Chapter 3

The Purview of Phytotherapy in the Management of Gastric Ulcer

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Abstract

Stomach/gastric ulcer is a debilitating disease affecting more than 10% of the global population. Sufferers often have chronic pains with life-threatening gastrointestinal haemorrhage or perforation. Since the first diagnosis of stomach ulcer (SU) in the 19th century, excessive gastric juice that eroded the mucosa of the stomach was opined as its major cause. Efforts were channelled toward effective control of the resulting acid build-up through the use of antiulcer medications and reduction in stress-induced activities, which may aggravate gastric hyperacidity. An intense treatment option involved vagotomy (surgically severing the nerves surrounding an ulcer) to prevent hyperacidity and further perforation of the stomach epithelium. Despite these interventions, SU disease remained an impediment to clinical practice. Literatures revealed that many botanicals have been used to treat SU and this is hinged on their being endowed with antiulcerogenic phytonutrients of therapeutic significance. In this review, attempts have been made to highlight the main mechanisms of action and limitations of the conventional antiulcerogenic drugs, various antiulcerogenic experimental models, as well as compile selected medicinal plants and their implicated phytonutrients that will ultimately and eventually present effective and globally competitive exciting opportunities for the development of new lead therapeutics for the management of SU disorders.

Keywords: antiulcerogenic, gastric ulcer, gastropathy, hemorrhage, *Helicobacter pylori*, pepsin, perforation, phytonutrients, vagotomy

1. Introduction

Ulcer is an open sore of the biological membrane characterized by sloughing of inflamed dead tissue [1]. More specifically, it could either occur as a lesion on the surface of the skin

or a mucous membrane with significant superficial loss of tissue. Although, ulcers may be encountered at almost any part of the body, they are mostly found on the skin of the lower extremities and in the gastrointestinal tract [2]. There are many types of ulcer including mouth, esophageal, peptic and genital ulcer. Of these, peptic ulcer (PU) is the most prevalent [2]. The PUs are erosion of lining of either the stomach or duodenum [3] and this has availed the two most common types of PU as the gastric/stomach ulcer (SU) and duodenal ulcer. A person may have both gastric and duodenal ulcers at the same time. SUs are located in the stomach and mainly characterized by hemorrhage and pain. Other symptoms may include nausea, vomiting, and weight loss. Although patients with SU have normal or diminished acid production, yet ulcers may occur even in complete absence of acid [3]. Generally, pain occurs when the stomach is empty and relieves after eating. In some cases, SU can be life threatening with symptoms like bloody stool, severe abdominal pain, and cramps coupled with blood vomiting [4].

Under normal conditions, a physiologic balance exists between gastric acid secretion and mucosal defense. The epithelial cells of the stomach secrete mucus in response to irritation of the epithelial lining and as a result of cholinergic stimulation [5]. Ordinarily, the superficial portion of the gastric mucosa is jelly-like and impermeable to acid and pepsin. Other gastric cells secrete bicarbonate, which buffers acid that lies penultimate to the mucosa. Also, the prostaglandins of the E (PGE) type of the epithelia offered significant protection by increasing the bicarbonate content and consequently strengthening the mucous layer. However, when the acid and pepsin enters the epithelial cells, further fortifying mechanisms are triggered to ameliorate injury [5]. This may be best observed within the epithelial cells, where ion pumps in the basolateral cell membrane aids intracellular pH regulation through removal of excess H^+ and subsequent migration of healthy cells to the site of injury. By so doing, the acid that diffused through the injured mucosa is effectively removed by the flow of blood in the mucosa. This also provides bicarbonate to the superficial epithelial cells. However, when there is disequilibrium between offensive (acid, pepsin, and *Helicobacter pylori*) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide, and growth factors), the pathophysiological features of SU become evident [6]. Although, SU was once believed to be caused by spicy food and stress, they have however been established to be mere aggravating factors while the real causes include reaction to various medications, particularly nonsteroidal anti-inflammatory drugs (NSAIDS) and *H. pylori* infection [7]. *H. pylori*, NSAIDS, emotional stress, alcohol abuse, and smoking are the principal etiological factors associated with SU [8]. Usually, SU occur as breaks across the entire length of the stomach epithelia and in some cases, the deeper layers of the muscle wall are considerably affected. This disruption of the mucosal integrity may potentiate perforation, bleeding, obstruction, pain and death, if proficient treatments are not timely administered. The exclusive production of urease by *H. pylori* renders its microenvironment alkaline and allows its long-lasting survival in the hostile acidic environment of the stomach, where it either worsens the severity of SU disease or merely causes mucosal inflammation. More often in SU cases, inflammation is secondary to the colonizing action of *H. pylori* on the gastric mucosa [5]. In patients infected with *H. pylori*, high levels of gastrin and pepsinogen

and reduced levels of somatostatin have been measured [5]. Most patients with SU have impaired gastric bicarbonate secretion, which has also proven to be caused by *H. pylori* because its eradication reverses the defect [9]. Similarly, pepsin (a proteolytic enzyme) and HCl are both essential for food digestion but at the same time have the tendency to erode the cell linings of the digestive system if secreted in excess. Although, the stomach defends itself from these aggravating factors by creating a mucus coating and producing bicarbonates, *H. pylori* infection and NSAIDS can impair the protective functions and make the linings of the gastrointestinal tract susceptible to HCl and pepsin action and consequently results in the formation of ulceration [10].

Globally, SU is the most prevalent gastrointestinal disorder ever known, affecting more than 10% of people and accounting for an estimated 15,000 mortality yearly [11]. The annual incidence of SU perforation and hemorrhage were 3.8–14.0 and 19.4–57.0 per 100,000 persons, respectively and this is anticipated to further worsen if no practical and viable alternatives are sought [12]. Specifically in the United States, PU disease affects approximately 4.5 million people annually and about 10% of the US population has evidence of a SU at some point in their life time [5]. Initially, PU diseases were more prevalent in the male populations but the current statistics suggest quite similar figures in both males and females with the overall lifetime prevalence tending toward 8–11% and 11–14% in women and men, respectively [5]. The age trends for the occurrence of PU show appreciably declining rates in younger males, while it is increasing steadily in older women. The statistics for SU disease in other countries is variable and is hinged primarily on the major causes of the disease: *H. pylori* and NSAIDs [13].

Although, orthodox medicine has provided succor in the management of SU disease over the years, a significant percentage of the global population still use traditional systems of medicine to manage and treat SU due to better cultural acceptability, improved compatibility, affordability, and lesser side effects [14]. The present study was conducted to review medicinal plants considered as gastroprotective and healing agents on SUs with particular focus on selected antiulcerogenic botanicals and their implicated phytonutrients. To achieve this, information were retrieved from online databases (Google, Pubmed, MEDLINE, Science Direct, Scopus and SID) in form of published articles, books, conference proceedings and other high profile intellectual resources. The retrieved studies either showed effectiveness of these plants or indirectly their efficacy on the involved mechanisms in the treatment of SU.

2. The conventional therapy for stomach ulcer management

SU therapy has witnessed many strides over the last decades and a number of drugs are now available for its treatment. Since the occurrence of SU disease is attributable to either pepsin action and hyperacidity or inadequate mucosal resistance, hence, its effective management lies exclusively in stemming the aggressive factors or fortify the defensive mechanisms. A

corner stone in this approach was the advent of histamine H_2-receptors and the respective antagonist [15], which signified a landmark achievement in the management of disorders characterized by gastric hypersecretion. The H_2-antagonists were instantaneously identified as potent and safe agents which may replace the previously used drugs. For instance, the appearance of cimetidine (an H_2-antagonist agent), led to the virtual disappearance of drugs of unknown mechanism like gefarnate, sulphoglycopeptide, amilopectine, zolimidine, xylamide, etc. Despite the inherent improvement witnessed with the use of the H_2-antagonist over the previously used drugs, their untoward reactions have undermined their appreciable application. Generally, the antiulcer drugs may be classified according to the site and/or mechanism of action as: (a) antacids; (b) gastric muscle stimulants; (c) agents which protect the mucosa, increase mucosal resistance or coat ulcer craters; (d) antisecretory drugs, which may be anticholinergic agents; (e) corticohypothalamic drugs; and (f) proton pump inhibitors.

2.1. Antacids

It is noteworthy that either antacid mixtures or combinations of antacids with other compounds are more commonly used than single-entity antacids [15]. These kinds of formulation have been made to elicit a better neutralizing effect and to extenuate side effects associated with single constituent entities. The calcium and aluminium combinations reduce diarrhea while magnesium caters well for constipation. Similarly, a combination of slow- and fast-acting agents could increase the total buffering time. More improved benefits are claimed for mixtures having alginic acid (a foam-forming agent), which floats above the gastric juice with eventual aiding of contact between the antacid and the mucosa. In the event of gastroesophageal reflux, the alginic acid appears to prevent reflux by being the first to come in contact with the esophagus. By so doing, further erosion by the gastric acid is effectively prevented. Also, when simethicone (dimethylpolysiloxanes with characteristics antifoaming and water-repellant properties) is used, defoaming the gastric juice to reduce flatulence and gastroesophageal reflux is achieved. However, the resulting contributory adverse effects of the respective constituent in the antacid especially gastric irritation are a major challenge consistent with the use of antacids.

2.2. Gastric muscle stimulants

In individuals with stomach atony where there is consequential prolonged contact time between acid and mucosa due to the delay in gastric emptying, stimulants of gastric motility produce satisfactory outcomes. Domperidone and metoclopramide are the two most widely used compounds in this category. While both accelerates gastric emptying in experimental animals and humans, the metoclopramide still acts via other four important mechanisms that have made it more potent: (i) a cholinergic effect on muscarinic receptors; (ii) a direct effect on smooth muscle; (iii) an effect on specific centers regulating gastrointestinal motility; and (iv) a release of motilin which could be strongly responsible for the effects on the proximal bowel [15].

2.3. Mucosa protecting agents

Compounds like sucralfate, carbenoxolone and chelated bismuthate belong to this class of drugs. The sucralfate (a complex of sucrose and aluminium hydroxide) potentiates its action by inhibiting gastric hydrolysis with significant affinity for ulcerated mucosa. It forms a complex with susceptible proteins (fibrinogen, albumin etc) that adhere to the ulcerated area, thereby shielding against acid, pepsin action and penetration of bile acid. The merits of sucralfate over other antiulcer drugs relate to a lack of systemic effect due to the poor absorption of the compound [16]. The disadvantages include a certain delay in gastric emptying and constipation which affects almost 2% of the sufferers. Furthermore, compliance is another issue of concern as sucralfate must be taken four times daily (q.i.d.) and at least one hour before meals to be optimally effective. While chelated bismuthate and carbenoxolone works quite similar to sucralfate, appreciable incidence of aldosterone-like adverse effects (sodium and fluid retention, hypertension etc) have hampered their use.

2.4. Drugs with antisecretory effect

2.4.1. Anticholinergics

Despite that the drugs in this class have been used for many years, information on their ulcer healing capacity is still elusive. This may be attributable to the radiological method that was initially used but later found not to be very effective in wound healing assessment. Hyoscyamine, atropine, phentonium, propantheline and methantheline with characteristic ganglion-blocking and antimuscarinic effects are the classical examples of anticholinergics. Subsequent to the discovery and acceptance of the H_2-antagonists, the anticholinergics virtually disappeared due to inherent adverse effects of dry mouth, blurring of vision, delay in gastric emptying, tachycardia, possible constipation, and urinary retention.

2.4.2. H_2-antagonists

Undoubtedly, the H_2-antagonists are the most significant agents for the management and treatment of SU and for pathological conditions characterized by hyperacidity. Burimamide (the prototype of H_2-antagonists) was faced-out because of low oral activity and toxicological concerns. Similarly, metiamide (the 2nd agent in the series), was orally active but potentiated significant bone marrow toxicity in clinical trials. Cimetidine (still the most widely used antiulcer drug), is the 3rd drug in this class and well over 70 million sufferers have so far benefitted from its pharmacological efficacy till date. This was closely followed by ranitidine, which was the first agent with an alkyl furan ring, which substituted the imidazole ring of the preceding H_2- antagonists. More recent reports however suggest that optimum H_2-antagonism may also be achieved also with other different agents. For this class of drugs, not only could potency and efficacy be optimized, the pharmacokinetics could also be modified with the known duration of action of 4–6 h, exclusive to the 'short-acting' H_2-blockers [17], optimized to and beyond 24–48 h to have 'long-acting' H_2-blockers. Generally, over the last

three decades, the most frequently used H_2-antagonists in clinical practice are cimetidine, ranitidine and famotidine [2]. However, many adverse reactions such as effects on the endocrine, cardiovascular and central nervous systems (CNS) have been associated with these drugs.

2.5. Corticohypothalamic drugs

A role has been established for the CNS in the regulation of gastric secretion and in the pathogenesis of peptic ulcer, although clarification is required in many areas. It is not surprising that drugs which act specifically on the CNS may exert a beneficial effect on SU, which sometimes is significantly better than other drugs. Trimipramine is a tricyclic antidepressant which causes a slight decrease in gastric secretion that is apparently not connected with its anticholinergic action. Like other traditional tricyclic antidepressants, it may have some H_2-antagonistic effects and may also act on α-adrenoceptors enhancing catecholamine availability at central synapses [18], or may depress central vagal function. However the use of trimipramine in non-depressed ulcer patients is questionable.

2.6. Proton pump inhibitors (PPIs)

At present, PPIs are the most commonly prescribed class of antiulcer drugs. Their mode of action involves blockage of the site of gastric acid secretion in the parietal cell of the stomach [19]. However, because the parietal cells are constantly reproducing in millions, effective inhibition of gastric acid secretion is almost unachievable and this partly explains their relative safety compared to other groups of antiulcer drugs. In general, the incidence of short-term adverse effects subsequent to PPI usage is relatively low and this may be the reason for their being well tolerated. Their long-term use has not been frequently studied and the dearth of information in this regards has made it difficult to make definitive statements [20]. For all the PPIs (omeprazole, lansoprazole, dexlanprazole, esomeprazole, pantoprazole, rabeprazole and ilaprazole), the occurrence of adverse effects are similar, though they have been reported more frequently with omeprazole. This may be due to its longer availability. The common adverse effects with PPIs include headache, nausea, diarrhea, abdominal pain, fatigue and dizziness. Infrequent adverse effects may also include rash, itch, flatulence, constipation, anxiety, depression, myopathies and rhabdomyolysis [21].

3. Ulcer inducing agents/models

The pathological mechanisms of SU disease that compromises its functional capability and the structural integrity has been established to arise mainly through either production of too much acid and pepsin, or weakening of the gastric epithelia that consequently results in too little mucosal resistance [2]. **Table 1** shows some of the known ulcerogenic agents/models and the pathological mechanism involved in their ulcer pathogenesis. A good understanding of the pathogenic mechanism of action of these models is crucial to spotting and either managing or preventing ulceration and the associated disorders.

Agent/model	Underlying mechanism	Reference(s)
NSAIDs (aspirin, indomethacin and ibuprofen)	Gastric acid secretion and inhibition of prostaglandin synthetase activity	[22]
Water-immersion/cold-restraint stress	Release of histamine resulting in increased acid secretion, decreased mucus production and poor flow of gastric blood	[23, 24]
Ethanol	Solubilizes mucous membrane and renders it vulnerable to the proteolytic and hydrolytic actions of HCl and pepsin	[25]
Acetic acid	Induces round, deep ulcers in the stomach through over production of acid secretion	[26]
Histamine	Acid stimulating and vasodilating effect that results to increased vascular permeability of the gastric mucosa	[27]
Reserpine	Degranulation of gastric mast cells consequent to histamine liberation that is facilitated by cholinergic system	[28]
Serotonin	Causes vasoconstriction thereby reducing gastric mucosal blood flow resulting to acute mucosal injury	[29]
Pylorous-ligation	Accumulation of gastric acid that consequently produces ulcer subsequent to the breakdown of gastric mucosal barriers	[30]
Ischemia-reperfusion	Causes erosion of the gastric epithelia due to free radicals formation	[31]
Acetic acid-*H. pylori*	Increased acid secretion and decreased mucus production	[32]
Iron-ascorbic acid	Linked with lipid peroxidation mediated by oxygen radicals	[33]

Table 1. Commonly used experimental models for ulcer induction.

4. Some scientifically validated antiulcerogenic medicinal plants

Despite the rapidly changing concept of SU disease management from conventional vagotomy, H_2-receptor antagonists and antacids to proton pump inhibitors, gastrointestinal toxicity and other inherent adverse effects remain significant impediments to their application in clinical practice. Investigation on the phytotherapeutic applications of medicinal plants that are highly valued and widely used in the traditional systems of medicine have been and still providing efficient formulation for better management of SU [2, 22].

The under-listed medicinal plants have been pharmacological reported to possess antiulcer activity as previously compiled [34–39]. They are:

Acacia arabica (Family: Mimosaceae); *Abutilon indicum* L. (Family: Malvaceae); *Adansonia digitate*; *Aegle marmelos* (Family: Rutaceae); *Allium sativum* (Family: Liliaceae); *Allophylus serratus* Kurz (Family: Sapindaceae); *Aloe vera* (Family: Liliaceae); *Alstonia scholaris*; *Annona squamosa* (Family: Annonaceae); *Asparagus racemosus; Azadirachta indica* (Family: Meliaceae); *Bacopa monnieri*; *Benincasa hispida*; *Bauhinia purpurea* (Family: Leguminosae); *Bauhinia variegate* (Family: Caesalpiniaceae); *Berberis aristata*; *Beta vulgaris*; *Buchanania lanzan* Spreng. (Family:

Anacardiaceae); *Butea frondosa* Roxb. (Family: Fabaceae); *Boswellia serrata* (Family: Burseraceae); *Careya arborea* (Family: Myrtaceae); *Carica papaya* (Family: Caricaceae); *Capsicum annuum* L. (Family: Solanaceae); *Centella asiatica; Cissus quadrangularis* L. (Family: Vitaceae); *Curcuma longa* L. (Family: Zingiberaceae); *Desmostachya bipinnata* (L.) Stapf (Family: Gramineae); *Desmodium gangeticum; Emblica officinalis* (Family: Euphorbiaceae); *Excoecaria agallocha* (Family: Euphorbiaceae); *Garcinia cambogia; Glycyrrhiza glabra* (Family: Leguminosae); *Ficus arnottiana*; *Ficus religiosa* (Family: Urticaceae); *Hemidesmus indicus*; *Hibiscus rosa sinensis* (Family: Malvaceae); *Ipomoea batatas* L. (Family: Convolvulaceae); *Ixora pavetta* (Family: Rubiaceae); *Kielmeyera coriacea* Mart (Family: Guttiferae); *Lagenaria siceraria* (Family: Cucurbitaceae); *Leucas lavandulifolia* Sm. (Family: Labiatae); *Mangifera indica* (Family: Anacardiaceae); *Mimosa pudica* (Family: Fabaceae); *Mentha arvensis* L. (Family: Lamiaceaea); *Momordica charantia* (Family: Cucurbitaceae); *Momordica cymbalaria* Hook. (Family: Cucurbitaceae); *Morinda citrifolia*; *Moringa oleifera* (Family: Moringaceae); *Musa sapientum*; *Myrtus communis* (Family: Myrtaceae); *Ocimum sanctum* (Family: Lamiaceae); *Oryza sativa* (Family: Gramineae); *Phyllanthus niruri* (Family: Euphorbiaceae); *Plectranthus amboinicus*; *Polyalthia longifolia* (Family: Annonaceae); *Psidium guyava* (Family: Myrtaceae); *Rhus coriaria* (Family: Anacardiaceae); *Rhizophora mangle* L. (Family: Rhizophoraceae); *Sapindus trifoliatus* L. (Family: Sapindaceae); *Sesbania grandiflora* (Fabaceae); *Shorea robusta* (Family: Dipterocarpaceae); *Solanum nigrum* (Family: Solanaceae); *Tamarindus indica* (Family: Caesalpiniaceae); *Tamarindus indica* (Family: Caesalpiniaceae); *Tecomaria capensis* (Family: Bignoniaceae); *Terminalia chebula* (Family: Combretaceae); *Terminalia pallida; Utleria salicifolia Bedd*. Ex.Hook. F. (Family: Periplocaceae); *Vinca minor* L. (Family: Apocynaceae). A comprehensive list of some selected plants being embraced as antiulcerogenic agents is presented in **Table 2**.

Plant	Family	Plant used	Phytonutrients	Reference(s)
Acacia arabica	Mimosaceae	Gum, leaves	Arabic acid, malate, sugar, mineral elements, tannins	[40, 41]
Achyranthus aspera	Amaranthaseae	Root, seeds	Saponin, glycosides	[42]
Adansonia digitata	Malvaceae	Leaves	Mucilage, glucose, albuminoids, adansonin, tannin	[43]
Aegle marmelos	Rutaceae	Leaves	Flavonoid, tannins, saponin	[44]
Aleo vera	Liliaceae	Whole plant	Aloin, isobarbaloin, emodin, saponin	[45]
Alhagi maurorum	Fabaceae	Root	Terpenes, saponin, tannins	[46]
Allium sativum	Liliaceae	Bulb	Mucilage, starch, albumen, vitamins, sugar, allicin, alliin	[47]
Annona squamosa	Annonaceae	Leaves	Alkaloids, flavonoids, saponini, tannins	[48]
Azadirachta indica	Meliaceae	Leaves	Saponin, flavonoids, phenolics, tannin	[49]
Bauhinia variegate	Caesalpiniaceae	Stem-bark, root	Rutin, quercetin, apigenin, tannin	[50]
Berberis aristata	Berberidaceae	Root	Alkaloids	[51]
Bata vulgaris	Chenopodiaceae	Root	Betin	[52]
Carica papaya	Caricaceae	Fruit, seeds	Papain, pectin, carpaine, carposide	[53]

Plant	Family	Plant used	Phytonutrients	Reference(s)
Centella asiatica	Apiaceae	Whole plant	Flavonoids, narigin, alkaloids, saponin, asiatic acid	[54]
Cordial myxa		Fruit	Tannins, carbohydrate, saponin	[55]
Ficus exasperata	Moraceae	Leaves, stem-bark	Flavonoids, saponin, alkaloids, glycosides, tannins	[2]
Ficus religiosa	Urticaceae	Stem-bark	Tannins, wax, cochtone	[56]
Gossypium barbadense	Malvaceae	Leaves	Gossypol, saponin, steroids, cardiac glycosides	[22]
Gossypium herbaceous	Malvaceae	Flowers	Flavonoids, phenolics, saponin	[57]
Hibiscus rosa sinensis	Malvaceae	Root	Phenolics, cyanidin, hydrocitrate	[58]
Langeneria breviflora	Cucurbitaceae	Fruit, leaves	Saponin, phenolics, cucurbitacin	[59]
Langeneria siceraria	Cucurbitaceae	Fruit	Flavonoids, steroids, phenols, saponin	[42]
Mangifera indica	Anacardiaceae	Leaves	Alkaloids, sterols, saponin, tannins, flavonoids, mangiferin	[60]
Momordica tuberose	Cucurbitaceae	Tubers	Alkaloids, tannins, saponin	[61]
Moringa oleifera	Moringaceae	Leaves	Quercetin, β-sitoterol, β-carotene, alkaloids, tannins, saponin	[62]
Musa paradisiacal	Musaceae	Root, leaves, trunk	Tannins, starch, vitamin C, albuminoids	[42]
Myrtus communis	Myrtaceae	Leaves	Resin, tannins, citrate, malate, sugar	[63]
Nerium indicum	Apocynaceae	Flowers	Alkaloids, glycosides, flavonoids, phenolics, tannins	[64]
Ocimum sanctum	Lamiaceae	Leaves	Alkaloids, tannins, saponin, flavonoids, sterols	[65]
Oryza sativa	Gramineae	Grain, bran	Starch, mineral matter, protein	[66]
Phyllanthus niruri	Euphorbiaceae	Whole plant	Alkaloids, tannins, flavonoids, carbohydrate, glycosides	[67]
Prunus amygdalus	Rosaceae	Seeds, fruit	Ursolic acid, quercetin, flavonoids	[42]
Psidium guyava	Myrtaceae	Leaves, stem-bark	Resin, tannins, cellulose, flavonoids, quercetin, quajaverin	[68]
Rhus coriaria	Anacardiaceae	Whole plant	Tannins, flavonoids	[69]
Sesbania grandiflora	Fabaceae	Leaves	Saponin, tannins, triterpenes	[70]
Smilax china	Smilacaceae	Root	Tannins, resin, saponin, flavonoids	[71]
Solanum nigrum	Solanaceae	Leaves	Flavonoids, saponin, alkaloids, phytosterols	[72]
Spondias mombin	Anacardiaceae	Leaves	Tannins, saponin, flavonoids, phenolics, glycosides	[73]
Tamarindus indica	Caesalpiniaceae	Leaves, seeds	Albuminoids, fiber, pectin, tannins	[74]
Terminalia chebula	Combretaceae	Leaves	Gallic acid, sorbitol, tannins, mucilage	[75]

Table 2. Some selected medicinal plants with antiulcerogenic properties.

Following the experimental demonstration that many medicinal plants are endowed with good antiulcerogenic activity with relatively lesser adverse effect compared with the conventional drugs, further steps have been taken in presenting a good number of them for clinical trials. Despite this giant stride, not many of the medicinal plants have passed market entry stage. To the best of our knowledge, of the many presented for developmental evaluations in 2004, only *Azadirachta indica* (Family: Meliaceae) received remarkable attention at its advance stage of clinical trial. It exhibited significant therapeutic potency by reducing gastric hypersecretion, gastroesophageal and gastroduodenal ulcers [76].

5. Phytonutrients associated with antiulcerogenic activity

Several phytonutrients have proven health benefits and have been reported to elicit significant antiulcerogenic potential in both humans and experimental animal models [73]. While steroid glycosides, tannins, terpenoids and flavonoids have been shown to preserve gastric mucosal against oxidative insults of reactive metabolites and oxidative stress [22, 59], the tendency of phenolic compounds and alkaloids to regulate gastric acid secretion and protect the gastric mucosal epithelia against erosion and other aggressive factors in different ulcer models have been demonstrated [77]. While **Table 1** also presents some of these phytonutrients as being responsible for the elicited antiulcerogenic properties of the plants, several others have also been identified and isolated from diverse plants. Some of these include; saponins, phobaphenes, glucose, luvangetin, tartarate, potash, nimbidin, quercetin, apigenin, papain, chymopapain, pectin, carposide, carotenoids, antheraxanthin, carpaine, resin, euphorbon, caoutchouc, rutin, anthocyanins, cyanindin, kaempferol, sterols, mucilage, terpenoids, kaepferom, ash, starch, fats, proteins, glycosides, ellagic acid, beta sitosterol, gallic acid, limonene, pinene, albuminous matter, cellulose, chlorophyll, mineral salts, myricitin, triterpenes, and sorbitol [37]. These compounds have either been elucidated to decrease acid/pepsin secretion or confer cytoprotection via effective modulation on mucosal defensive factors.

6. Some selected medicinal plants with antiulcerogenic properties in Nigeria

In Nigeria, SU remains a significant public health challenge affecting people of all ages. While its management through orthodox medicine has recorded substantial successes over the years, a considerable proportion of the populace still rely exclusively on complementary and alternative medicine (CAM) in seeking aid to treat and manage SU. This may be due to the ease of accessibility, affordability and minimal side effect associated with the use of medicinal plants [22]. A compilation of selected antiulcerogenic medicinal plants in Nigeria revealed that the most widely used plants in the management of SU are *Occimum basillicum*, *M. paradisiaca*, *Aloe vera*, *Azadiracter indica*, *Brassica oleracae* and *Carica papaya* [78]. Others include but not limited to the following: *Diodia sarmentosa*, *Cassia nigricans*, *Ficus exasperate*, *Synclisia*

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scabrida, *Artocarpus heterophyllus* Lam., *Blighia sapida* Konig., *Dialium guineense* Willd., *Emblica officinalis* Gaertn., *Gongronema latifolium*, *Ageratum conyzoides*, *Aloe vera*, *Artocarpusaltilis*, *Aspilia africana*, *Bryophyllum pinnatum*, *Fluerya aestuans*, *Musa paradiasiaca*, *Musa sapientum*, *Persea Americana*, *Talinum triangulare*, *Fluerya aetuans*, *Brassica oleracae*, *Acacia nilotica* L., *Alchornea cordifolia Schum & thonn*, *Anacardium occidentale* L., *Balanites aegyptiaca* L., *Bridelia ferruginea* Benth, *Carica papaya* Linn, *Ficus thonningii* Blume, *Guiera senegalensis* J. F. Gmel, *Hibiscus sabdariffa* L., *Mangifera indica* L., *Momordica charantia* L., *Ocimum gratissium* L., *Piliostigma reticulatum* (DC) Hochst, *Pisidium guajava* L., *Scoparia dulcis*, *Vernonia kotschyana* Sch. Bip., *Zingiber officinale* Rosc [79].

7. The role of medicinal plants in oxidative gastropathy

Reactive oxygen species (ROS) are a by-product of normal metabolism and have roles in cell signaling and homeostasis [80]. Mechanisms exist that regulate cellular levels of ROS, as their reactive nature may otherwise cause damage to key cellular components including DNA, protein, and lipids [81]. A good number of NSAIDS have been implicated in cellular toxicity leading to oxidative gastropathy [82]. Despite the use of NSAIDS as antipyretic and anti-inflammation agents, and in the treatment of rheumatic, musculoskeletal, and cardiovascular diseases [83], gastrointestinal toxicity through ROS formation has limited their application [84, 85]. It has been proposed that NSAID-mediated gastrointestinal lesions involve the uncoupling of oxidative phosphorylation and inhibition of electron transport chain causing incomplete reduction of oxygen [82]. This they do by tenaciously binding to a site near complex I and ubiquinone, thus facilitating events leading to ROS generation [86, 87]. Subsequently, when the gastric antioxidant capacity is overwhelmed, the epithelia mitochondrial aconitase is inhibited, resulting in the release of iron that reacts with H_2O_2, producing hydroxyl radical. These cascades of event amplify gastric oxidative stress whose consequential effect is manifested as gastropathy [88]. Oxidative stress-induced functional loss is well correlated with numerous disease states including cardiovascular, neurological, cancer, aging processes and gastropathy [83] and is also implicated in a variety of drug-induced toxicities such as SU [2]. Antioxidative and free radical scavenging mechanisms play an important role in the protection against ROS mediated toxicities [89]. Over the past decades, interests in medicinal plants, especially the antioxidative ones, have increased appreciably and they have been elucidated to significantly either protect against or ameliorate ROS-mediated oxidative gastropathy [22, 90]. Such annihilation of ROS in SU diseases have been achieved through induction of enzymic antioxidants (superoxide dismutase, catalase, glutathione reductase and peroxidase) and optimization of reduced glutathione (GSH) contents [2, 22, 59]. Harmonizing the foregoing, a probable mechanism of antioxidative and gastroprotective activities of medicinal plants may be idealized as illustrated in **Figure 1**. This ultimately involves induction and optimization of preventive (catalase, glutathione peroxidase) and chain-breaking (superoxide dismutase, glutathione reductase) antioxidants that subsequently improve gastric GSH level, annihilate liberated reactive metabolite and effectively scavenge ROS (O_2^-, OH^-) (**Figure 1**). This may also be opined to regulate mucosal fluidity and strengthens defensive mechanisms against oxidative gastric damage.

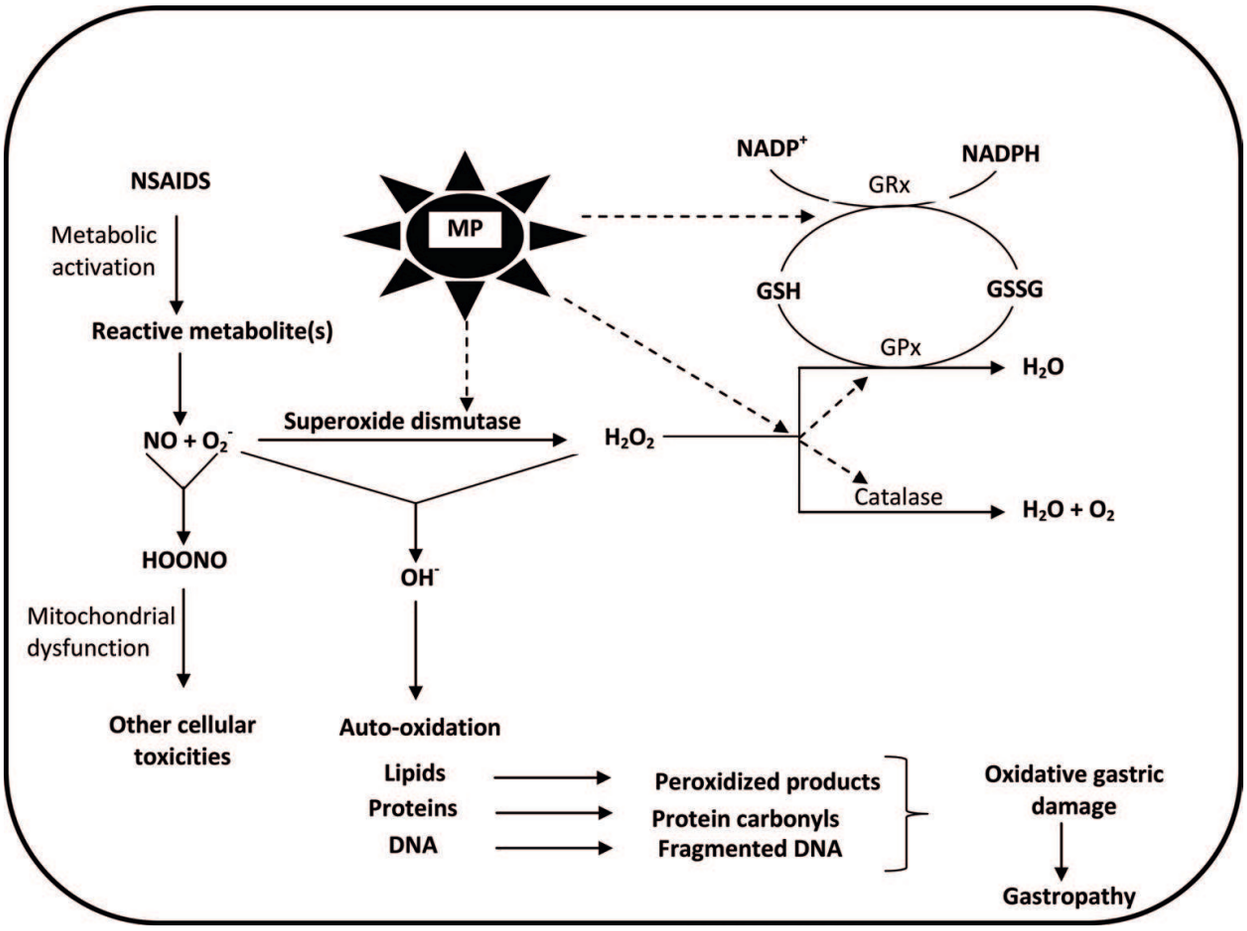

Figure 1. Probable mechanism of antioxidative and gastroprotective capabilities of medicinal plants. The dotted arrows represent sites of induction and optimization by the plants that consequently promote scavenging of O_2^- and OH^-. This will normalize and increase gastric reduced glutathione (GSH) content and promotes its mobilization toward detoxification of the liberated reactive metabolites. NSAIDS, nonsteroidal anti-inflammatory drugs; MP, medicinal plants; GPx, glutathione peroxidase; GRx, glutathione reductase; GSSG, oxidized glutathione.

8. Conclusion

Globally, SU is a devastating disease posing serious threat to the quality of life of humans. It affects significant proportion of the populace in both developed and developing countries. Although, conventional drugs have been used to manage and treat SU sufferers, affordability and inherent side effects have limited their application. Consequently, alternatives are being sought in medicinal plants, which provide a potential source of antiulcerogenic drugs and are widely used in traditional systems of medicine. Several medicinal plants have been investigated for their proven health benefits in SU management with their phytonutrients playing significant roles. Of the phytonutrients, tannins seem to top the list and has suggested probable focus on their characterization for antiulcer therapy. In spite of the impressive experimental evaluation of medicinal plants for the treatment of SU, very few have reached clinical trials and not very many have been marketed. This indicates that the intended benefits of CAM research are not yet having far-reaching effect. Nevertheless, the continuous search for

antiulcerogenic agents of plant origin (available as gifts of nature) is imperative. This will ultimately and eventually present effective and globally competitive exciting opportunities for the development of new lead therapeutics for SU and other related disorders.

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