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Herbal Essential Oil use as Ulcer Protective Activity: A Systematic Review

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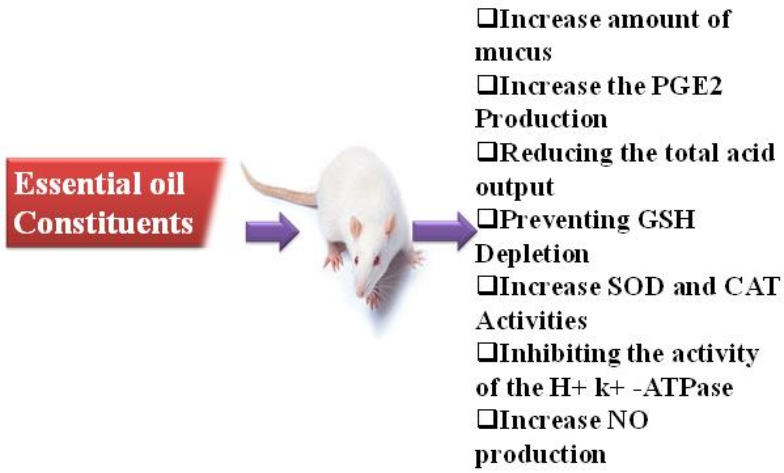
GRAPHICAL ABSTRACT



ABSTRACT

Around the course of the past few decades, essential oils have been an increasingly prominent subject of research all over the world. These naturally occurring chemicals may find applications in a wide variety of medical and biotechnological fields. In light of the urgent need to find new anti-ulcer agents and the significant amount of effort that has been put into developing medications for the treatment of ulcers, the purpose of this review is to investigate the anti-ulcer activities of fifteen different bioactive compounds that can be found in essential oils.

***Keywords*- Essential oil, Ulcer, Gastroprotective, Alkaloid-flavnoid and tannins based compounds**.

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I. INTRODUCTION

The great incidence of peptic ulcer in the global population has made it the focus of experimental and clinical investigations [1]. Peptic ulcer is a public health problem with a high rate of morbidity and substantial mortality. Having an unbalanced ratio of destructive to defensive elements in the stomach is a common contributor to peptic ulcers [2].

Exogenous factors include excessive ethanol consumption, indiscriminate use of nonsteroidal anti-inflammatory drugs (NSAIDs), stress, smoking, and infection by Helicobacter pylori bacteria [3-6]. Endogenous factors include HCl, pepsin, biliary reflux, lipid peroxidation, and the formation of reactive oxygen species (ROS). The mucus-bicarbonate barrier, mucin secretion, surface phospholipids, prostaglandins (PGs), nitric oxide (NO), blood flow in the mucosa, cellular renewal, growth factors, and antioxidant enzymes all play a role in defence [2, 4, 5].

Oxidative stress is a component of the process that leads to gastric ulceration. This stress stimulates the generation of reactive oxygen species (ROS), which can affect the integrity of epithelial cells. It is possible for the body's natural antioxidant defences to be depleted if there is an oversupply of reactive oxygen species (ROS) metabolites [7]. In addition, when there is an ulcer in the stomach, there is a collection of neutrophils in the mucosa tissues because of ROS. There is evidence to suggest that neutrophils are activated by proinflammatory cytokines, which plays a key role in ulcer damage [8, 9].

Peptic ulcers can be effectively treated with alternatives that regulate acidic hypersecretion and the impact that acidic hypersecretion has directly on the stomach mucosa. Histamine type 2 receptor antagonists, often known as H2RAs, are able to inhibit hydrogen ion discharge by blocking the histamine receptor found on parietal cells [10]. In the parietal cell, the hydrogen pump can be stopped directly by proton pump inhibitors, also known as PPI. This occurs regardless of any membrane receptor stimulation. The proton pump inhibitor (PPI) has been related to a potentially hazardous side effect known as parietal cell hyperplasia of the gastric glands [11], despite the fact that it is widely used. Long-term usage of H2RA has been associated to a number of negative side effects, including gynecomastia, galactorrhea, and alterations to the composition of the microbiota in the gut [12].

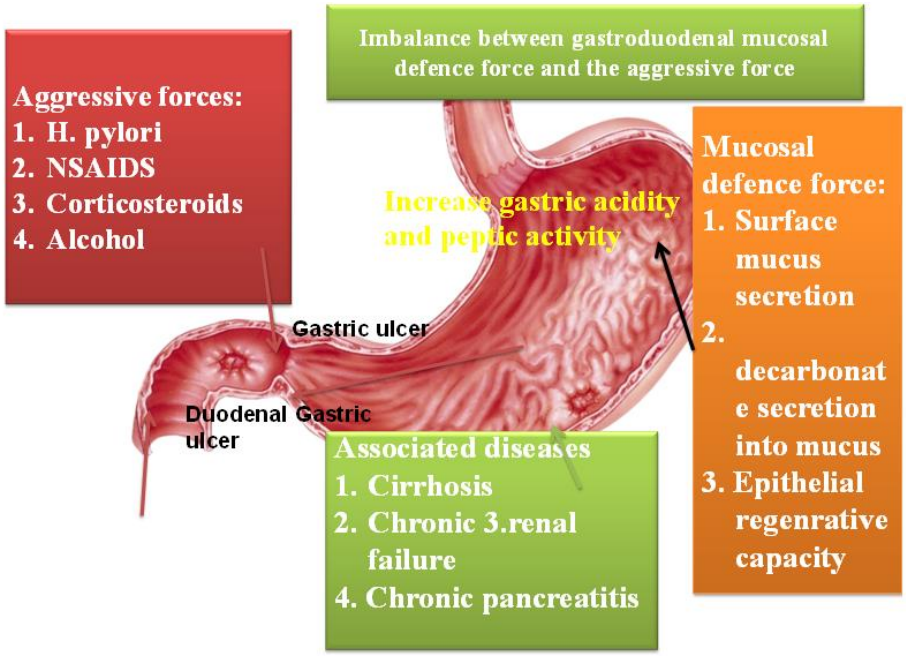

Fig. 1: Disease Reference of Ulcer

Due to the high prevalence of peptic ulcer disease among people all over the world, [1] researchers have focused a lot of their attention on this medical condition. A high rate of morbidity and a significant death rate are both associated with peptic ulcer disease, which is a public health concern. [2] One of the major risk factors for developing peptic ulcers is having an imbalanced ratio of elements that are destructive to those that are defensive in the stomach.

Exogenous causes include an excessive consumption of liquor, an inappropriate use of nonsteroidal anti-inflammatory medicines (NSAIDs), stress, smoking, and an infection by the bacteria Helicobacter pylori [3-6]. Pepsin, hydrochloric acid, biliary reflux, lipid peroxidation, and the generation of reactive oxygen species are all examples of endogenous factors (ROS). Defense mechanisms include the mucus-bicarbonate barrier, the secretion of mucin, surface

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phospholipids, prostaglandins (PGs), nitric oxide (NO), blood flow in the mucosa, cellular renewal, growth factors, and antioxidant enzymes [2, 4, 5]. Blood flow in the mucosa is also essential to the defence mechanism.

Oxidative stress is a component of the process that leads to gastric ulceration. This stress stimulates the generation of reactive oxygen species (ROS), which can affect the integrity of epithelial cells. It is possible for the body's natural antioxidant defences to be depleted if there is an oversupply of reactive oxygen species (ROS) metabolites [7]. In addition, when there is an ulcer in the stomach, there is a collection of neutrophils in the mucosa tissues because of ROS. There is evidence to suggest that neutrophils are activated by proinflammatory cytokines, which plays a key role in ulcer damage [8, 9].

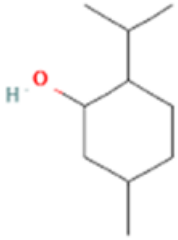
Peptic ulcers can be effectively treated with alternatives that limit acidic hypersecretion and its direct effects on the stomach mucosa. Histamine type 2 receptor antagonists (H2RAs) block the histamine receptor on parietal cells, resulting in a decrease in the production of hydrogen ions [10]. In the parietal cell, the hydrogen pump can be stopped directly by proton pump inhibitors, also known as PPI. This occurs regardless of any membrane receptor stimulation. The proton pump inhibitor (PPI) has been related to a potentially hazardous side effect known as parietal cell hyperplasia of the gastric glands [11], despite the fact that it is widely used. Long-term usage of H2RA has been associated to a number of negative side effects, including gynecomastia, galactorrhea, and alterations to the composition of the microbiota in the gut [12]. Herbal therapy is still used as primary health care by anywhere between 75% and 80% of the world's population today, especially in less developed countries [12]. This is primarily due to the fact that herbal therapy enjoys greater cultural acceptance, is more compatible with the human body, and has fewer negative side effects. Histological examination has provided evidence that particular medicinal plants are free of the acute toxicity that can be caused by other organisms. The early photochemical screening of this medicinal plant revealed the presence of secondary metabolites such as flavonoids and tannins, which are the active components responsible for the antiulcer effect [13].

The objective of the current research was twofold: first, to review the existing ayurvedic literature in search of a synopsis of medicinal plants that are thought to be gastroprotective and healing agents on ulcers; and second, to gather evidence supporting the effectiveness of these medicinal plants and the biological mechanisms by which they work.[14]

In order to achieve this goal, we searched the Indian ayurvedic book Meteria Medica as well as several online databases (including science direct, pubmed, scopus, and google scholar) for articles on each medicinal plant for peptic ulcers. We then analysed the results for in vitro, in vivo, and clinical evidence of their efficacy as well as possible mechanisms. The research that was collected demonstrates that these herbs are effective in the treatment of peptic ulcers by altering the systems that are affected, whether directly or indirectly.[15]

There are a variety of antiulcer drugs that are detailed in the Meteria Medica. Many of these substances have been tested in clinical trials, and many have been shown to be successful in treating ulcers. Reports and research have been consulted in order to compile information regarding the antiulcer qualities of the medicinal plants listed below. [16-18]

2.1. Menthol



Essential oils of the mint species Mentha canadensis L (American wild mint) and Mentha x piperita L (peppermint) contain the cyclic monoterpene alcohol menthol [5-methyl-2-(1-methylethyl)cyclohexanol, 2-isopropyl-5-methylcyclohexanol, or p-methan-3-ol]. Menthol is an analgesic and anti-inflammatory agent [19]. Studies conducted both in vitro and in vivo have shown that menthol has a safe profile and that it poses a small risk of harm to humans [20]. These studies validated menthol's safety profile. Recently, Rozza and colleagues [18] demonstrated that a high dose of menthol (50 mg/kg) delivered orally created a considerable protective impact on the stomach mucosa. This impact was observed to be 88% protective against ethanol and 72% protective against indomethacin. In addition, the protective mechanism seems to involve an increase in mucus formation as well as the production of PGE2 through the participation of SH compounds and the stimulation of K+ATP channels. However, this does not appear to occur through the activation of calcium ion channels or the production of nitric oxide. The oral administration of menthol to rats that had their pylori ligated for four hours resulted in a significant reduction in the volume of total acid output; however, there was no effect on the volume. When administered intra-duodenally, menthol decreases the volume of gastric juice without changing the amount of H+ present in the juice. The results of this study demonstrated that oral administration of menthol at a dose of 500 mg/kg for a period of 14 days did not result in any adverse effects.[20]

In recent years, there has been a lot of interest in the area of choosing between alternative promoieties of ibuprofen in order to develop prodrugs that lower gastrointestinal (GI) toxicity [21,22]. This is a field that

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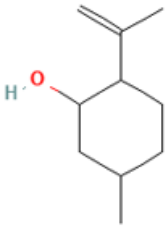
has a long history. It has been demonstrated that the use of ester derivatives of ibuprofen as mutual prodrugs with promoieties like menthol (IME), thymol (ITE), and eugenol can improve the therapeutic efficacy of racemic ibuprofen (150 mg/kg, p.o.) by reducing the adverse effects that are experienced by the gastrointestinal tract [23]. (IEE). It is possible that the improved anti-inflammatory activity seen is the result of a synergistic action caused by the conjugation of ibuprofen to natural molecules. In addition, as evaluated by the ulcer index, there is a considerable improvement in gastrointestinal ulcers in comparison to ibuprofen (2.41 0.27; 0.91 0.15 (IME); 0.83 0.17 (ITE); 1.08 0.15 (IEE)).[23][24] In conclusion, the results of the trials showed that the prodrug technique is an effective means of attaining the goal of reduced gastrointestinal toxicity while still keeping the intended anti-inflammatory benefits. [25]

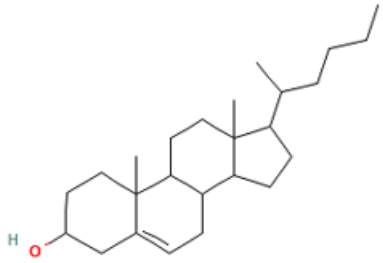
2.2. Isopulegol



When the protective and destructive forces that are typically operating on the mucosa of the stomach become unbalanced, this can lead to the development of peptic ulcers, which are benign lesions of the stomach or the mucosa of the duodenum. [26][27] [28] This disorder can be identified by the breakdown of the gastric epithelial lining into the muscularis propria layer. Peptic ulcers can develop from a variety of different causes. In the vast majority of instances that have been recorded, there is a significant relationship between the infection caused by H. pylori and the irresponsible use of nonsteroidal anti-inflammatory drugs (NSAIDs) (NSAIDs). Peptic ulcers can currently be treated with a variety of medications, including bismuth quadruple treatment, prostaglandin analogues, proton pump inhibitors (PPIs), a triple antibiotic plus PPI regimen, and mucosal cytoprotective drugs [29].

Several studies have demonstrated that the use of natural components in a product can result in favourable effects on the digestive system. Recent research on animals has revealed that the antiulcer properties of isopulegol are effective against ethanol-induced stomach ulceration. Isopulegol, when given before to exposure to ethanol, had a dose-dependent cytoprotective effect and reduced the damage that the alcoholic beverage generated to the stomach. This effect was minimised by the use of isopulegol.[30] The ability of isopulegol to serve as an antioxidant was established by the fact that it was able to restore GSH levels in tissues of the stomach that had been depleted.[31,32,33] KATP channels are responsible for controlling a number of the physiological processes that occur in the digestive system. Particularly, channel openers have a curative effect in peptic ulcer disease and are therefore an important therapeutic target. They swiftly improve epithelial integrity and continuity and begin mucosal healing in the early stages of the condition. A decrease in gastric mucosal prostaglandin levels, which is a role in the activation of KATP channels, was observed after pretreatment with isopulegol. Isopulegol's gastroprotective effects against ethanol and indomethacin-induced stomach ulcers are mediated via control of endogenous prostaglandins levels, opening of the KATP channel, and antioxidant properties of the compound. [34,35,36]

2.3. Nymphayol



The ailment known as stomach ulcer disease affects a significant number of people all over the world. An ethanol-induced ulcer model was used to assess whether or not nymphayol (NYM), a chemical isolated from Nymphaea stellata, could suppress the formation of ulcers in rats. [37] [38] The goal of this study was to establish whether or not NYM could do this. After ethanol administration, there is an increase in the ulcer index (UI), as well as a significant rise in the levels of lipid peroxidation and myeloperoxidase (MPO). On the other hand, there is a significant decrease in the levels of gastric mucus, catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), and prostaglandin E2 ((PGE2). Antioxidant, gastrointestinal mucus, and PGE2 levels all considerably increased in rats that were pretreated with NYM (45 mg/kg),[39][40] while UI, lipid peroxidation, and MPO levels all significantly decreased. In ethanol-induced ulcerated animals, the levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1 (IL-1), tumour necrosis factor- (TNF-), and interferon- (IFN-) were increased, whereas the levels of anti-inflammatory cytokines such as interleukin-10 (IL-10) were decreased; however, NYM pretreatment corrected these imbalances. [41] [47] When compared to the group that had an ulcer caused by ethanol, the group that had been pretreated with NYM had much lower levels of pro-apoptotic markers, such as caspase-8, caspase-9, and caspase-3, and significantly higher levels of anti-apoptotic markers, such as Bcl-2. The ulcer protective activity of NYM (45 mg/kg) was substantially attenuated by pretreatment with indomethacin, SC560, rofecoxib, and N-nitro-L-arginine methyl ester (L-NAME). [48][49] These results

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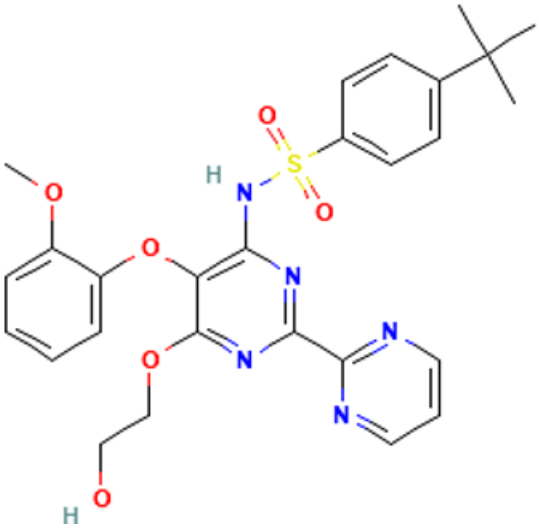
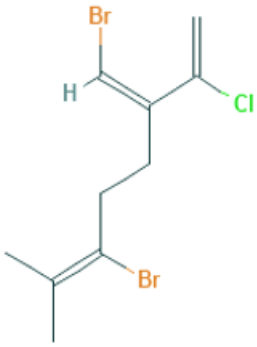
indicate the involvement of cyclooxygenase (COX) and nitric oxide synthase (NOS) in NYM-mediated gastroprotection against ethanol-induced ulcer. According to these findings, the gastroprotective activity of NYM may be mediated by the modification of inflammatory mediators and apoptotic indicators, as well as the elevation of antioxidants. [50][51]

2.4. BST-104



In murine models of gastritis and peptic ulcer, the gastroprotective qualities of BST-104, which is a water extract of Lonicera japonica, as well as the processes that are involved, were investigated.[52] In order to evaluate the gastroprotective capabilities of BST-104 and the active components that make it up in rats, gastric ulcer models including acetic acid and hydrochloric acid were used. After BST-104, chlorogenic acid, rebamipide (the positive control), or vehicle was orally supplied in each animal model, the severity of gastric lesions, the presence or absence of gastric mucus, the levels of proinflammatory cytokines, and the presence of oxidative stress were all examined. [53] The levels of the antioxidant enzymes superoxide dismutase (SOD), catalase, and malondialdehyde (MDA), as well as the ratio of oxidised glutathione (GSH) to reduced glutathione, were measured in order to determine the amount of oxidative stress in the gastric mucosal tissue (GSH).[54] In order to gain a deeper comprehension of the mechanism by which BST-104 exerts its effects, we investigated, by means of real-time polymerase chain reaction, whether or not the nuclear factor (NF)-B pathway is involved (PCR). After oral administration of BST-104 at doses of 50, 100, or 200 mg/kg, stomach lesions in an acetic acid-induced ulcer model were reduced by 38, 43, and 55 percent, respectively, when compared to vehicle control groups.[55] The levels of hexosamine, sialic acid, and prostaglandin E2 all increased along with the substantial increase in the amount of mucus produced in the stomach as a result of the administration of BST-104. In addition, after receiving BST-104 treatment, levels of catalase, SOD, oxidized/reduced GSH, and malondialdehyde (MDA) were all increased. Furthermore, real-time PCR indicated that BST-104 significantly prevented rises in proinflammatory cytokines and that it significantly downregulated the production of NF-B. Both of these effects were confirmed by BST-104 (tumour necrosis factor-, interleukin [IL]-6, and IL-1). [56] To summarise, it was discovered that the anti-oxidant and anti-inflammatory properties of BST-104 and its active component, chlorogenic acid, had gastroprotective effects through the downregulation of NF-B expression.

2.5. Monoterpenes



Eliminating the H. pylori infection that is the root cause of stomach ulcers is a frequent approach to treating these sores. The antibacterial effects that certain monoterpenes had in vitro against H. pylori were similar to the anti-ulcerogenic and gastroprotective qualities that they possessed. The bactericidal effects of monoterpenes can be traced back to their capacity to break the lipid membrane of bacteria, which ultimately leads to an increase in cell permeability and an inhibition of microbial metabolism. It seems that the antibacterial effect of the molecule is related to a hydroxyl group that is present in the structure of the drug. There is a correlation between the number of hydroxyl groups and the level of biological activity [57]. 92% of H. pylori growth was stopped by geraniol at a concentration of 2 mg/L, while the minimum inhibitory concentration (MIC) for carvacrol was 40 mg/L [58]. [59] The minimal inhibitory concentration (MIC) for limonene was determined to be 75 g/mL, while the MIC for -myrcene was found to be 500 g/mL. It was determined that the MIC50 value for safranal was 32 g/mL [60]. Citronellol was shown to be microbicidal against H. pylori infections in both in vitro and in vivo studies [61]. It was discovered by Bergonzeli and colleagues (2002) that the two isomers eugenol and isoeugenol differed in the position of the double bond in the aliphatic chain. This finding lends credence to the hypothesis that a particular conformation of the molecule is required for the molecule to be able to pass through the H. pylori membrane. Isoeugenol shown superior activity against H. pylori when compared to eugenol. Nevertheless, in

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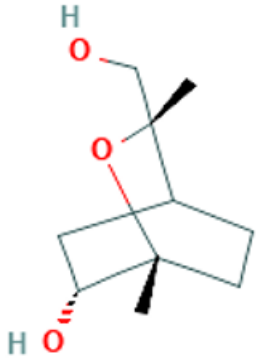
contrast to thymol [62], a number of monoterpenes do not have an anti-H. pylori activity (in vitro), despite the fact that they have remarkable healing and gastroprotective benefits.

2.6. 1,8-Cineole



Excipient in the pharmaceutical and cosmetics industries [62], mainly in nasal sprays and as a disinfectant; [63] flavouring agent in food According to the findings of a number of investigations, 1,8-cineole has been proven to have a wide variety of biological effects, including an activity that is gastroprotective. [64]

We showed that pretreatment with CIN protected the stomach mucosa of rats in both the ethanol and acidified ethanol models. This indicates that the chemical exhibits a potent cytoprotective action by preventing the development of ulcerative lesions. In all of these models, we used ethanol. CIN dramatically decreased mucosal damage in the indomethacin-induced gastric ulcer, a model using NSAID, at all of the doses that were examined in order to further demonstrate its gastroprotective characteristics and to hint at the potential involvement of prostaglandins and/or mucus formation in antiulcer activity. This finding suggests that prostaglandins and/or mucus formation may play a role in antiulcer activity. In their article [65], Santos and Rao address some previous data that is consistent with these findings.

Several studies have established a connection between the development of gastric ulcers and the emptying and motility of the stomach; however, the data from these studies are inconsistent [66]. An investigation into the effects of CIN on gastrointestinal motility found that higher dosages of the drug taken by mouth slowed the emptying of the stomach but had no impact on the movement of food through the intestines. Even the smallest dose caused an increase in the amount of dye that was found in the stomachs of the rats, which is evidence that these animals were more likely to undergo intestinal transit. According to the findings of Magalhes and colleagues [67], administering rats 1,8-cineole intravenously slowed down both the rate at which their stomachs emptied and the rate at which fluids passed through their intestines.

We examined 1,8-cineole's gastroprotective effect by investigating the function of mucosal protection factors such as antisecretory activity, nitric oxide, and sulfhydryl groups. This was done since 1,8-cineole demonstrated antiulcer activity in the mice described above. The purpose of this research was to establish whether or not 1,8-cineole had an effect on the volume, pH, and total acidity of gastric secretion when the stomach was at rest and after it had been stimulated with agonists (secretagogues) of histamine (H2), acetylcholine (M3), and gastrin receptors (CCK2). In contrast to what Santos and Rao [69] observed, the data reveal that CIN caused a drop in the volume of baseline acid secretion without causing a reduction in the amount of overall acidity. [70] In addition, there were no alterations seen in the parameters for the gastric acid secretion that was triggered by histamine, pentagastrin, or bethanechol, which suggests that the antisecretory action may not have been present. [71]

Nitric oxide (NO) and other non-protein sulfhydryl groups are two of the stomach defence mediators that have received the greatest attention from researchers (-SH groups). Nitric oxide increases the amount of blood that flows to the stomach mucosa, controls the generation of mucus, and stops neutrophils from sticking to endothelial cells [70]. Non-protein sulfhydryl groups, also known as -SH groups, are directly linked to the preservation of gastric mucosa integrity [71]. This is due to the fact that they limit the formation of free radicals and assist the synthesis and preservation of mucus units. When the gastroprotective effects of 1,8-cineole (100 mg/kg) were examined in rats that had been pretreated with L-NAME, an inhibitor of NO-synthase, there was shown to be no dependence on NO for these effects. It would appear that the protective function of 1,8-cineole is dependent on the existence or synthesis of sulfhydryl groups. This is supported by the fact that the gastroprotective impact of CIN was diminished in rats that had been pretreated with NEM, an inhibitor of sulfhydryl groups. [72]

Important cytoprotective factors in the stomach include mucus, prostaglandins, a sufficient amount of blood flow to the mucosa, nitric oxide, and sulfhydryl compounds. Agents such as ethanol, which contributes to the production of lesions in the stomach mucosa, can help reduce these defence systems, which in turn makes it easier for them to be suppressed [73]. In addition to the mechanisms described above, the administration of ethanol is associated with an increase in lipid peroxidation, a decrease in non-protein sulfhydryl groups (-SH groups), which results in an increase in the species reactive oxygen (ROS), and the destruction of epithelial cells in the stomach, which ultimately results in the infiltration of inflammatory cells and the production of hemorrhagic lesions [73]. In stomachs that had been damaged by ethanol, researchers found that the production of mucus and the levels of non-protein sulfhydryl groups (-SH groups) had decreased. On the

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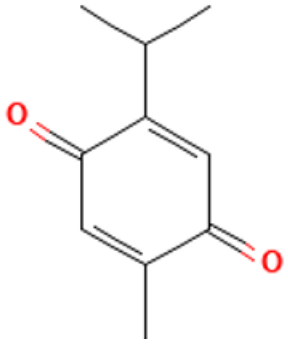
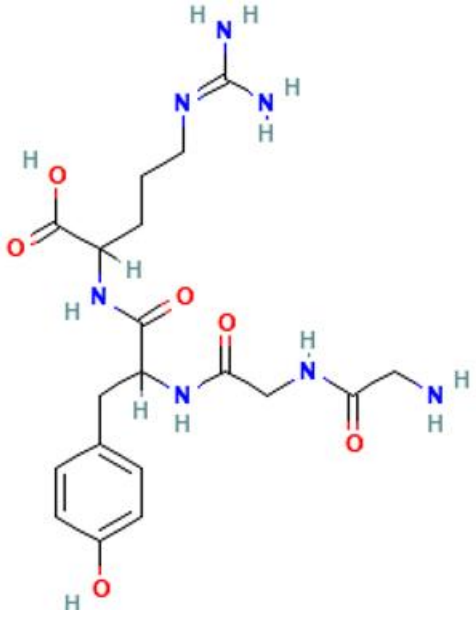
other hand, the levels of malondialdehyde (MDA) and myeloperoxidase activity (MPO) had increased when compared to levels found in animals that had not been injured. The gastroprotective action that was seen in the past and the involvement of these groups in this effect were explained by our discoveries that 1,8-cineole (100 mg/kg) significantly increased the amount of mucus adhering to the gastric mucosa and in the basal levels of-SH groups in animals that were treated with the compound. These findings were based on the observation that 1,8-cineole significantly increased the amount of mucus adhering to the gastric mucosa. It appears that pretreatment with 1,8-cineole prevented lipid peroxidation as well, as seen by the decreased levels of malondialdehyde found in injured stomach mucosa. Peptic ulcers have been associated to higher levels of the enzyme myeloperoxidase (MPO), which is a marker for neutrophil infiltration into inflamed tissue, in a number of studies [74, 75]. This association has been made in a number of different ways. Santos et al. [76] conducted research on male Wistar rats that had been induced with acute colitis to investigate the efficacy of 1,8-cineole as both an anti-inflammatory agent and a potential prophylactic treatment for gastrointestinal ulcers. They found that a dosage of 1,8-cineole containing 400 milligrammes per kilogramme was effective to reduce MPO activity and bring glutathione levels back to normal in the tissues of the colon. There was a significant decrease in myeloperoxidase activity after treatment with 1,8-cineole at a dose of 100 mg/kg, which is four times the lower dose. This protected the stomach mucosa by stopping neutrophil infiltration. These findings, when taken together, suggest that the antioxidation mechanism of CIN may be a possible component to the gastroprotective activity of CIN.

2.7. Thymoquinone



It has been demonstrated that thymoquinone (TQ), the major component of Nigella sativa oil, has a gastroprotective effect; nevertheless, the whole molecular influence on the etiopathogenesis of stomach ulcers is not yet fully known.[77] The current work is attempting to elucidate some of the possible mechanisms so as to better understand the situation. TQ at doses of 10 and 20 mg/kg, omeprazole at doses of 10 and 20 mg/kg, and both drugs together at a dose of 10 mg/kg were were given to the animals. Following an initial 30 minutes of ischemia, the pyloric ligation procedure was carried out. Following an additional 30 minutes of ischemia, the stomach was allowed to recover for an additional 120 minutes before being re-perfused. Ischemia and reperfusion injury induced increases in stomach acid secretion, acid output, and pepsin, as well as lipid peroxide, proton pump, myeloperoxidase, and ulcer index in the gastrointestinal mucosa. These changes occurred as a result of damage to the gastrointestinal mucosa caused by ischemia and reperfusion.[78] The levels of gastric mucin, reduced glutathione, total nitric oxide, and superoxide dismutase all went down, on the other hand. [78] TQ, especially at the high dose level, was able to restore the aberrant parameters to values that were comparable to those that were attained by the reference medicine omeprazole. In addition, the combination of the low dosages produces an effect that is comparable to that produced by a large dose of either medication. These findings demonstrated that in addition to its well-documented capabilities as an antioxidant, TQ also possesses unique gastroprotective mechanisms. These mechanisms include, for example, suppressing the proton pump, acid secretion, and neutrophil infiltration, and boosting the secretion of mucin and nitric oxide. [79]

2.8. Papain



Due to the fact that ulcers are such a common ailment that impact the digestive system, the majority of the population of the world has been afflicted by them at some point. Some of the potential risk factors for this illness include smoking, stress, alcohol, nutritional deficits, nonsteroidal anti-inflammatory drugs (NSAIDs), and infections (Helicobacter pylori). [80] The

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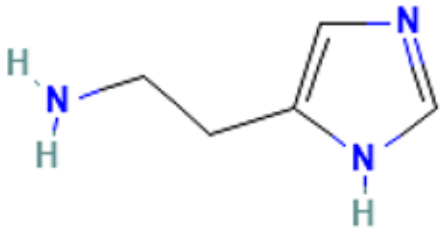
ethanolic extract of papaya leaf was investigated by Odo et al. for its capability of curing stomach ulcers that were artificially produced in rats in the laboratory. The findings demonstrated that in rats with an aspirin-induced stomach ulcer, there was a reduction in both the ulcer index and the volume of gastric juice, while there was an increase in the pH of gastric juice. It was discovered that the aqueous leaf extract of this plant might reduce the stomach ulcer index in an alcohol-induced rat model. In general, PLE shows potential as a therapeutic agent for the treatment of stomach ulcer; nevertheless, more research is needed before definitive conclusions can be drawn.[81]

2.9. Allantoin

Gastric ulcer is a disorder that affects people all over the world, and the high recurrence rate of the ailment is what has prompted researchers to look for treatments that are both effective and long-lasting. Although allantoin has been utilised for years in the medical and cosmetic industries, no studies have been conducted on the effect that it has on gastric ulcers.[82] In light of this, the purpose of the current investigation was to evaluate the pharmaco-mechanistic efficacy of allantoin against common hazardous substances that cause to stomach injuries. Pylorus ligation, measurement of vascular permeability, glutathione (GSH), gastric adhered mucus, prostaglandin (PGE2), pro-inflammatory cytokines, myeloperoxidase (MPO), and catalase (CAT) activities, as well as the utilisation of ethanol-, indomethacin-, and stress-induced gastric ulcer models, were all utilised in this study. Analyses were performed on the gross, histological, and ultrastructural properties of stomach lesions. [83] Treatment with allantoin (orally administered at a dose of 60 mg/kg) was observed to reduce the formation of stomach ulcers in all models. In addition, the indices of stomach acid secretion and MPO activity in the blood vessels were both lowered by allantoin. [84] The levels of pro-inflammatory cytokines fell concurrently with the restoration of CAT activity and GSH reserves. Notably, after the injection of ethanol, the therapy with allantoin maintained levels of gastric-adherent mucus as well as PGE2. [85] Allantoin stopped ethanol from destroying the tissue structure and changing the shape of the cells, according to research conducted at both the microscopic and ultrastructural levels. Last but not least, we demonstrated that allantoin possesses gastroprotective effect through anti-inflammatory, anti-oxidative, anti-secretory, and cytoprotective pathways. To the best of our knowledge, this is the first publication of its kind. A possible connection can be made between an increase in PGE2 levels and the antisecretory and cytoprotective processes.[86]

2.10. Histamine



In Cameroonian traditional medicine, voacanga africana is frequently utilised as a treatment for peptic ulcers. An alkaloid called TN that was isolated from the fruit extract has been the subject of research because of the possibility that it possesses cytoprotective, anti-secretory, and ulcer healing properties. [87] After oral administration of TN at doses ranging from 50 to 100 mg/kg, a dose-dependent protection against ulcer formation was observed. This protection was observed against HCl/ethanol (36–75%), absolute ethanol (43–75%), HCl-ethanol/indomethacin (58–84%), Pylorus ligation (31–100%), cold restraint stress (68–100%), and histamine (49–100%). The inhibitory activity of indomethacin at 50 and 100 mg/kg against HCl/ethanol was unaffected by pretreatment with 20 mg/kg intraperitoneally administered indomethacin. [88] The levels of shay-ligated stomach acid secretion were reduced by TN when administered at doses of 50 and 100 mg/kg, respectively, bringing them down from 77 mEq/l in the controls to 46 and 25 mEq/l. The amount of acid that was released in response to histamine was reduced from 84 mEq/l in the controls to 45 and 21 mEq/l, respectively, when TN was administered at a dose of 50 mg/kg. [89] Additionally, the development of gastric and duodenal ulcers was totally halted by this dose. When the TN dose of 50 mg/kg was compared to the TN dose of 100 mg/kg, the rate of healing of chronic acetic acid-induced ulcers was 62% and 83%, respectively. TN decreases stomach secretion in a manner that is analogous to that of drugs that block histamine receptors. The ability of this compound to increase gastric mucus production and so strengthen the mucosal defences of the stomach is at the root of its cytoprotective and ulcer-healing properties.

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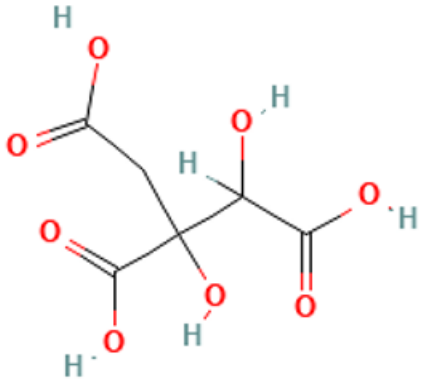
2.11. Hydrocitric acid

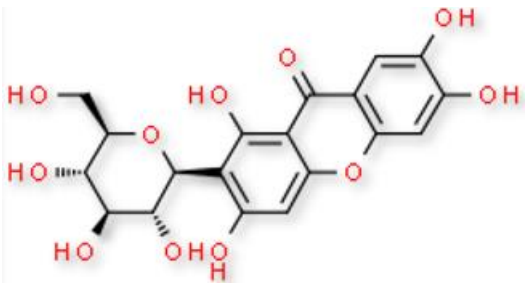


It is widely known that ethanol can cause stomach ulcers by increasing oxidative stress, and that reactive oxygen species (ROS) are a crucial factor in the pathophysiology of this condition [90]. It has been demonstrated in a number of studies that powerful antioxidants and free radical scavengers can reduce oxidative stress, which in turn slows the process of lipid peroxidation [91]. It is believed that the fruit of G. cowa contains chemicals such as phenolics, flavonoid compounds, and ascorbic acid, all of which have the potential to have this effect [92]. According to the findings of this investigation, a pre-treatment with GCE improves cellular antioxidant defence. In line with the findings of previous studies, the current investigation discovered that orally administering ethanol to rats dramatically raised the level of MDA found in their stomachs. MDA can be used as a biomarker to determine the extent of lipid peroxidation in tissue [93]. Antioxidant activities were demonstrated by a decrease in the MDA level following pretreatment with GCE (200 and 400 mg/kg), revealing its potentials to protect lipid peroxidation generated by ethanol in rats. The antioxidant activities were demonstrated by the reduction in the MDA level. In addition, GCE preserved the stomach mucosal lesion by recovering the antioxidant activity of the SOD enzyme, which had been reduced due to the delivery of ethanol. Based on these observations, it appears that the experimental protective effect of G. cowa fruit extract in the gastric lesion may be attributable, at least in part, to the presence of endogenous antioxidants.[94]

In the current investigation, histological examination of the stomachs was also carried out in order to provide additional verification of the findings. According to the findings of the histological examination, the administration of ethanol to rats led to the development of hemorrhagic necrosis of the gastrointestinal mucosa. By receiving GCE pretreatment, there was a decreased likelihood of developing stomach antrum ulcers and bleeding. The findings of these measurements lend credence to those obtained through pharmacological and biochemical analyses. In a sub-acute toxicity assessment, GCE doses up to 5000 mg/kg when administered parenterally were found to be non-toxic. The human equivalent dosage of GCE was calculated by applying the method for dose translation based on body surface area [60], which was found in the literature. Assuming a weight of 60 kilogrammes, the daily allowance of GCE that is advised for people is 3.89 grammes. For the purposes of conducting clinical research on the effects of G. cowa extract, the recommended daily dose for people could be used.[95]

The findings indicate that GCE may be a preferred alternative treatment to conventional antiulcer therapies due to its capacity to scavenge free radicals and its inexpensive cost in comparison to the cost of other herbal drugs. Herbal remedies have been shown to be equally as effective as prescription drugs like ranitidine and omeprazole, according to several studies [93-96] that were conducted on both humans and animals. This was further reinforced by the current experiment, which demonstrated that GCE was equally as effective as the gold-standard antiulcer medication ranitidine at reducing the number of stomach lesions. In toxicity studies [62], it was discovered that the use of Garcinia by humans is perfectly safe, with a significant margin of safety.

2.12. Mangiferin



Although it has been demonstrated that the xanthonoid mangiferin (MF) from the plant Mangifera indica possesses antisecretory and antioxidant gastroprotective activities against many models of gastric ulcers, the molecular mechanism that underlies these actions is yet unknown. In light of this, the objective of this study was to make use of the ischemia/reperfusion paradigm in order to investigate the moderating effect that it has on a variety of signalling pathways. When treating animal models, MF, omeprazole (OMP), and the vehicle were all subjected to in-vivo tests for comparison. Analyses of the mechanisms behind MF's gastroprotective action revealed that it was mediated in part by the substance's ability to stimulate the expression of Nrf2, HO-1, and PPAR- while at the same time decreasing NF-B. Surprisingly, with the exception of Nrf2, the effect of MF was significantly higher than that mediated by OMP [94] . This was especially true at the high dose. The antioxidant effect of MF was reflected in the biomarkers that were examined, with total antioxidant capacity and glutathione levels both increasing while malondialdehyde levels returned to normal. In conclusion, in contrast to OMP, MF was successful in

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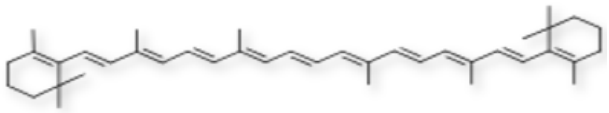
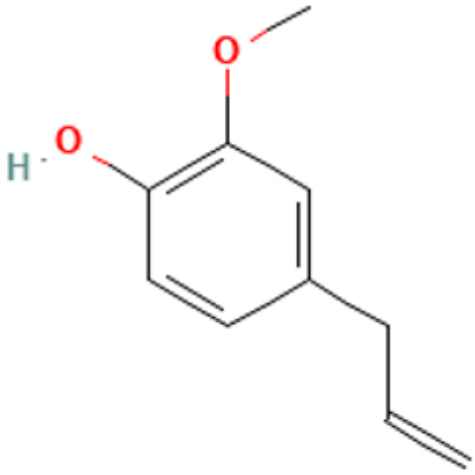
lowering the rise in levels of nitric oxide that was brought on by I/R. In a dose-dependent way, MF was found to enhance endothelial nitric oxide synthase in the blood while simultaneously decreasing the inducible isoform. After treatment with MF, levels of myeloperoxidase, which indicates the presence of neutrophil infiltration, and interleukin-1 beta (IL-1), which is a signal of inflammation, were both lowered in the serum. This effect was also duplicated in the tissue. In a dose-dependent manner, the capacity of MF to enhance Bcl-2 while simultaneously lowering caspase-3 provided further evidence that it possesses antiapoptotic effects. It would suggest that the Nrf2/HO-1, as well as the PPAR- and NF-B signalling pathways, each play a part in the process of mediating the gastroprotective effects of MF. [97]

2.13. Beta –carotene



It has been established that the naturally occurring pigment beta-carotene is beneficial to human health in a number of important ways. Naturally present in foods like vegetables and fruits. The three most important roles are those associated with the immune system, cell gap junction-related activities, and antioxidant effects. Because of the wide number of applications for beta-carotene, it is widely believed that it can both prevent and treat a wide range of chronic conditions. The ability to repair stomach cancer is one of its most important therapeutic applications. [98] The cancer of the stomach, also known as gastric cancer, is one of the most frequent types of cancer. The pathophysiology is difficult to understand, and the aetiology could be caused by anything from the environment to genetics. The devastation that stomach cancer may do to a person's health is unfathomable. Beta-carotene is a naturally occurring nutrient, and its potential role in the development of stomach cancer has been the subject of investigation in a great number of studies. These studies have taken a wide variety of approaches, ranging from those that investigate molecular mechanisms to those that investigate epidemiology. The majority of the research that has been done on the molecular level of beta-carotene in gastric cancer has focused on its role in oxidative stress, the cell cycle, signal transduction pathways, and immune-related systems. In the numerous epidemiological surveys and cohort studies conducted on people who have stomach cancer, inconsistent conclusions have been found as a result of the use of a variety of research approaches and geographic focuses.[98] By compiling a summary of the findings of these investigations, primarily in terms of molecular mechanisms and epidemiological research results, this study will provide a methodical framework for future research into the treatment and prognosis of stomach cancer. This will be accomplished by providing a systematic framework. [99]

2.14. Eugenol



In this study, eugenol, the principal bioactive component that can be found in the essential oil of clove (Syzygium aromaticum), was explored for its ability to assist in the regeneration of damaged tissue in the stomach. [100] After being exposed to an acetic acid-induced ulcer model, five different groups of female Wistar rats were given either Vehicle (one millilitre per kilogramme, orally), eugenol (one, ten, or one hundred milligrammes per kilogramme, orally), or omeprazole (twenty milligrammes per kilogramme, orally), twice daily, by seven or fourteen days. In addition to performing biochemical analysis, an examination of the ulcerated region was carried out using macroscopic and microscopic methods. It has been demonstrated that taking eugenol at a dose of 1 mg/kg orally over the period of either 7 or 14 days will accelerate stomach recovery by 33% or 52%, respectively. The restoration of normal levels of superoxide dismutase and catalase activity, as well as the repair of the tissue's histological architecture, occurred simultaneously with the therapeutic effects of eugenol. In addition, oral administration of eugenol at a dose of 1 mg/kg resulted in a reduction in myeloperoxidase activity and an increase in mucin secretion in the stomach mucosa. Eugenol reduced the ulcer area by 49% when it was administered at a dose of 100 mg/kg over the course of seven days. However, it had no effect when it was administered at a dose of 10 mg/kg over either seven or fourteen days. Despite the unfavourable results caused by a worsening of the gastric lesion as a result of using eugenol, the antiulcer potential of this molecule is obvious and manageable in an adequate dose. This is the case despite the fact that using eugenol worsens the gastric lesion. [100][101]

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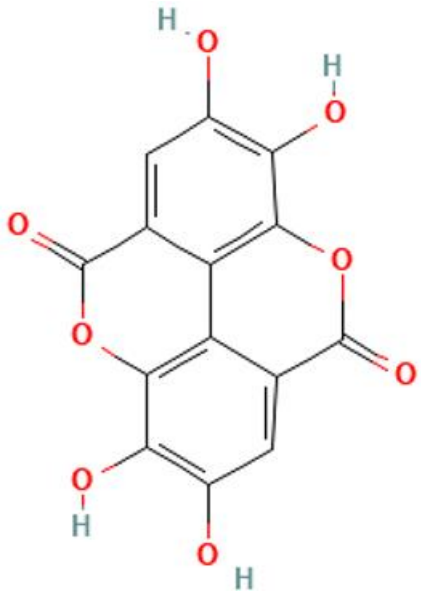
2.15. Ellagic acid



Ellagic acid (EA), a polyphenol found in plants, has qualities that make it antioxidant, anti-inflammatory, and gastroprotective. Neither the effects that it has on chronic ulcers nor the procedures that it uses to protect the stomach have been reported in the literature before. In order to accomplish this goal, ulcer models that were either acute (ethanol and indomethacin) or chronic (acetic acid) were induced in Wistar rats in order to evaluate the efficiency of EA as an antiulcer drug. After oral administration of EA, the severity of stomach ulcers brought on by ethanol, indomethacin, and acetic acid was found to be significantly decreased in this study. A decrease in plasma leukotriene B levels is one of the factors that contribute to its gastroprotective effect in ulcers caused by indomethacin.[102] On the other hand, in ulcers caused by ethanol, this effect was due to an increase in the body's endogenous production of nitric oxide, an antioxidant effect caused by the replenishment of depleted endogenous nonprotein sulfhydryls, and an attenuation of the increase in tumour necrosis factor (4). In patients with an acetic acid ulcer, decreased levels of tumour necrosis factor-, interferon-, and interleukin-4 and -6 led to the enhancement of ulcer-healing effects. According to these findings, the antiulcer effect of ellagic acid is most likely done by increasing the activity of protective factors while simultaneously decreasing the activity of irritating factors. [103][104][105]

II. CONCLUSIONS

The limited number of studies conducted on the efficacy and safety of herbs as gastroprotective and antiulcer medicines is indicated by the current body of published research. Despite this, there are a number of botanical items that have been shown to have a high level of efficacy despite having a low level of toxicity. These products show promise as potential treatment solutions. According to the findings of this research, terpenes and phenylpropanoids found in a variety of essential oils have been investigated for the potential role they play in the treatment of peptic ulcer disease. There are many different types of bioactive chemical classes that can be found in essential oils. Some examples of these classes are alcohol, phenol, aldehyde, carboxylic acid, ether, quinone, and bifunctional molecules. Due to the vast diversity of experimental conditions, dosages, and animals used for testing, it is not possible to construct a structure-activity link using this review as a basis. Instead, we will move on to the next section. In any event, these macromolecules have the characteristic of having a low molecular weight and being composed of relatively simple chemicals. The anti-ulcer activity of these naturally occurring chemicals has been attributed to a number of different pathways, including the scavenging of free radicals, the suppression of acid secretion, activity against Helicobacter pylori, and the strengthening of the stomach mucosal barrier. These results highlight the value of essential oil constituents as prospective agents for the treatment of stomach ulcers, a worldwide problem with significant unmet requirements due to the limitations of current treatment options in terms of efficacy, safety, and cost. These results highlight the value of essential oil constituents as prospective agents for the treatment of stomach ulcers.

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