotective due to the presence of flavonoids = protect the gastro mucosa against numerous ulcerogenic agents via stimulation of the secretion of bicarbonate and prostaglandin, = increase mucus produc tion, =scavenging of free radicals and antioxidant properties =and the	[74] [75]

						inhibition of the growth of H. pylori	
Persia americana (Lauraceae)	Alkaloids, flavonoids, cellulose, polyuronoids, saponins, β-galactoside, fatty alcohols, glycosylated abscisic acid, peptone and polyphenols, triterpenoids, tannins and cyanogenic, glycoside	Cyclopenol, Cytosporin, Hyperoside (quercetin-3-galactoside), quercetin-3-O-rhamnoside isolated from flavonoids, naamine, Quercetin. Hyperin	anaemia, gastritis, hypercholesterolemia, stomach ache, bronchitis, diarrhoea, diabetes, exhaustion, hypertension and peptic ulcers	Nigeria, Kenya	ethanol and indomethacin-induced lesions	= prevention of histamine-stimulated gastric acid secretion = suppress acid-induced gastric lesions	[76] [77]
Spondia mombin Anacardiaceae	flavonoids, glycosides, saponins, phenolics, alkaloid, tannins.	chlorogenic acids and isoquercetrin, Gallic acid and ellagic acid	haemorrhoid, stomach ache and discomfort, diarrhoea, dysentery, inflammation	Tropical Africa	=Indomethacin, ethanol and acetic acid-induced ulcer model =Ibuprofen, alcohol and pylorus ligation induced ulcer =pylorus ligation-induced ulcer model,	=possess gastroprotective property = possess anti-H. pylori activity = antisecretory and gastric cytoprotective effects	[78] [79]
Citrus aurantifolia	flavonoids, cardiac glycosides,	quercetin, rutin, sitosterol and	stomach illnesses,	West tropical Africa-	H.pylori model Aspirin-induced	= decrease in H. pylori bond to	[80]

(Rutaceae)	steroids, alkaloids, tannins, sa ponins and reducing sugars	kaempferol, benxanthracene; bergamottin, coumarins; terpinolene; lycopene and quercetin	diarrhoea, malaria and urinary tract infection	Senegal	ulcer model ethanol-induced ulcer model	the mouse tissue Stomach =gastro protective effect = cytoprotection of gastric membrane	
Bidens pilosa L. (Asteraceae)	polyenes, flavonoids, phenylpropanoids, fatty acids, and phenolics, fla vonoids, cardiac glycosides, saponins, tannins, alkaloids and steroids	1-phenylhepta-1,3,5-triyne, urones and Chalcones,	Gastrointestina l disorders, ulcers, hypertension, bleeding and cardiovascular diseases.	West Africa	Indomethacin pylorus-ligated animal model	= gastric cyto protective activity = reduction in gastric lesions, gastric juice volume, acid secretion, as well as pepsin secretion	[81]
Carapa procera (Meliaceae)	alkaloids, saponins, flavonoids, coumarins, tannins, astringents, anthocyanins, phenolic acid, glycosides, triterpenoids, reducing sugars, steroids	Anthocyanins, phenolic acids, 5 flavonols,	gastrointestinal disorders, paralysis, epilepsy, external anti-inflammation, anthelmintic, treatment of fever	West Africa	H.pylori model	= possess anti-H. pylori activity = anti-oxidant mechanism of action	[82]
Maytenus senegalensis (Celastraceae)	Alkaloids, flavonoids, triterpenes,	3,5,7-tetraen-carboxylic acid-methylester, 3-	infection, cough, asthma, diarrhea ma	West Africa	Ethanol-induced model	=reduction in gastric mucosal lesions	[83]

	saponins, phenol, tannins and glycosides	hydroxy-20-lupen-28-ol, 20α)-3-hydroxy-2-ox-o-24-nor-friedela-1, phytol and 2(4H)-Benzofuranone, 5,6,7,7a-tetrahy-dro, epicatechin	laria, inflammatory diseases, healing of chronic wounds, rheumatism, snakebites and dyspepsia			= increase in gastric mucus secretion =stabilization of the mucosal lining in addition to =reduction of acid distribution, gastric mucosal absorption	
Trichilia monadelpha (Meliaceae)	Alkaloids, flavonoids, glycosides, saponins, sterols, tannins, terpenoids, anthraquinones and reducing sugars	scopoletin, stigmasterol, protocatechuic acid, β-sistoterol coixol and ellagic acid. Sisquiterpenes; trichins A and B and limonoid derivatives; monadelphins A and B	epilepsy, inflammation, healing of chronic wounds, diabetics, pains, cough, gonorrhoea, syphilis	Ghana	Indomethacin-induced model	= decrease in ulceration of the colon = restoration of the mucosal strength/blood flow	[99]
Cassia sibieriana (Fabaceae)	Quercitrin, and anthraquinones, flavonoid, saponins, steroids, terpenoids, tannins and cardiac Glycoside, reducing sugars.	Quercetin, isoquercitrin piceatannol, dihydrokaempferol, kaempferol, emodin, islandicin, physcion and chrysophanol, epiafzelechin, stigmasterol and β-sitosterol	gastric ulcer, pains, fever, diabetes mellitus, gonorrhoea, malaria, leprosy, dropsy and dysentery	West Africa	ethanol-induced ulcer	= reduction in function levels of some enzymes like superoxide dismutase, catalase and glutathione peroxidase. =Inhibition of ethanol-induced reduction in	[84] [60]

						serum total antioxidant capacity = inhibition of lipid hydroperoxides quantity and myeloperoxidase function was also prevented	
Telfairia occidentalis	flavonoids, alkaloids, phenols			West Africa	Indomethacin-induced	= gastro-protective effect	[100]
Moringa oleifera Moringaceae	flavonoids, alkaloids, phenols, vitamins, minerals, proteins, glycosides, Glucosinolates and Isothiocyanates, terpenes, saponins, tannins,	Mo-LPI	arthritis and other joint pain (rheumatism), asthma, cancer, constipation, diabetes, diarrhoea, seizures, stomach pain, stomach and intestinal ulcers,	Kenya, Ethiopia (leaves and fruits)	ethanol-induced and pylorus ligation-induced, stress-induced model	=increased protection of surface epithelium with more mucus globules	[64]
Ficus asperifolia Moraceae	Alkaloids, Carbohydrates, Tannins, Phenols, cardenolides, and saponins,	β-sitosterol, Gluanol acetate and Glucose, Friedelin, Sterols,	Venereal diseases, oedema, and nasopharyngeal infections.	West Africa-Sierra Leone, Nigeria	Indomethacin-induced	=Gastro protective effect	[61]
Alstonia scholaris Apocynaceae	Triterpenoids Alkaloids, coumarins,	Echitamine , echitamidine voacangine and	Arthritis, fever, malaria, diabetes	Ghana	=ethanol-induced ulcer model	= possess cytoprotective action	[85]

	flavonoids, phlobatannin, reducing sugars, simple phenolics, steroids, saponins and tannins.	akuammidine, Nα-formylechitamidine, and Nα-formyl-12-methoxyechitamidin				similar action to that of prostaglandin other binding of bile salt	
Asparagus racemosus (Asparagaceae)	Saponins. Isoflavones, asparagamine, racemosol, polysaccharides, mucilage, vitamins A, B1, B2, C, E, Mg, P, Ca, Fe, and folic acid	Aspargamine, quercitin, rutin and hyperoside	epilepsy, kidney disorders, chronic fevers, excessive heat, stomach ulcers and liver cancer, increases milk secretion in nursing mothers and regulate sexual behaviours.	West Africa	Aspirin-induced model	=Strengthening mucosal resistance, prolonging the lifespan of mucosal cells increasing secretion and viscosity of mucous and reducing H+ ion back diffusion. = possess cytoprotective action similar action to that of prostaglandin other bindings of bile salt	[20]
Azadirachta indica Meliaceae	Nimbidin, Nimbin, Nimbolide, Gedunin, Azadirachtin,	Azadirachtin, Nimbidin, Nimbin Quercetin, Neem seed oil, Quercetin	Skin diseases, rheumatism, and malarial fever.	Nigeria	Indomethacin, stress and ethanol-induced	=inhibits H+-K+-ATPase activity in vitro in a	[19]

	Mahmoodin, Cyclic trisulphide	and ß-sitosterol				concentration-dependent manner to inhibit acid secretion. = prevents *OH-mediated mucosal DNA damage in vitro by scavenging the *OH. = preventing oxidative Damage and apoptosis.	
Carica papaya (Caricaceae)	Vitamin C, phenolic acids, and flavonoids, papain alkaloids, flavonoids, terpenoids, saponins, steroids, tannin, vitamins, 953uinines, minerals	Organic acids such as citric acid, fumaric acid, malic acid, tartaric acid, benzyl isothiocyanate	Gastrointestinal tract disorders, intestinal parasite infections, sedative and diuretic, nerve pains, (neuralgia) and elephantoid growths.	West Tropical Africa	pylorus ligation induced model	= antioxidant mechanism of action.	[86]
Annona senegalensis (Annonaceae)	triterpenes, anthocyanins, glycosides, coumarins, flavonoids and alkaloids	1, 2 benzenediol, butylated hydroxytoluene (BHT), Phenol, 2, 6 bis (1, 1-dimethylethyl-	yellow fever, tuberculosis, and small pox	West Africa-Burkina Faso	pylorus Ligation-Induced, Ethanol-Induced model	= gastric cytoprotection	[87]

		4methyl, methylcarbamate, n hexadecanoic acid, hexadecane, 13-hexyloxacyclotridec-10-en-2one, oleic acid, tetracosane, 9-octylheptadecane, heneicosane					
Chasmanthera dependens (Menispermaceae)	quaternary protoberberine alkaloids and the non-phenolic quaternary alkaloids, steroids, oleic acid, tannin and phenol	berberine palmatine, colombamine and jateorhizine, chasmanthin, columbin, palmarin	sexual disorders, abdominal pain, sprained joints and bruises	Sierra Leone east, Somalia, Tanzania Angola, Zambia, Zimbabwe, Ghana.	indomethacin-induced model	=enhancement of antioxidant status, the release =release of growth factors that induce angiogenesis like VEGF and PGE_2 and =suppression of pro-inflammatory cytokines and intrinsic apoptotic pathway	[88]
Solanum nigrum	alkaloids, terpenoids, flavonoids, saponins, steroids and phenols.		Antibacterial for respiratory pathogen	Cameroon, Nigeria and Gabon	Stress-model indomethacin model, pyloric ethanol (EtOH) induced gastric ulcer model	= blocking acid secretion Through inhibition of H(+)K(+) ATPase	[89]

						And decrease of gastrin secretion.	
Guiera senegalensis	Alkaloids, saponin, flavonoids		GI disorder, anti-malaria, respiratory infections	West Africa	NSAID-induced model	Activation of prostaglandin Synthesis	[63]

From the table above, some plants such as Trema orientalis, Spondia mombin, Citrus aurantifolis, Biden pilosa, Asparagus racemosus, moringa oleifera and Maytenus senegalensis, carry out cyto-protective effect by promoting the synthesis and production of prostaglandin. They facilitate mucus and bicarbonate production and prolong the life span of mucosal cells increasing secretion, viscosity of mucous, strengthening mucosal resistance.[66] They also augment the protection of surface epithelium with more mucus globules.[64]

Cassia siberiana facilitates cyto-protection via reduction in function levels of enzymes – superoxide dismutase, catalase and glutathione peroxidase. It also inhibits /prevents hydroperoxides quantity and myeloperoxidase function (84). Psidium guajava, Trichilia monadelpha contributes to cyto-protection by boosting the mucosal blood flow.

Again, Azadirachta indica, Carapa procera, carica papaya and Zingiber officinale contributes to cyto-protection on mucosal wall through prevention of oxidative stress and suppression of apoptosis and promotion of antioxidant activity.[19] Meanwhile, plants such as Cnestis ferruginea promote cyto-protection and mucus production on mucosal surface via reduction in mucosal ischemia to enhance gastric blood flow.[67] Morinda Lucinda induces intestinal motility and gastric emptying time.[66]

However, these medicinal plants produce these biological effects via the presence of plant secondary metabolites including flavonoids, alkaloids, saponins, triterpenoids, steroids and glycosides. Phyto-chemical constituents with gastro-protective and anti-ulcerogenic properties include tannins, flavonoids, alkaloids, terpenoids and phenolic glycosides. Plants extracts produce therapeutic effects which are attributed to the presence of single or combined activity of a mixture of these phytoconstituents.[90] Flavonoids are a group of poly-phenolic compounds with known properties that include free-radical scavenging, inhibition of hydrolytic enzymes and anti-inflammatory action. Flavonoids represent a class of secondary metabolites widely distributed in the plant kingdom and richly found in the diet. They possess gastro-protective, anti-secretory, cyto-protective and antioxidants properties.[91] Flavonoids participate in the healing of gastric ulcer via the suppression or modulation of peptic ulcers. Study has shown that flavonoid shield the gastrointestinal mucosa from lesions produced by different necrotic agents.[46] Quercetin and flavanol are the most commonly studied flavonoids. They protect the gastrointestinal mucosa from acute lesions, increase mucus production and reduce histamine levels[93] Alkaloids are important plant secondary metabolites that have good solubility in acidic mediums (stomach juice). Cavidine, a major

alkaloid compound isolated from Corydalis impatieus, ameliorates gastric damage. It also enhances mucosa GSH, SOD and PGE_2 levels while reducing interleukin -6 (IL-6) and tumor necrosis factor, TNF-α level.[94] Terpenes and Terpenoids, especially the monoterpene B-myrcene obtained from Citrus aurantium reduces gastric and duodenal injuries, enhance gastric mucus production and mucosal MDA levels, and reduces SOD activity in ulcer models induced by ethanol, stress, H. pylori and ischemia-reperfusion.[95] Saponins display a strong antioxidant antiulcer activity. Phenolic acids, for instance, ellagic and gallic acids display a potent antiulcer effect related to prostaglandins and nitric oxide.[96] A combinatory effect of the antiulcer effect of gallic and famotidine was seen against aspirin/pylorus induced ulcer in rats; which yielded elevation in the level of SOD, CAT and G6PD and reduced the level of lipid peroxidation and myeloperoxidase in gastric tissues.[97] A constituent of Galipea longiflora plant, 2-phenylquinoline has been found to normalize SOD and GST activity, elevate GSH with minimal LPO and TNF-α levels in gastric mucosa.[98]

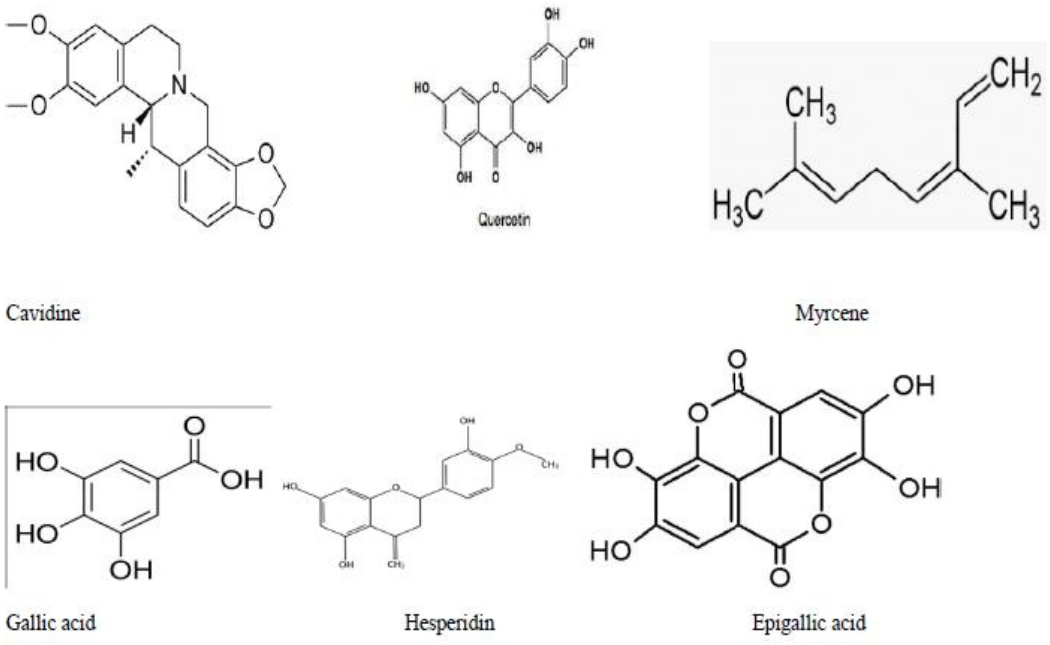


Fig. 4: Chemical structures of some phyto-chemical constituents responsible for antiulcer cytoprotective properties of plants.

Limitation to study

This literature search is restricted by the various challenges faced by the different studies utilized for this review. This investigation is also faced with the essential inadequacy of systematic reviews which include dependent on the available literature. The systematic search is also restricted by the likely exclusion of some valuable studies due to the choices of

keywords employed as well as the choices of databases utilized for the literature search. There may also be the existence of publication bias in the information used for review and cannot be excluded.

CONCLUSION

Much research has shown that secondary compounds, present in various plants exert beneficial effects in cytoprotection and ulcer healing. Plant components when consumed, release substances that protect the mucosal surface of the gastrointestinal wall thereby acting as defensive factors. They suppress gastric acid secretion; enhance mucus production to promote the healing of ulcer. Therefore, this review supports an increase in the consumption of plants and plant products as a source of gastric ulcer healing.

Credit author statement

Doris designed the study and carried out an intensive research on the investigation while Dr. Stanley corrected, supervised and collated the result. He also went further to harmonize the tables.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding authors.

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