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Ethnopharmacological Relevance of Selected Plants Used in The Treatment of Peptic Ulcer Disease

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Peptic ulcer illness is indicated by an internal sore on the stomach or duodenum due to an imbalance between defensive components such as (blood fluid, prostaglandins, and antioxidants) and offensive factors (excessive gastric acid, elevated free radicals and Helicobacter pylori). The two main things interfering with mucosal resistance to tissue injury are H. pylori infection and non-steroidal anti-inflammatory drugs (NSAIDs). NSAID-induced injury to the gastroduodenal mucosa mostly results from systemic suppression of constitutively expressed cyclooxygenase-1 (COX-1), the enzyme that synthesises prostaglandins. Similar to this, H. pylori travels toward the gastric epithelium after entering the stomach and uses its urease to neutralize the stomach's acidity. There, it uses its adhesion molecule to bind to the gastric epithelial cell receptors. Most prominent plant species used when managing peptic ulcer illness include Carica papaya (Caricaceae), Zingiber officinale (Zingibireceae), Musa parasidiaca (Musaceae), Allium sativum (Amaryllideceae). Various naturally occurring chemicals having gastroprotective properties can be found in these medicinal plants such as kaempferol, quercetin and diosmin in flavonoids; rutaecarpine, rohitukine and piplartine in alkaloids; castalagin, casuarictin and corilagin in tannins. In summary, a great deal of plant species has been discovered, assessed, and recognized by science for their possible gastro-protective and anti-ulcer qualities. This will ultimately present beneficial chances for the development of innovative lead treatments to treat peptic ulcer disease

1. Introduction

Peptic ulcer disease (PUD) is the medical term for duodenal or stomach ulcers caused by stomach acid damaging the digestive tract. Peptic ulcers, or damage to the digestive tract caused by stomach acid, cause mucosal tears that penetrate the submucosa (Del Valle, 2015). Due to acid-induced gastrointestinal tract lesions that manifest with particular deficits, peptic ulcer disease occurs in the stomach or proximal duodenum (Narayanan *et al*., 2018). The mortality rate from the condition has significantly decreased, according to epidemiological research, although between 5 and 10% of the general population still has peptic ulcer disease (Lanas and Chan, 2017). Sreide *et al*. (2015) list *H. pylori* infection, alcohol intake and NSAID abuse as some of the causes of peptic ulcers.

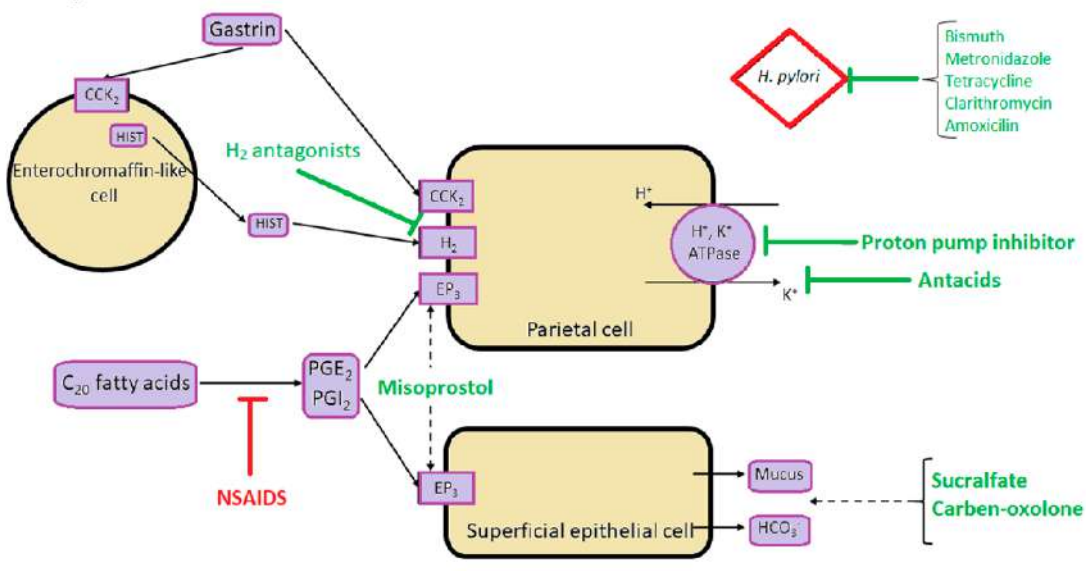


Figure 1: The pharmacological and principal agents responsible for the development of ulcerations (Kuna *et al*., 2019).

2.1 Drivers of Mucosal Injury

About 90% of stomach ulcers are caused by *H. pylori*, which increases the stomach's acidity and prevents the formation of bicarbonate (Malik *et al*., 2021). The probability of mucosal healing is considerably increased through the use of medications such as potassium chloride, steroids, bisphosphonates and corticosteroids (Malik *et al*., 2021).

Different molecular and cellular mechanisms generate NSAID-induced lower stomach damage than upper gastrointestinal injury (Whittle, 2004; Wallace, 2012). It damages mucosa and inhibits COX-1, just as it does in the stomach. However, unlike gastric injury, intestinal injury brought on by NSAIDs is patho-physiologized by intestinal flora and bile acid (Otani *et al*., 2017). NSAIDs and gut flora have a complex and dynamic connection. Through biotransformation into metabolites, the stomach microbiota can directly affect the effectiveness of NSAIDs, or indirectly, it can modify human metabolism (by interfering with hepatic function, for example) (Maseda and Ricciotti, 2020). Conversely, NSAIDs can affect the host's physiological processes, indirectly changing the gut microbiota's composition and function (Maseda and Ricciotti, 2020).

Gram-positive bacteria contribute to the deconjugation of primary bile acids in the intestinal lumen, resulting in the generation of dangerous bile acid secondary products generation of dangerous (Hegyi *et al*., 2018). The gut microbiota's composition, which is affected by bile acids, controls the type and amount of the bile acid pool (Urdaneta and Casades, 2017; Ticho *et al*., 2019). Thus, there is interaction between the bacteria and bile acids. After being transported to the duodenum, these bile acid-NSAID complexes are reabsorbed by the enterohepatic circulation and returned to the ileum. In the lumen of the intestine, especially in the colon, gram-positive bacteria are essential for deconjugating conjugated conjugated primary bile acids become secondary bile acids, which are more dangerous (Hegyi *et al*., 2018). The kind and quantity of the bile acid pool are determined by the gut microbiota's makeup, which is influenced by bile acids (Urdaneta and Casades, 2017; Thicho *et al*., 2019).

2.2 Anti-ulcerative Potentials of Medicinal Herbs

Herbal products have been utilised as lead compounds to identify several bioactive chemicals throughout history. Given that they are thought to be more secure than manufactured medications, they are frequently utilised in the conventional medical system to provide additional health advantages and to treat a variety of illnesses (Zakaria *et al*., 2019). Herbal medicines are frequently investigated by researchers as possible substitutes for synthetic ones (Salehi and Sener, 2019; Sharifi-Rad *et al*., 2019). In recent decades, various preclinical and clinical studies have demonstrated the effectiveness and safety of plant-derived medicines in a variety of pathological conditions (Choi *et al*., 2016; Quansah and Karikari, 2016). However, a sizable part of the world's population prefers herbal remedies or pharmaceuticals containing herbal components to preserve their health (Khandokar *et al*., 2021).

Kayode *et al*. (2019), studied the most prevalent plant species used to cure stomach ulcers in South Western and North-Central Nigeria using the use-mention index. Among these are the following species: *Allium sativum* (Amaryllideceae), *Zingiber officinale* (Zingibireceae), *Musa parasidiaca* (Musaceae), and *Carica papaya* (Caricaceae),

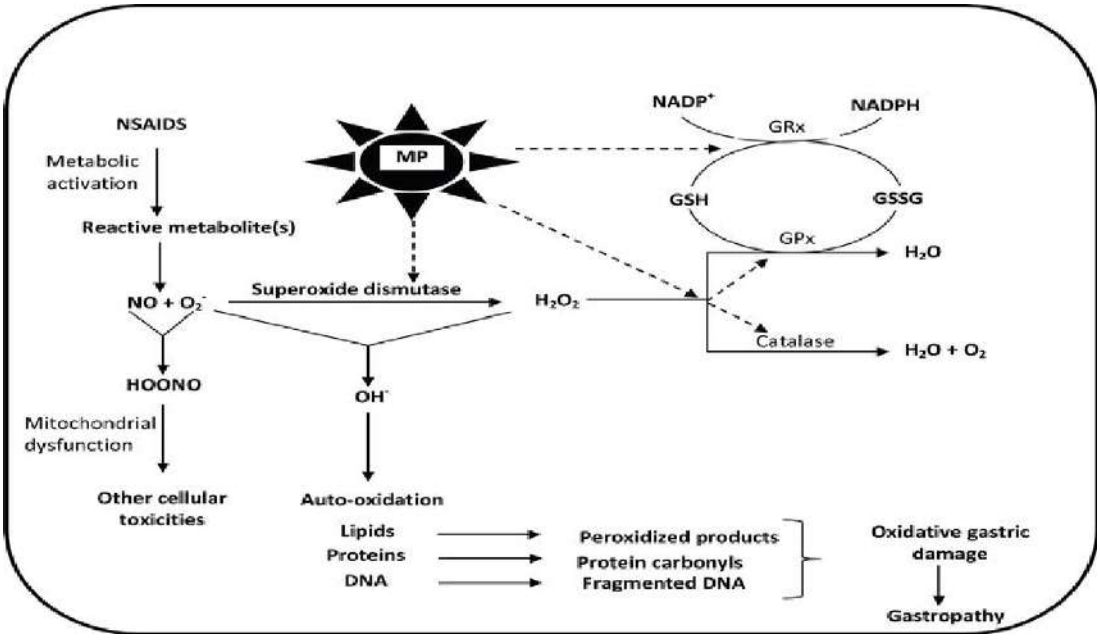


Figure 2: Potential mechanism of medicinal plants' gastroprotective and antioxidant effects (Saheed *et al*., 2018).

2.3 Flavonoids' Function in Peptic Ulcer

Pain alleviation, ulcer healing, and preventing complications and recurrences are the goals of treatment for peptic ulcers. The three mainstays of contemporary peptic ulcer therapy are cytoprotectors, histamine H_2 receptor antagonists, and proton pump inhibitors (PPIs) (sucralfate salts and bismuth) antimicrobials are required when *H. pylori* infection develops (Scally *et al*., 2018). PPIs represent a significant advance in the management of peptic ulcers. Still, several problems limit the efficacy of pharmacological treatment for peptic ulcers. These include side effects, which are especially problematic for individuals on long-term medication, and *H. pylori*'s increasing resistance to antibiotics (Yu *et al*., 2017). They also have poor ulcer healing and recurrence rates, which put a heavy financial strain on patients and the public health system. This is primarily because of the side effects, which include bleeding and perforation (Varcus *et al*., 2018). Several medicinal plants and their constituents have the gastroprotective and antiulcerogenic properties, which aid in the development of supplemental therapies aimed at the seriousness of ulcerative illnesses and avoiding recurrence intervals (Kuna *et al*., 2019).

The significance of medicinal plants as a source of chemicals with therapeutic potential is supported by historical evidence. Moreover, several of its constituents have acted as models or guides for developing new drugs and substances (Barreiro, 2019). Medicinal plants contain a family of secondary metabolites called flavonoids. The pigments that give leaves their colour belong to a vastly diverse class called polyphenolic chemicals, which are commonly found in nature. The phytochemicals of these substances are also crucial for disease and predator resistance, UV radiation defence, and heat tolerance (Mathesius, 2018).

2.4 Kaempferol

There are numerous foods that contains such as broccoli and cabbage. It is also found in propolis, *Ginkgo biloba*, and *Moringa oleifera* (Devi *et al*., 2015). Numerous studies have shown this flavonoid has various pharmacological actions, including antioxidants (Du *et al*., 2018). By preventing neutrophil build-up, lowering MPO activity and the levels of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, and increasing gastric mucus and NO levels, kaempferol (40, 80, and 160 mg/kg, p.o.) and the placebo omeprazole (20 mg/kg) protect against ethanol-induced gastric ulcers in mice (Li et al., 2018). Moreover, kaempferol suppresses *H. pylori* growth *in vitro* at a minimum inhibitory concentration (MIC) of 0.05 mmol/L. This function lowers TNF-α levels, which in turn lessens the inflammatory response that this bacterium induces. It involves the production of the genes for cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (Vac A) (Yeon *et al*. 2019).

2.5 Quercetin

According to David, Arulmoli and Parasuraman, (2016) demonstrates antiviral, vasodilatory, anti-hypertensive activities when consumed. Numerous researches have examined quercetin's possible in vivo gastroprotective benefits (Suzuki, Ishihara and Segami, 1998; Coskun *et al*., 2004). The gastroprotective properties of 2.5 mg of nano-quercetin in a rat model in a rat model of ulceration caused by ethanol. Based on the available data, it appears that there is a block to oxidative damage, the synthesis and expression of matrix metalloproteinase 9 (MMP-9) and the invasion of inflammatory cells. Quercetin also regulates the activity of nitric oxide synthase, COX, and apoptosis, among other processes (Chakraborty *et al*., 2012). Research has examined the application of conventional drug mixes containing certain chemicals with demonstrated gastroprotective effects to boost their effectiveness. As examples of these combinations, consider quercetin in conjunction with pantoprazole and famotidine (Abourehab *et al*., 2017).

3. Results and Discussion

3.1 Alkaloids' Effect on Peptic Ulcer

Alkaloids and other compounds derived from plants that may have therapeutic value were examined as part of the continuous search for natural plant products with bioactivity. Alkaloids perform various biological functions and serve as therapeutic agents in medicine.

3.2 Rutaecarpine

The interplay between both haemorrhagic and non-haemorrhagic lesions in the stomach mucosa is suggested by the fact that this increases the ulcer index and promotes H^+ back diffusion into the mucosa (Wang *et al*., 2005). Stress stimulates the sympathetic and parasympathetic nervous systems (SNS and PNS). Sympathetic activation reduces blood flow to the mucosa, causing local hypoxia and ischemia, and also increases levels of ROS, lipid peroxidation, and glutathione depletion. Higher SNP stimulation results in impaired motility of gastrointestinal muscle contractions and increased acid secretion due to mucosal ischemia (Ramsay and Carr, 2011; Morsy *et al*., 2012). Most capsaicin-sensitive sensory neurons in the gastrointestinal tract contain the neuropeptide calcitonin gene-related peptide (CGRP). The synthesis of CGRP, a neurotransmitter that may mediate the gastroprotective function of these neurons. Increased mucosal blood flow, reduced stomach acid output, protection against apoptosis, and reduction of oxidative damage are some of the positive effects of CGRP (Luo *et al*., 2013).

3.3 Phenylquinoline

Galipea longiflora bark contains an alkaloid called 2-phenylquinoline, which Zanatta et al. (2009) and Campos-Buzzi *et al*. (2010) have isolated. Zanatta *et al*. (2009) assessed the gastroprotective qualities of 2-phenylquinoline extracted from *G. longiflora* bark. They started with the whole alkaloids fraction, eluted it with ethyl acetate to yield 2-phenylquinoline, and then chromatographed it on a silica gel column. By adopting the HCl/ethanol-induced ulcer model in pharmacological research, 50 mg/kg of 2-phenylquinoline was found to be effective against ulcers. According to this hypothesis, ethanol breaks down the mucus-bicarbonate-phospholipid layer, which causes H^+ ions to be released. This process activates mast cells and damages epithelial cells, which attracts neutrophils that produce reactive oxygen species, exacerbating cellular damage and inducing tissue necrosis.

3.4 Rohitukine

Rohitukine is another term for it. The chromane alkaloid is found in the plants *Amoora rohituka* and *Dysoxylum binectariferum*, both of which belong to the Meliaceae family (Naik *et al*., 1988; Yang *et al*., 2004). According to Naik *et al*. (1988) and Singh *et al*. (2012), this alkaloid effects anti-inflammatory, immunomodulatory, and gastroprotective qualities. In the pylorus ligature ulcer model, researchers examined rohitukine at 20 mg/kg to assess mucin levels, peptic activity, and gastric juice. To assess rohitukine's anti-ulcer qualities, they also tested it at 10 mg/kg in an ulcer model caused by ethanol. Additionally, they measured intracellular calcium ions, gastrin levels, and H^+/K^+ ATPase activity, investigating the latter two in vitro (Singh *et al*., 2012).

In relation to the control group, rohitukine decreased the ulcerative lesion index in the ulcer models generated by stress and ethanol. Furthermore, by raising the levels of prostaglandin E_2 (PGE_2) and mucin, rohitukine improved the protective mechanisms of the gastric mucosa (Singh *et al*., 2012). Parietal cells produce gastric secretion (Ramsay and Carr, 2011), which helps transform pepsinogen into pepsin, an enzyme necessary for protein breakdown. It also promotes the absorption of iron and vitamin B_{12} and inhibits the growth of germs and potential infections (Schubert, 2009).

Some Selected Nigerian Plants in the Treatment of PUD

Figure 3: *Zingiber officinale* (Khanpara and Mavani, 2022).

Zingiber officinale is a common ingredient both as a spice in Indian food and in conventional medicine. Researchers have discovered that volatile oils, comprising 1-4% of ginger's proximate chemical makeup, contribute to its medicinal properties (Yoshikawa, Yamaguchi and Kunim, 1994). Gingerol and zingerone make up most of the phenols in solvent-extracted ginger. It was observed that phenolic acids significantly suppress the ulcer. *H. pylor*i, inhibit H^+ K^+-ATPase in parietal cells, and demonstrate antioxidative properties *in vitro* (Siddaraju and Dharmesh, 2007). *Zingiber officinale* Roscoe, a naturally occurring dietary rhizome in the Zingiberaceae family, possesses various biological qualities and actions. Compounds such as gingerols, shogaols, paradols, and zingerones are believed to be responsible for its therapeutic properties. Gingerols exhibit antibacterial activity against *H. pylori*, causative bacteria causing PUD and dyspepsia. Ginger has proven effective against peptic ulcer diseases (Mahady *et al*., 2005). One of the key active chemicals in ginger is called shogaol (Roli *et al*., 2020). The benefits of ginger extract have been investigated in studies on ulcer prevention in ethanol- and stress-induced ulcer model in mice. Ginger extract has anti-inflammatory and free radical-scavenging qualities that help treat and prevent ulcers and *H. pylori* infection (Nanjundaiah *et al*., 2011).

Moringa oleifera

Figure 4: *Moringa oleifera* leaves (Chaudhary *et al*., 2022).

In a pylorus ligation experiment, the antiulcer activity of *M. oleifera* seed extracts were examined at oral doses of 150 and 200 mg/kg and contrasted with that of the reference drug, omeprazole (20 mg/kg). The results demonstrated a significant ($P^{\wedge}$ 0.05) decrease in the ulcer index, as evidenced by a decrease in stomach volume and a drop in free and total acidity comparable to the norm (Kansara and Singhal, 2013).

Allium sativum

Figure 5: *Allium sativum* (Khanpara and Mavani, 2022).

Garlic (*Allium sativum*, family: Amaryllidaceae) has been employed medicinally and as a spice since ancient times to treat different number of ailments such as such as stomach discomfort, asthma and hypertension (Sadacharam *et al*., 2013). Keiss *et al*. (2003) suggest that Garlic Powder Extract's (GPE) anti-ulcer activities result from its ability to regulate pro-inflammatory cytokine levels, including interleukins and tumour necrosis factor-alpha. Mice in the treatment group had a lower ulcer score than animals in the control group after pretreatment with an *A. sativum* methanolic extract, suggesting it anti-ulcer potential. Because they can lessen stomach perforations in male Wistar rats administered with indomethacin, *Allium sativum*, *Brassica oleracea*, and *Aloe barbadensis* have potential application in the treatment of ulcers (Adeniyi *et al*., 2006; Tope *et al*., 2014; Akinbo and Eze, 2016).

Curcuma longa

Figure 6: Pictures of the botanical sources of turmeric (Basnet and Skalko-Basnet, 2011).

Curcumin, the primary naturally occurring polyphenol in the rhizome of *Curcuma longa*, a member of the Zingiberaceae family used in the different of several ailments. Researchers have used various animal models, including those induced by indomethacin and reserpine examining curcumin's anti-ulcer properties in several preclinical investigations. The extract formulation offers significant protection against chemicals that cause cyst destructive changes. The gastro protective effects in rats are believed to be caused by a noteworthy rise in stomach wall mucus, as well as the restoration of GSH levels and non-protein sulfhydryl content (Akbik *et al*., 2014). Turmeric's anti-inflammatory effects are thought to arise from suppressing the COX enzyme and reducing inflammatory mediator levels (Koosirirat *et al*., 2010; Hosseini and Hosseinzadeh, 2018).

Ocimum tenuiflorum

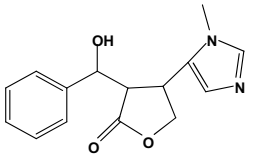
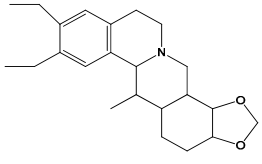
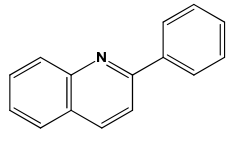
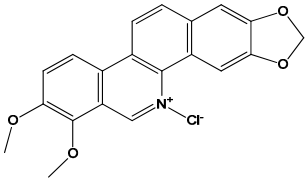
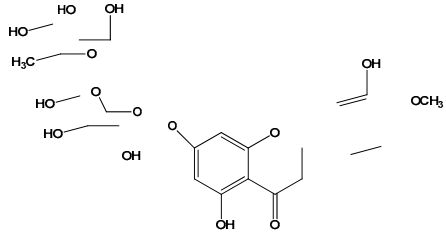
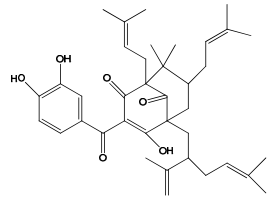
Figure 7: *Ocimum tenuiflorum* (Almatroodi *et al*., 2020).

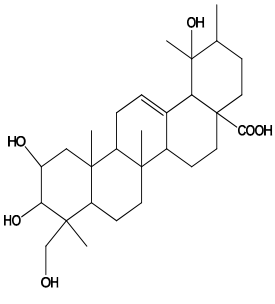
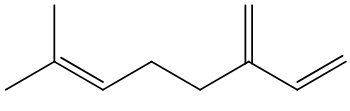
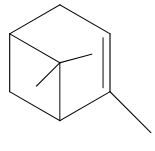
Ocimum tenuiflorum, a fragrant shrub in the Lamiaceae family of basil plants, is used medicinally to treat various conditions, including inflammation, rheumatism, cancer, bronchitis, and helminthiasis. Researchers have evaluated Tulsi in several preclinical studies for its anti-ulcerogenic properties, which are believed to result from the presence of eugenol (Dharmani *et al*., 2004).

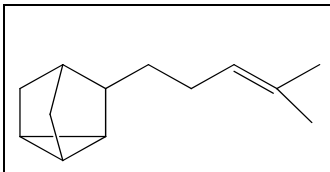
Carica papaya

Figure 7: *Carica papaya* (Khanpara and Mavani, 2022).

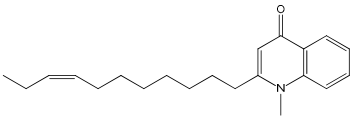
Carica papaya, an herbaceous succulent plant in the Caricaceae family, is indigenous to tropical and subtropical regions across the globe. Papaya is used to cure a variety of illnesses because of its potent antibacterial and numerous properties (Vij and Prashar, 2015; Anjana *et al*., 2018). Papaya contains a variety of bioactive substances, including b-carotene, xylitol, caffeic acid and lycopene (Yogiraj *et al*., 2014). Researchers evaluated the anti-ulcerogenic efficacy of *C. papaya* methanolic extracts using a range of ulcer models, including pyloric ligation. Through a marked reduction in stomach acidity as well as an increase in mucus production and GSH levels, they were able to demonstrate the gastroprotective benefits of the aqueous and methanolic extracts (Pinto *et al*., 2015). Furthermore, they observed no toxicological symptoms following extract therapy (Ezike *et al*., 2009). In another investigation, researchers used rats with ethanol-induced ulcers to test the anti-ulcer effects of *C. papaya* seed aqueous extract. In contrast to the group under control, they observed that the treatment groups had noteworthy decreases in acidity, total stomach volume, and ulcer index. This suggests that *C. papaya* seed aqueous extract could be a potentially effective medicinal substance for the course of treatment of ulcers (Okewumi and Oyeyemi, 2012).

 Epiisopiloturine	 Cavidine	 2-Phenylquinoline
 Chelerythrine	 Hesperidin	 Garcinol

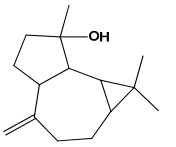
 23-Hydroxytormentic acid 28-*O*-glucoside	 β-Myrcene	 α-Pinene



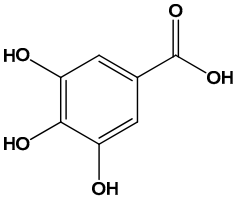
α-Santalene



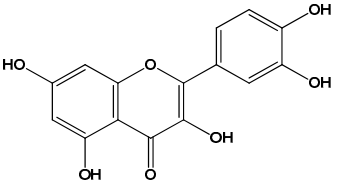
1-methyl-2-[(*Z*)-8tridecenyl]-4-(1H)quinolone



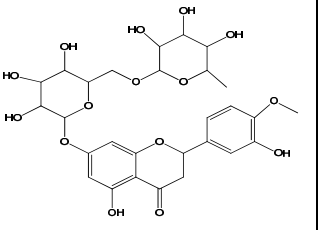
Spathulenol



Gallic acid



Quercetin



Hesperidin

Figure 8: The structural analysis of certain phytochemicals as potential antiulcer agents (Sharifi-Ras *et al*., 2018)

4. CONCLUSION

It is clear that a large number of plant species have been recognized, assessed, and formally acknowledged by science for their gastro-protective as well as anti-ulcer qualities in suitable animal models. The search is now on for substitutes in medicinal plants, which are utilized extensively in traditional medical systems and offer a possible source of anti-ulcerogenic medications due to the important functions that their phytonutrients play. In the end, this will present stimulating, lucrative, and globally competitive chances for the development of novel lead medications for PUD and other associated illnesses.

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