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ROLE OF OXIDATIVE STRESS IN THE PATHOGENESIS OF ULCER

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Abstract: One important component in the pathophysiology of diseases affecting the mucosa of the stomach is oxidative damage. oxygen species that react (ROS) are produced as metabolic byproducts of regular cellular activity. Catalase, glutathione peroxidase, and superoxide dismutase are the enzymes that help shield cells from the harmful effects of ROS. In response to UV light, `tobacco smoke, alcohol, NSAIDs medications, IR injury, persistent infections, and inflammatory diseases, ROS are generated. Redox signalling's disruption of normal cellular equilibrium can lead to cancer, neurological illnesses, and heart problems. Although the gastrointestinal (GI) tract produces ROS, little is known about how these molecules function in pathophysiology and the genesis of disease. We have covered certain medicinal plants in this review article that have been shown to have antiulcer action due to their antioxidant properties, as well as the function that free radicals play in ulcers that are scavenged by antioxidants found in the herbs. Antioxidants and oxidative stress play a complicated and multidimensional role in ulcers. Antioxidants are important preventive factors against ulcer development, however oxidative stress also plays a major role. To precisely understand the processes causing oxidative damage in ulcers and to create customised antioxidant-based treatments for ulcer management and prevention, more study is required.

Keywords: Oxidative stress, gastric mucosa, peptic ulcer, helicobacter pylori, free radicals, antioxidants.

INTRODUCTION

Being a sensitive digestive organ, the stomach can get infected by outside bacteria that originate from food. The stomach's response to these infections is oxidative stress, which may contribute to the development of both functional disorders. like functional dyspepsia and pathological disorders of the stomach including gastritis, ulcers, and gastric cancer. The helicobacter pylori bacteria, in particular, is largely responsible for inducing and addressing oxidative stress in the stomach. Increased activity of the hypothalamic-pituitary-adrenal axis and alterations in gastrointestinal tissue are examples of physiological reactions to stresses. The general adaption syndrome, as proposed by Selye, links an increase in adrenocortical activity to a rise in the frequency of gastrointestinal ulcers. Oxidative stress is the leading theory as the aetiology of stress ulcers. There is evidence that psychological stress can cause oxidative stress in the stomach in addition to biological illnesses like Helicobacter pylori and physical stressors like surgical procedures. Oxidative stress causes a high production of ROS, which can result in a range of events that either encourage the synthesis of more ROS or the weakening of antioxidant defences. In addition to stomach inflammation, ulcerogenesis, and carcinogenesis in H. pylori infection, oxidative stress is involved in the pathogenesis of lifestyle-related illnesses such as diabetes mellitus, cancer, hypertension, and ischemic heart disease. It is commonly known that defective antioxidant qualities are linked to several phenotypes of gastrointestinal diseases, such as gastroparesis and peptic ulcer disease[1-3].

PREVALENCE

One of the most prevalent gastrointestinal disorders, peptic ulcers can raise mortality rates in certain areas if left untreated. The purpose of this research was to use a systematic review and meta-analysis to ascertain the global prevalence of peptic ulcers, taking into account the findings of several studies conducted worldwide that have indicated varying prevalences. A search of the Scopus, Embase, Web of Science, PubMed, Science Direct, Google Scholar, Magiran, Irandoc, and Scientific Information Database databases was conducted for papers pertaining to the prevalence of peptic ulcers in this systematic review and meta-analysis. The search was conducted without a time constraint until April 2020. The random effects model was employed to assess the eligible research, and the I2 index was used to look into the heterogeneity of the reports. It was found that 8.4% (95% CI 5–13.7) of 788,525 participants in 21 research, ranging in age from 17 to 82 years, had peptic ulcer prevalence worldwide. Based on the findings of the meta-regression analysis, the global prevalence of peptic ulcers declined as sample size grew and increased as study years and participant age increased. Statistical significance was observed for these differences as well ($P < 0.05$). In summary, the 8.4% prevalence of peptic ulcer disease means that health system policy makers must look into effective elements in order to prevent and cure this condition[4].

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PATHOGENESIS

An unbalanced relation between the aggressive stomach luminal components, acid and pepsin, and the defensive mucosal barrier function is the cause of the complex and multifaceted pathophysiology of peptic ulcers, which has been investigated over several decades. By enhancing stomach acid secretion or impairing the mucosal barrier, a number of environmental and host variables can lead to the development of ulcers. Smoking, binge drinking, and drug use are the environmental factors that are most frequently mentioned; nevertheless, none of them—aside from the use of NSAIDs—have been specifically linked to ulcers. The development of ulcers is often shown to be significantly influenced by emotional stress and psychosocial factors. Convincing proof that stress is the only cause of duodenal ulcers is rare, despite the fact that it cannot be ignored as a contributing component. The spike in gastric ulcer bleeding in the elderly following a powerful earthquake in Japan is an excellent illustration of stress as a contributing cause. If bleeding ulcers occur in the setting of serious organic sickness, including brain trauma, burns, or sepsis with multiorgan failure in intensive care units, then those ulcers should only be considered stress ulcers.

PATHOPHYSIOLOGY OF PEPTIC ULCER DISEASE

Previously, suppression of acid as a therapeutic approach and anomalies in the release of pepsin and stomach acid were central to our comprehension of the peptic ulcer disease's pathophysiology. Currently, antral G-cell hyperplasia, gastrinoma in Zollinger-Ellison syndrome, a rise in the mass of parietal cells as well as an anatomical mismatch between the stomach hormones gastrin and somatostatin, which are antagonistic are all linked to gastric hypersecretion, which is still a major problem in the condition of ulcers in the stomach. It is also known that the stimulation of pepsin—which is frequently disregarded as a contributing element to the harmful damage that occurs to the stomach mucosa— The acid hydrochloric receptor is linked to parasympathetic domination and cholinergic hypersensitive. It has been demonstrated that peptic ulcer disease is exacerbated by psychological stress, alcohol consumption, cigarette smoking, and the usage of NSAIDs, such as aspirin, potassium chloride, oral bisphosphonates, and immunosuppressive drugs. It is also caused by an age-related decrease in prostaglandin levels. But it was the discovery that Helicobacter pylori is the primary cause of ulcer disease and its isolation that prompted researchers to investigate the function of inflammation and the cytokine cascade that is set off in the process of producing stomach acid. Several techniques are employed by H. pylori to evade the host immune system and cause long-lasting, non-inflammatory inflammation. Helicobacter pylori can damage the mucosal defence system by weakening the mucus gel layer, reducing mucosal blood flow, and interacting with the stomach epithelium at every stage of the infection. A H. pylori infection can also enhance the production of stomach acid due to the production of several antigens, virulence factors, and soluble mediators that cause inflammation and increase the bulk of parietal cells, which in turn increases the ability to release acid. The gene linked to cytotoxin in the bacterium H. pylori CagA also plays a significant role in the regulation of cellular responses, disruption of the stomach epithelial cells' phenotypic, interleukin-8 secretion, and apical junction barrier. It accomplishes this by obstructing the signalling channels of stomach epithelial cells. Since the mechanism causing damage to duodenal and stomach ulcer vary significantly peptic ulcer disease pathophysiology is currently at a crossroad. Helicobacter pylori related disease an increase in the pepsin and acid and gastric metaplasia in duodenal cap are the primary cause of duodenal ulcers. NSAID consumption is most commonly associated, at least in Western nations, with stomach ulcers; yet, H. pylori. People with stomach ulcer, chronic superficial and atrophic gastritis even put a normal acid level can be linked to ulcer in mucosa. Helicobacter pylori in the earlier was one of the most important developments in the history of disease called peptic ulcer and it has an immense impact on the therapy of peptic ulcer. The cornerstone of treatment for peptic ulcer disease is currently the eradication of the H. pylori infection, This, especially in cases of duodenal ulcers, has resulted in extraordinarily rapid rates of healing of the ulcer and noticeably lower rates of recurrence. As a result of growing knowledge about the role aspirin and NSAIDs play in GI injury, curative Hand prevention strategies include the use of many drugs which have been developed[5-11].

Helicobacter pylori linked ulcer

Earlier about 90 percent duodenal ulcers patients and & 70% of stomach ulcers patients had infection which was caused due to H. pylori. In industrialised nations, Peptic ulcer rates and prevalence are declining in line with the H. pylori infection's declining prevalence, particularly in high-infected groups. The only proven treatment for both duodenal and stomach ulcers is the removal of H. pylori. Antisecretory medications are effective in managing symptoms and promoting ulcer healing; nevertheless, In terms of healing on its own, getting rid of the H. pylori infection entirely has minimal benefit. According to a recent meta-analysis, duodenal healing was greatly increased to 83% when the H. pylori infection was eradicated and an ulcer-healing medication was given. The relative risk of the ulcer continuing was 0.66 as compared to the use of ulcer-healing medications alone. However, there was no discernible increase in the relative risk of stomach ulcer healing with eradication as compared to taking ulcer-healing medication alone[12-16].

Non-steroidal inflammatory drugs-related damage

In Western countries, NSAID use is likely the most typical factor damaging GI mucosa, Although their well-proven benefits as analgesics and anti-inflammatory drugs. NSAIDs, such as aspirin, dramatically raise the chance of unpleasant stomach symptoms, especially those that are associated with damage to the gastric and/or duodenal mucosa, such as ulcers, bleeding ulcers, and erosions. According to an endoscopy examination, 3 to 4.5% of users of NSAID develop clinically significant upper gastrointestinal events, such as complications related ulcers, while around 30 percent of regular NSAID users have more than a one lesions. Individuals who are using low-dose aspirin to prevent thrombotic stroke or myocardial infarction are also more vulnerable to gastrointestinal problems and injuries. 47.83% of asymptomatic patients using low-dose aspirin for at least three months have endoscopically detected ulcers or erosions. With an odds ratio of 6.3 for 1.2 g of aspirin and 3.3 for 300 mg of aspirin, the risk of upper gastrointestinal bleeding episodes is dose-dependent. An increased incidence of ulcer haemorrhaging has been independently associated with small amounts of aspirin use. The above-discussed suppression of COX1 and its involvement in normal mucosal defence mechanisms, as well as the suppression of thromboxane A2, which impairs functioning of platelet and induces GI bleeding, are the main causes of the harmful gastrointestinal

effects of NSAIDs. Clinical trials have shown time and time again that coxibs are superior to nonselective NSAIDs in terms of reducing ulcers, gastrointestinal bleeding, and ulcer complications. However, this benefit is mitigated when low-dose aspirin is concurrently used. Many patients are likely to revert to nonselective NSAIDs as a result of the withdrawal of numerous coxibs, which is projected to raise the possibility of bleeding from the gastrointestinal tract, especially in elderly individuals [17-25].

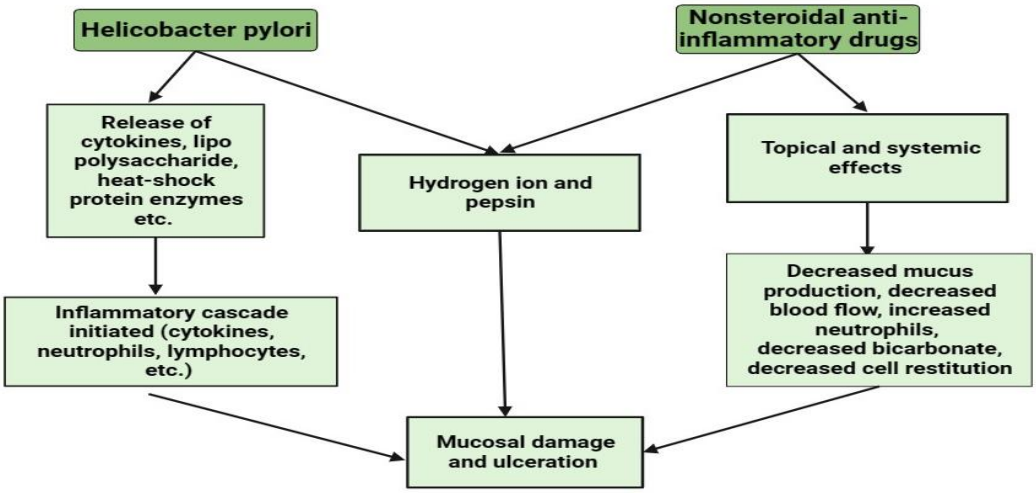

Figure 1: Nonsteroidal anti-inflammatory medications and Helicobacter pylori have a synergistic effect on stomach mucosal injury. It has been discovered that the potential for injury to and ulceration of the duodenum and stomach mucosa is independently & significantly increased by both use of NSAIDs and H. pylori infection. H. pylori and NSAIDs work together to promote ulcer formation and haemorrhage via inflammatory pathways.

PEPTIC ULCER AND GASTRITIS: THE ROLE OF FREE RADICALS

Multiple etiopathogenetic variables contribute to gastritis and peptic ulcers. It is commonly acknowledged that the production of free radicals is a significant underlying element in this illness. The pathophysiology of tissue damage, including damage to the digestive system, appears to be significantly influenced by oxygen-produced free radicals, according to compelling data. It is also commonly known that the pathophysiology of ischemic injury to the gastrointestinal mucosa and other models of mucosal damage caused by ethanol, H. pylori, NSAID medications, and ingesting restriction stress involve oxygen-derived free radicals, such as the superoxide anion, hydrogen peroxide, and hydroxyl radical. In this investigation, MDA levels were higher in the GI mucosa of people with gastritis and stomach ulcers.. It is believed that cell membrane damage caused by free radicals is reflected in MDA levels. Carotenoids, glutathione redox system, and alfa tocopherol are examples of radical scavengers that are recognised to be important in shielding membranes from oxidative damage. When the GSH levels in the stomach mucosa are low, free radicals build up and can cause lipid peroxidation, which damages membranes. Lower stomach mucosal GSH levels were discovered by the current authors in patients with gastritis and peptic ulcers.

Salim et al. observed that antioxidative treatment promotes the healing of therapy-resistant gastric and duodenal ulcers by examining the impact of free radical scavengers on the healing process. According to research by Santra et al., H. pylori infection is linked to the production of reactive oxygen molecules, which causes oxidative stress in the stomach mucosa. It was discovered that patients with duodenal ulcers, whether or not they had an H. pylori infection, had considerably lower gastric mucosal GSH levels and higher MDA levels. According to Galaktinova et al., patients with H. pylori infection had higher plasma concentrations of MDA and lipid H. pylori as well as overall oxidative activity, Ferrinati et al. discovered that gastritis was associated with considerably elevated stomach MDA levels and higher-than-normal glutathione turnover. According to Maity et al., glutathione is crucial for cytoprotection against ulceration. These observations are consistent with our findings.

Activated inflammatory cells, vascular endothelial cells, the hypoxanthine-xanthine oxidase system, the disrupted mitochondrial electron transport system, and the lipoxygenase pathway involved in arachidonate metabolism can all be sources of free radicals. The a etiology of mucosal damage may involve activated inflammatory cells and the lipoxygenase pathway. Gastro-oxygenase and lipoxygenase pathways, along with inflammatory cell infiltration in the stomach mucosa, are responsible for the metabolism of arachidonic acid by gastric mucosal cells. Inflammation can flare up as a result of H. pylori. In patients with duodenal gastric metaplasia and H. pylori-infected gastric mucosa, there is active inflammation in the stomach's lamina propria. In the acute stage of the infection, neutrophils are infiltrated, whereas in the chronic stage, macrophages, monocytes, lymphocytes, and plasma cells are present. These macrophage/monocytes and neutrophils generate a lot of oxygen-derived free radicals, which may harm cells and ultimately result in mucosal injury. Prior research has demonstrated that compared to gastritis strains, H. pylori strains from patients with duodenal ulcers exhibit higher neutrophil activity. Patients with peptic ulcers had greater stomach mucosal MDA levels in this study than did patients with gastritis or the H. pylori negative control group. Assessing H. pylori strains and neutrophil density in the stomach mucosa was not feasible, though. There was no discernible difference in the GSH levels between patients with gastritis and

those with peptic ulcers. The authors of this study believe that although neutrophil activitiy could not be quantified, the existence of greater mucosal MDA levels and lower mucosal GSH levels may suggest increased neutrophil activitiy in our peptic ulcer patients.The study's conclusions imply that gastritis and peptic ulcers are pathological conditions caused by oxygen-derived free radicals.

The exact mode of action of Helicobacter pylori, often known as H. Pylori, remains unclear despite its etiological association with multiple major gastroduodenal disorders. Free radicals, on the other hand, may be intimately linked to gastritis and peptic ulcers. Free radicals that are low in oxygen are harmful to biological tissues and are responsible for their damage.

3.0++e. Lipid peroxidation is the damaging mechanism that releases intracellular components such lysosomal enzymes and damages cell membranes, causing more tissue damage. By completely altering cell metabolism, inducing DNA damage, and degrading components of the epithelial basement membrane, radicals also contribute to mucosal injury. It is widely known that the production of superoxide anion causes damage in a variety of acute and chronic injury models; however, it is unclear if stomach mucosal damage is caused by this radical[26-32].

HYDROXYL RADICAL: THE MAJOR CAUSATIVE FACTOR IN STRESS INDUCED GASTRIC ULCERATION

The impact of hydroxyl radical (OH) generation catalysed by metal on rat stomach ulcers brought on by restraint-cold stress was investigated. Stress results in a roughly seventy percent rise in oxidised protein as determined by its carbonyl content, a 50% increase in thiobarbituric acid reactive species (TBARS), a 40% decrease in glutathione content of the fundic stomach, and an increase in lipid peroxidation. These findings suggest oxidative damage caused by stress. Additionally, stress results in a time-dependent rise in mitochondrial superoxide dismutase activity and a fall in peroxidase activity, both of which are positively correlated with an increase in ulcer severity as determined by the ulcer index. The considerable inhibition of stomach ulceration by specific OH scavengers like benzoate or DMSO and free radical traps like -phenyl and N-tert-butyl nitrone (PBN) suggests the involvement of OH in this oxidative damage. A benign transition metal ion chelator called desferrioxamine (DFO) dose-dependently shields the mucosa against stress-ulceration. DFO or antioxidants like glutathione or vitamin E also prevent increased levels of TBARS and the inactivation of gastric peroxidase, indicating the crucial role that metal ions and OH play in oxidative damage. The purified gastric peroxidase is inactivated in vitro by a metal-catalyzed OHi producing system consisting of Cu^{2+}, H2O2, and ascorbate (reducing equivalent of $O2^{-}$), which can be successfully avoided by DFO. Pretreatment with amanitin totally prevents the stress-induced activation of superoxide dismutase, suggesting enhanced production of the enzyme through higher transcription of its m-RNA. Stress increases the formation of OH fivefold, according to a quantitative assessment, and this rise is highly correlated with an increase in the ulcer index as stress increases. The findings suggest that the oxidative damage to the stomach mucosa is the cause of the stress-induced gastric ulceration. This is brought on by the OH produced by the metal-catalyzedHaber-Weiss reaction between $O2^{-}$ and H2O2, the latter of which is created when the superoxide dismutase is stimulated and the gastric peroxidase is inactivated[33].

ROLE OF ANTIOXIDANT

To deal with the generation of ROS, the body has created a number of endogenous antioxidant mechanisms. Groups of these systems can be classified as enzymatic or nonenzymatic.SOD, catalase, and glutathione peroxidase are examples of enzymatic antioxidants. SOD catalyses the conversion of oxygen to hydrogen peroxide and water, whereas catalase converts hydrogen peroxide to water and oxygen. GSH decreases hydrogen peroxide to water. Glutathione reductase then catalyses the re-reduction of glutathione in its oxidised state (GSSG). For these enzymes to function at their best, they also need trace metal co-factors, such as iron for catalase, copper, zinc, or manganese for SOD, and selenium for glutathione peroxidase.

The lipid-soluble vitamins, provitamin A (beta-carotene) and E, as well as the water-soluble vitamins, GSH and C, are examples of nonenzymatic antioxidants. Intracellular glutathione is produced from glutamate, glycine, and cysteine. Glutathione peroxidase can enzymatically scavenge reactive oxygen species or directly scavenge them. Furthermore, GSH plays a critical role in maintaining enzymes and other cellular constituents in a decreased form. The liver is the primary site of GSH production. It is thought that its biological function is to protect the body from food xenobiotics and lipid peroxidation. The development of ulcers may be significantly influenced by shifts in the amounts of antioxidant molecules.

The involvement of free radicals produced by oxygen in gastritis and peptic ulcers has been the subject of numerous investigations. Nevertheless, animal models were used for the majority of them.

Patients with gastritis and peptic ulcers are susceptible to oxidative damage to their membranes. was evaluated in this study by measuring the concentration of malondialdehyde (MDA), the byproduct of lipid peroxidation in the gastric mucosa. Reactive oxygen species formation may have an impact on the levels of the antioxidant peptide, hence mucosal GSH quantities were also examined[34-38].

ROLE OF FREE RADICALS IN ULCER SCAVENGED BY ANTIOXIDANTS PRESENT IN THE HERBS

GUTGARD

By considerably reducing stomach mucosal lesions in rats caused by pylorus ligation, cold-restraint stress, and indomethacin, *GutGard* demonstrated anti-ulcerogenic efficacy. Cyclooxygenase inhibitors such as indomethacin restrict the secretion of gastroduodenal bicarbonate, lower the amount of prostaglandins produced naturally, and cause disruptions to the blood flow and mucosal barrier in animals. It is known how harmful oxygen radicals contribute to the etiopathogenesis of stomach injury brought on by indomethacin. It has been demonstrated that stomach tissue harmed by indomethacin has lower antioxidant properties. It's also commonly recognised that the gut mucosa produces a lot of prostaglandins, which can stop ulcerogens from inducing experimental ulcers. Gutgard may have mimicked prostaglandin secretion. possess compounds that resemble prostaglandins. The cytoprotective action of *gutGard* may be partially attributed to its flavonoid concentration and its capacity to scavenge reactive oxygen species. An established method for determining the antioxidant ability of natural products is the Oxygen Radical Absorbance ability test (ORAC). The product's antioxidative mechanism was reinforced by the high ORAC value

of the *GutGard'M* gastric mucosal lesions, a measure of their antioxidant effectiveness in vitro[39].

JASMINUM GRANDIFLORUM L.

The purpose of this research was to evaluate the antioxidant and antiulcer qualities of *Jasminum grandiflorum L.* (JGLE) leaf 70% ethanolic extract. To evaluate the antiulcerogenic efficacy of JGLE rats with acute stomach ulcer models induced by AL, APL, and a chronic ulcer model created by AC were employed. The concepts of cytoprotection and antisecretory action were assessed. To explain the role of antioxidant principles in the antiulcerogenic activity of the extract, the antioxidant activity of JGLE has been evaluated using in vitro techniques such as the DPPH assay, reductive ability, superoxide anion scavenging activity, nitric oxide scavenging activity, and total phenolic content. Free radicals that damage tissue, which are created when hydroperoxyl is changed into hydroxy fatty acids and cause cell death, are the route via which aspirin-induced ulcers occur. The generalised lipid peroxidation that occurs with cell injury and the degradation of mast cells produce the hydroperoxyl fatty acids. Gastritis caused by ethanol have been extensively employed to assess the gastroprotective efficacy. When the body breaks down ethanol, free radicals called hydroperoxy and superoxide anion are released. Scavenging these free radicals can significantly aid in the healing of gastric ulcers, as it has been discovered that oxygen-derived free radicals are involved in the process of both acute and chronic ulceration in the stomach mucosa. The APL rats' lower stomach fluid volume, higher pH, and lower overall acidity were indicative of JGLE's antisecretory effect. Furthermore, after 20 days of treatment, pathological examinations demonstrated that JGLE completely cured the ulcer in the AC model. JGLE has concentration-dependent free radical scavenging capabilities that increase with extract concentration, much like its antiulcer characteristics. These results suggest that the antioxidant action of Jasminum grandiflorum leaves may be linked to their antiulcer capabilities[40].

MADHUCA INDICA

This research was done on rats to evaluate the antioxidant and anti-ulcer activities of *M. indica*. Preventive antioxidants like SOD and CAT enzymes primarily offer protection against reactive oxygen species. GSH is an important low molecular weight scavenger of free radicals in the cytoplasm and an essential inhibitor of lipid peroxidation brought on by free radicals. Compared to control mice, the levels of SOD, CAT, and GSH increased significantly following the administration of *M. indica* leaf methanolic extract, indicating the plant's efficacy in preventing damage caused by free radicals. Superoxides produced by peroxidases within the tissues have the potential to damage the tissues and membranes of the stomach by increasing lipid peroxidation. Free radicals mediate a process called lipid peroxidation, which has been connected to a number of medical disorders. It includes the rearrangement of double bonds in unsaturated lipids, the oxidation of oxygen, and the production and propagation of lipid radicals. Biological membranes usually contain large amounts of unsaturated fatty acids. It follows that the fact that membrane lipids are prone to peroxidative breakdown is not surprising. On the other hand, the current investigation demonstrated a noteworthy rise in lipid peroxidation in the rat stomach tissues of the control group. On the other hand, lipid-peroxidation significantly decreased in both experimental models after *M. indica* at all doses was administered, indicating that the plant may have a protective impact[41].

SPONDIAS MOMBIN L.

Oral consumption of ethanol causes the stomach to develop extensive submucosal edoema, linear hemorrhagic lesions, brittle mucosa, infiltration of inflammatory cells, and death of epithelial cells. These gastrointestinal mucosal damages could be connected to intracellular oxidative stress, decreased glutathione levels, changes in the permeation of the barrier and the depolarization of the membrane that covers the mitochondria, which ultimately results in cell death. NSAIDs cause gastric ulcers by inhibiting cyclooxygenases, which in turn prevents prostaglandin production from occurring. By promoting the production of mucus and bicarbonate as well as the preservation of mucosal blood flow, prostaglandins in the stomach have a significant protective effect. Additionally, prostaglandins control the renewal of mucosal cells. Thus, NSAID-induced decrease of prostaglandin production raises the risk of stomach mucosal ulcers.

Biologically active antioxidants have the ability to strengthen defences against degenerative diseases and shield the stomach mucosa from oxidative stress-induced cell damage. Studies have linked the application of antioxidants, whether natural or synthetic, to the protection of the stomach mucosa against necrotic substances such as ethanol and nonsteroidal anti-inflammatory medications. Specifically, omeprazole, a proton pump inhibitor, possesses several qualities, such as the capacity to operate as an antioxidant in vitro and the capacity to lessen DNA fragmentation in gastric mucosal cells (antiapoptosis). The ethanolic extract of S. mombin contained classes of bioactive chemicals linked to antiulcer activity, according to an in vitro antioxidant study. This finding could support the plant's usage in traditional medicine[42].

SOLANUM NIGRUM AND ALTHAEA OFFICINALIS

This research examined the ability of extracts from Althaea officinalis and Solanum nigrum to operate as a gastro protectant both in vitro and in vivo on rats that have gastric ulceration caused by indomethacin induced/ pyloric ligation.

The mechanism by which indomethacin causes gastric ulcers is as follows: it inhibits prostaglandin synthesis, produces ROS, starts lipid peroxidation, causes stomach cell apoptosis and necrosis, decreases bicarbonate and mucus secretion, increases gastric motility, increases the production of pro-inflammatory cytokines, and, lastly, interferes with the production of nitric oxide in the stomach tissues. Indomethacin's ulcer-causing mechanism is complicated and still unknown. In summary, it was proposed that the mechanism causing indomethacin-induced stomach ulceration involves suppressing the release of protective factors, building up aggressive factors, and intensifying oxidant parameters while reducing anti-oxidant parameters. Consequently, the usage of medications that have anti-oxidant activity and the capacity to alter nitric oxide concentration can guard against stomach ulcers brought on by indomethacin.

Pyloric ligation-induced gastric ulceration was caused by the stomach wall breaking down naturally as a result of accumulating gastric juice (pepsin and gastric acid), disrupting the flow of blood through the stomach, and producing more free radicals. Pyloric ligation-induced stomach ulcerations can be avoided using medications that show an rise in production of mucus and a fall in gastric juice secretion.

Pretreatment with Althaea officinalis significantly reduced ulcers associated with oxidative stress, as indicated by a significant drop in MDA. Scopoletin, the tannin component of Althaea officinalis, mimics hepatic lipid peroxidation and increases the anti-oxidant activity of catalase and superoxide-dismutase. Moreover, studies have demonstrated the capacity of Althaea officinalis flavonoids to scavenge free radicals and stop lipid peroxidation. The notion that Solanum nigrum exerts its gastro-protective function by inhibiting lipid peroxidation and free radical scavenging activity suggests the likely mechanism of action[43].

SOME OF THE MEDICINAL PLANT WHICH WERE REPORTED TO POSSESS ANTIULCER ACTIVITY BY VIRTUE OF ANTIOXIDANT PROPERTY WERE LISTED BELOW.

S.NO	AUTHORS	TITTLE OF WORK	PART USED	IN-VITRO MODELS	IN-VIVO MODELS	CONCLUSION
1	Alimi H et al.,	antiulcerogenic & Antioxidant activities of root extract of *Opuntia ficus indica f.* inermis in rats	Roots	DPPH radical scavenging action, power reduction	ethanol induced ulcer	In conclusion, this is the first proof that *Opuntia ficusindicat f. inermis* (ORE) methanolic root extract has an anti-oxidant and gastro-protective impact on gastric lesions caused by ethanol. We propose because of their richness in flavonoid and phenolic substances, their moderate antioxidant activity in vitro, and their potent anti-ulcerogenic action in vivo, that ORE may have an antioxidant/ranitidine-like pathways in their antiulcerogenic activity. Subsequent investigations are underway to assess the unidentified bioactive compound(s) of ORE and determine its true mechanism of action prior to proposing *A root extract from Opuntia ficus indica f. inermis* as an innovative GI disease treatment.
2	Babu PN et al.,	Evaluation of antiulcer and in-vitro antioxidant activities of flowers and polyherbal extract of *ixora coccinea* in wistar albino rats	Flower	Lipid peroxidation inhibition activity Nitric oxide scavenging activity	pyloric ligation and aspirin induced ulcer	The current work demonstrated the strong antioxidant and antiulcer properties of the methanolic extract of *Ixora coccinea* flowers in rat stomach ulcer models caused by aspirin and pyloric ligation. Using the methanolic polyherbal extract of Neolamarckiacadamba leaves, Psidium guajava roots, and *Ixora coccina* flowers resulted in a synergistic effect. Comparing the outcomes, plant extract shown greater efficacy in ligating the pylorus than in ulcers caused by aspirin. Using more experimental models, further research must be done to identify the active ingredients and clarify the precise mechanism of antiulcer efficacy.
3	Mukherjee M et al.,	Antiulcer and antioxidant activity of *Gutgard*	roots	ORAC (oxygen radical absorbance capacity) -hydrophilic assay	Gastric lesions caused by indomethacin, cold-restraint stress, and Pylorus ligation	The current investigation verified the anti-ulcerogenic efficacy of the *GutGardTM* by showing that it was a major inhibitor of stomach mucosal lesions generated in rats by pylorus ligation, cold-restraint stress, and indomethacin. The flavonoid content and reactive oxygen species scavenging ability of *GutGardTM* may be partially responsible for the cytoprotective effect.With a high ORAC value, *GutGardTM's* in vitro antioxidant potency confirmed its antioxidative mechanism against stomach mucosal lesions. These findings bolster the traditional medicinal applications of licorice for ulcer relief.
4	M. Umamaheswari et al.,	in vitro antioxidant & Antiulcer and activities of *Jasminum grandiflorum L.*	leaves	Total phenolic content, super oxide anion scavenging capacity, DPPH, and NO scavenging activity	Acute stomach ulcer models and ulcer-healing activity by the AC chronic ulcer model, APL, and AL.	Our study's findings demonstrate the antiulceractivity of *Jasminium gradiflorum* crude extract against models of acute and chronic stomach ulcers created in experiments. Therefore, it is possible that the extract's antioxidant and antisecretory properties are what give it its antiulcer properties.

5	GU Chidrewar et al.,	Anti-ulcer and antioxidant activity of *Madhuca indica* leaves in rats	Leaves	pylorus ligation method Method of ethanol-induced ulceration	PL method Method of ethanol-induced ulceration	Both models showed a considerable decrease in the ulcer indexes and the pH of the gastric fluid and the quantity of mucin in the stomach increased, indicating that M. indica has anti-ulcer properties. Additionally, the total acidity and volume of gastric fluid, as well as the decrease in pepsin activity in rats with pylorus ligation, were significantly reduced. M. indica's antioxidant activity was demonstrated by the increase in lipid peroxidation, decreased glutathione, catalase, and superoxide dismutase in both models. Thus, due to its antioxidant mechanism of action, M. indica can be regarded to have anti-ulcer capabilities.
6	Brito SA et al.,	Antiulcer Activity and Potential Mechanis of the Leaves of *Spondiasmombin L.*	Leaves	phosphomolybdenum, ABTS, DPPH, and FRAP assays	Ethanol-Induced Ulcer Induced Gastric Ulcer by Indomethacin Gastric Ulcer Caused by Acetic Acid	Our research revealed that, in addition to its antisecretory and anti-Helicobacter pylori properties, SmEE possesses antiulcerogenic activity that is mediated by nitric oxide, sulfhydryl groups, antioxidant action, or stimulation of the formation of gastric mucus. All of these processes working together can aid in the chronic ulcer healing that the ethanolic extract of *Spondiasmombin* promotes. Separate gastric protectors GA and EA worked together harmoniously to shield the mucosa from ethanol-induced gastric lesions.
7	Zaghlool SS et al.,	Gastro-Protective and Anti-Oxidant Potential of *Althaea officinalis* flowers *and Solanum nigrum* fruits	*Althaea officinalis* flowers *Solanum nigrum* fruits	DPPH Assay	pyloric-ligation/indomethacin-induced gastric-ulceration method	The present research demonstrates the anti-oxidant potential of both in vitro and in vivo extracts from Althaea officinalis and Solanum nigrum. Furthermore, it has been demonstrated that giving rats extracts from Althaea officinalis and Solanum nigrum orally once a day for 14 days can shield them against stomach ulcers brought on by pyloric ligation and indomethacin. The antioxidant effects of the extracts, their reduction of histamine and gastrin release, their promotion of mucin, nitric oxide, PGE2, and PGI2 levels, and their suppression of the creation of pro-inflammatory cytokines such as TNFα and IL-1β are probably the causes of this protection. Furthermore, the fact that both extracts can increase the production of the protective HO-1 and CBS enzymes in stomach mucosal tissue is hopeful for upcoming treatment trials.
8	Song SH et al.,	Anti-ulcer & anti-oxidant activity of *Gallarhois extract*		DPPH radical scavenging assay	Ethanol/ HCL Induced Ulcer	It is concluded that the results of the biochemical, histological, and RT-PCR analyses in this study showed that GR had a protective effect against stomach ulcers caused by EtOH/HCl. EtGR's control of oxidative stress, suppression of IL-1b, IL-6, and COX-2, and its inhibitory effects on inflammatory cell infiltration were identified as the main mechanisms responsible for its anti-ulcer benefits. Furthermore, GR did not result in renal or hepatotoxic effects. It will take longer and more thorough research to fully understand GR's gastrointestinal defence mechanism.
9	Del Rey BG et al.,	The butanolic fraction extract from the leaves of Bauhinia forficata, a medicinal plant commonly used in Brazilian folk	Leaves	-	Ischemia-reperfusion-induced gastric ulcer (IR)	In summary, the ButFr derived from B. forficata leaves exhibits noteworthy antioxidant and antiulcer properties. Prior administration of ButFr (6.25 mg kg-1) decreased the level of MPO and the rate of lipid peroxidation, both of which are implicated in the development of gastric ulceration, but it dramatically increased the concentrations of the antioxidant enzymes GR, GPx, and SOD. The flavonoids rutin and kaempferitrin were the substances that exhibited this pharmacological action.

		medicine, has antiulcer and antioxidant properties.				
10	Ali MJ, Guesmi F et al.,	Investigation of Antiulcer and Antioxidant Activity of *Juniperus phoenicea L.* (1753) Essential Oil in an Experimental Rat Model	Leaves	-	hydrogen chloride (HCl)/ethanol-induced ulcers	Based on the significant antioxidant activity, we conclude that the essential oil of *Juniperus phoenicea* has strong anti-ulcer properties when taken orally. This supports the ethnomedical claims regarding the oil's significant gastroprotective effect, as it lowers MDA levels and raises GSH, GST, GPx, CAT, and SOD levels. An increase in the defensive mechanisms of the stomach mucosa may be connected to this impact. Our study's findings demonstrated histological preservation of the mucosa's integrity. Because of this, more research is necessary to ascertain the precise mode of action and pinpoint the active ingredients behind the essential oil's protective properties and low toxicity.
11	Srivastava AK et al.,	Antioxidant & Anti-ulcer activity of *NELUMBO NUCIFERAGAERTN* stalks in rats	Stalk	-	pylorus ligation and indomethacin induced gastric ulcer models	MENN demonstrates significant anti-ulcer action in addition to robust oxidant and antioxidant activities. To summarise, our research indicates that the methanolic extract of Nelumbo nucifera stalks possesses active phytoconstituents with anti-secretory, cytoprotective, and antioxidant properties, which may be responsible for the extract's anti-ulcer efficacy. These findings suggest that Nelumbo nucifera stalks could be applied as a supplement to treat stomach ulcers. Further research is needed to pinpoint the exact mechanism of action in the healing of stomach ulcers and to identify the active components that give rise to the anti-ulcer activity.
12	Tamboli FA et al.,	Evaluation of Antiulcer and Antioxidant Activity of *BarleriagibsoniDalz.* Leaves	Leaves	DPPH, NO activity	pylorus ligation-induced ulcer models	Oral administration of an ethanol extract of leaves considerably decreased the amount of stomach lesions caused by pylorus ligation-induced ulcers as compared to standard omeprazole. The IC50 values for the leaf extract were found to be 150 µg/mL. In the DPPH radical scavenging assay, the ethanol extracts showed good antioxidant ability and NO radical scavenging activity when compared to the standard. Gallic acid was used to measure the total phenolic content using the Folin-Ciocalteu reagent. Similarly, quercetin equivalence was used to calculate the total flavonoid content. In conclusion, these studies suggest that B. gibsoni leaves may have higher antioxidant and antiulcer potential than normal.The antiulcer and antioxidant properties of B. gibsoni (Acanthaceae) have never before been reported.
13	Onasanwo SA et al.,	Anti-ulcerogenic and in vitro antioxidant activities of whole fruit ethanolic extract of *Lagenaria breviflora (LB)*	Whole fruit	DPPH, NO,OH radical and Superoxide anion scavenging models	CRU, PL, ASP, AL induced gastric ulcer models	EELB (50, 100, 150, and 200 mg/kg, b.w.) provided dose-dependent protection against the CRU stomach ulcer. Similarly, 150 mg/kg b.w. of the LB extract was similar to omeprazole (10 mg/kg b.w.) or suscralfate (500 mg/kg b.w.) in terms of protecting against the PL, ASP, and AL gastric ulcers. The ability of LB to quench free radicals produced by nitric oxide and superoxide anion, along with a concurrent scavenging potential against DPPH-induced radical production, revealed its in vitro antioxidant activity. All things considered, the research demonstrated that the entire fruit extract had strong antioxidant and anti-ulcer properties.

14	Onasanwo SA et al.,	Anti-ulcer & antioxidant activities of *Hedranther abarteri* with possible involvement of H+ , K+ ATPase inhibitory activity	roots	DPPH, NO, OH radical and Superoxide anion scavenging models	CRU, PL, ASP, AL induced gastric ulcer models	DMHBR demonstrated both cytoprotective and anti-secretory properties in addition to anti-ulcer effectiveness against experimentally-induced peptic ulcer animals. It demonstrated the ability to inhibit the proton pump, and its antioxidant capabilities may contribute to its anti-ulcer characteristics.
15	Christophe M et al.,	Anti-ulcer and Antioxidant activities of *corchoruso litorius* (tiliaceae) leaf aqueous extract in rats	Leaves	DPPH assay, FRAP assay	Ethanol/HCl-induced stomach lesions Gastric ulcers caused by indomethacin ulceration and gastric secretion ligated by Pylorus Chronic ulcers caused by acetic acid, Alcohol and Aspirin	This study demonstrated the anti-ulcer efficaciousness of C. olitorius leaf aqueous extract using a range of experimental models of stomach ulcers.The extract's anti-ulcer properties are most likely caused by a variety of mechanisms, including the prevention of acid secretion by parietal cells, the enhancement of the in vivo antioxidant state through the reduction of MDA, and the stimulation of mucus secretion by a mechanism similar to endogenous prostaglandins and an increase in SOD concentration. The findings are consistent with the traditional folk medical application of herbal remedies for curing the peptic ulcer illness symptoms.

CONCLUSION:

Antioxidants and oxidative stress play a complicated and multidimensional role in ulcers. The pathophysiology of ulcers is significantly influenced by oxidative stress. while antioxidants serve as key protective factors. Further research is needed to elucidate the precise mechanisms underlying oxidative damage in ulcers and to develop targeted antioxidant-based therapies for their prevention and management.

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