FROM STRESS TO SECRETAGOGUES: CRITICAL APPRAISAL OF *IN-VIVO* ULCER MODELS

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Abstract
Worldwide, peptic ulcer disease is considered a primary gastrointestinal disorder. Experimental models are based on several factors, including stress, chemical administration, vascular mechanisms, and neurotransmitter depletion. Stress models that simulate stressulcers are good for mimicking acute ulcer production but not for chronic ulcers. Chemical models, such as ethanol and acetic acid administration, are reproducible and easy to understand, but tend to be severe and exaggerated forms of injury or invasive methods of administration. These models, specifically those addressing vascular function and free radical generation, are effective for revealing the involvement of reactive oxygen species and for assessing antioxidants;however, the surgical demands are considerable. Histamine pellet and cysteamine administration focus on hypersecretion of acid and duodenal damage; therefore, they are useful models for drugs with anti-secretory and cytoprotective actions but do not model human disease very well. Reserpine models are useful for studying neurotransmitter deficiency and the vascular mechanisms of ulcer production, but again, more for acute ulcers. Together, these models have been used to evaluate a number of different agents, including antioxidants (quercetin, sinapic acid, N-acetylcysteine), anti-inflammatory agents (mesalazine, gabapentin, apocynin), and cytoprotective and vascular modulators (fluoxetine, tadalafil, fenchone). Although these methods do not perfectly represent human ulcerogenesis individually, they are complementary to one another and allow for a comprehensive analysis of novel therapeutic agents, as well as the assessment of oxidative stress, inflammation, vascular injury, and neurotransmitter depletion hypotheses of peptic ulcer disease.

Keywords: Peptic ulcer, *in-vivo* models, Gastroprotective agents, Gastric ulcer models.

Introduction

Peptic ulcer is an acid -induced ulcers found in the stomach and proximal duodenum which is characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria [1].Clinically, peptic ulcer disease is defined as a deep mucosal injury to the stomach or duodenum that penetrates beyond the muscularis mucosa into the muscle layer. The primary contributors of ulcers include hypersecretion of gastric acid, dietary habits, and stress as primary contributors. Contemporary research, however, has identified *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug (NSAID) use as the two leading etiological factors. NSAIDS are also responsible for the production of gastric ulcer. Aspirin and indomethacin are also responsible for the occurrence of ulcers. Zollinger-Ellison syndrome (ZES) which is caused by gastrin-secreting tumors in the pancreas or duodenum, is also responsible for the prevalence of ulcers.The symptoms include hypergastrinemia which produces excessive acid production, which over whelms protective mechanisms and predisposes patients to recurrent and severe ulcers [2].

Globally, peptic ulcer disease (PUD) remains is a significant contributor to gastrointestinal morbidity. Data from 2019 reported approximately 8.09 million cases, representing a 25.82% increase compared to that in 1990. Yet, paradoxically, the age-standardized prevalence has declined, reflecting improvements in medical care and preventive strategies despite population growth and aging [3].Despite this decline in standardized rates, PUD remains one of the most common gastrointestinal disorders, affecting millions of people annually. Epidemiological studies indicate that 10–15% of adults in developed nations are at risk of developing ulcers during their lifetime. However, the distribution of cases was not uniform. Geographic variation, socioeconomic status, and demographic factors strongly influence both the incidence and prevalence. For example, regions with higher

Helicobacter pylori infection rates or widespread NSAID use tend to report greater disease burden [4].

Despite extensive research, the mechanism underlying *Helicobacter pylori*-associated gastroduodenal lesions remains incompletely defined. This pathogen exerts diverse effects on gastric physiology, producing hypochlorhydria or hyperchlorhydria. Such variability is clinically significant, as reduced acid secretion predisposes to gastric ulceration, whereas excessive secretion is often linked to duodenal ulcer formation. These contrasting outcomes highlight the complexity of host- pathogen interactions in peptic ulcer disease. Cytokines released during infection are considered central mediators because they inhibit parietal cell activity and reduce acid output. However, *H. pylori* also acts directly on the gastric proton pump, specifically the H+/K+ ATPase α-subunit, thereby disrupting acid regulation at the molecular level. In addition, the bacterium activates calcitonin gene-related peptide (CGRP) sensory neurons, which are associated with somatostatin regulation, and simultaneously suppresses gastrin synthesis. These combined actions disrupt the equilibrium between stimulatory and inhibitory signals in the gastric physiology. The downstream consequence of these alterations is increased histamine release. Histamine serves as a potent secretagogue that stimulates parietal and gastric cells to secrete acid and pepsin in excess. This hypersecretion accelerates mucosal injury and contributes to the persistence of gastroduodenal lesions. These abnormalities can be eradicated by therapy, which will lead to adecrease in gastric mRNA and an increase in somatostatin mRNA expression. Overall, the complexity of these interactions underscores the importance of eradication therapy in restoring mucosal balance and preventing ulcer recurrence [5-6].

The main mechanism of NSAID-induced gastroduodenal injury is systemic inhibition of COX-1, which normally drives prostaglandin synthesis. Loss of prostaglandins reduces mucosal blood flow, mucus and bicarbonate secretion, and cell proliferation. NSAIDs inhibit COX-1 reversibly and in a concentration-dependent fashion. Exogenous prostaglandins and COX-2 selective NSAIDs are effective in reducing mucosal damage and lowering ulcer risk [7].

IN-VIVO Experimental Models for Peptic Ulcer

In vivo experimental ulcer models are still used in gastro-duodenal studies and represent an interesting tool for studying the pathways involved in peptic ulcerogenesis (acid hypersecretion, oxidative stress, prostaglandin ablation, and vascular compromise). Regardless of the protocol used, stress induction, irritant, or pharmaceutical agent administration, each reveals a specific pathway in ulcer development and allows the demonstration of drug efficacy. Moreover, the reproducibility and clinico-biological interest of these models make them necessary for preclinical studies on peptic ulcer disease.

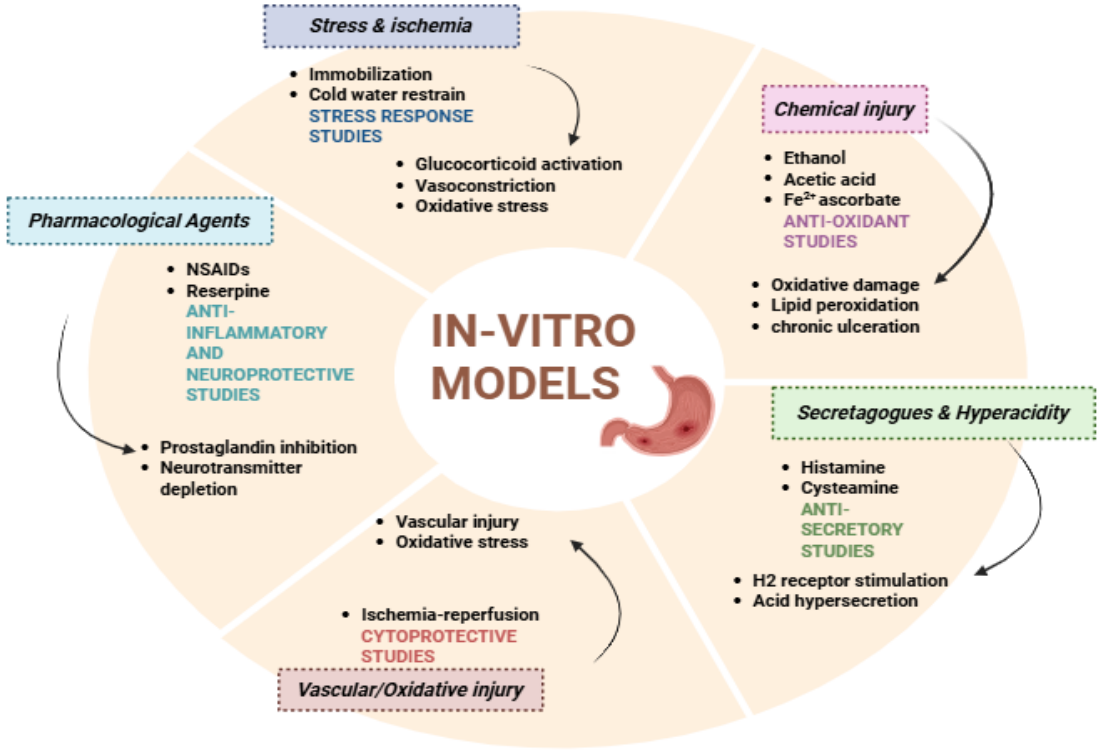

Fig. 1: Representation of different in-vitro models used to study anti-ulcer activity

Following are the different *in-vivo* models for induction of peptic ulcer-

Stress Based Models

Several studies have described methods to reduce the incidence of stress-related mucosal damage. Sucralfate forms a physical cytoprotective barrier by adhering to epithelial cells, thereby protecting the mucosa from acid and pepsin damage.H2 receptor antagonists block the binding of histamine to histamine receptors located in parietal cells. They do this by deactivating the action of H+/K+ ATPase on the surface of the parietal cells. Proton pump inhibitors are also used to study stress-induced ulcers. It acts by inactivating the H+/K+ ATPase enzyme at the surface of parietal cells[8].

Strengths

- Allow comparison of cytoprotective and antisecretory strategies.
- Provide reproducible endpoints (bleeding reduction, pH monitoring) [8].

Weakness

- Preventive drugs reduce bleeding but do not improve mortality or ICU stay.
- Cold restraint stress produces acute superficial lesions that lack chronicity.
- Artificial restraint and hypothermia limit translational relevance [9].

Stress Ulcer through Immobilization Stress

Principle: Stress ulcers are mucosal erosions caused by severe physiological stress. One factor leading to this is glucocorticoid activation caused by immobilization stress, which occurs as a result of immobilization in an external device or confinement during the problem periods of growth. This stimulation of the glucocorticoid response leads to increased gastric acid production, vasoconstriction of the gastric vasculature, and recruitment of inflammatory mediators, causing injury. This results in erosion of the mucosal surfaces and reduced repair.

Procedure: Immobilization stress ulcers were experimentally induced in female Wistar rats weighing 150-170 g. The animals were grouped for theexperimentation. Ten animals were included in each group. The animals were fasted for 24 hours prior to the experiment. Food and water were withheld for 24 hours. After oral or subcutaneous administration of the test compound or placebo, the animals were lightly anesthetized with ether. Their limbs were restrained with wire gauge and suspended horizontally in a dark chamber maintained at 20 °C for 24 hours. At the end of the exposure period, the rats were sacrificed under CO_2 anesthesia. The stomachs weredissectedand placed on a cork support. The ulcers are analysedby a stereomicroscope [10-11].

Stress Ulcers by Cold Water Immersion

Principle: The model demonstrates that cold water immersion causes hypersecretion of acid in the stomach. When rats are exposed to a cold environment, mucosal lesions appear quickly. This occurs due to the hypersecretion of acid, which exacerbates mucosal injury [12].

Procedure: Cold restraint stress ulcers were induced in Wistar rats weighing 150-200 g. Animals are fasted for 16 hours before oral administration of the test compound. The induction of ulcerswasinitiated by placing the animals in vertical restraining cages. They were then immersed in water maintained at a temperature of 22 °C for 1 hour. Following removal, the evan's blue was then injected intravenously through the tail vein. The dye was administered at a dosage of 30 mg/kg per animal.After 10 minutes, the rats were sacrificed under CO_2 anesthesia. After sacrificing the animals, the stomachs were surgicallydissected, ligated, and immersed in formol saline overnight. On the subsequent day, the stomach was opened along the greater curvature, rinsed, and inspected for ulcerative damage. Evan's blue which is used for the staining facilitatesthe visualization of lesions easily. Then the lesions were scored by summing their longest diameters. This approach of model confirms that even brief cold restraint stress for a short duration produces reproducible gastric mucosal lesions[13], [9].

NSAIDS Induced Ulcers

Principle: NSAIDS cause gastro-duodenal ulcers by causing irritation of the mucosa or by systemic inhibition of prostaglandin production. The inhibition of production of prostaglandins causes impaired defense mechanisms and reduced protective secretions and blood flow, causing ulceration and surface damage, compromising epithelial strength, and resulting in ulcer formation.

- **Aspirin-induced gastric ulcers:** The animals were fasted for 24 hours prior to the experiment to enhance ulcer susceptibility. Then the drug was established by oral administration. The dose was administered as a suspension at 200mg/kg to obtain a20mg/ml concentration. After the administration of drug, the animals were observed for the period of 4 hours. After that they were sacrificed and stomachs were excised, and opened along the greater curvature and rinsed with saline water gently to remove debris. ulcer scoring was done macroscopically and subsequently confirmed histologically. the ulcer index was calculated by summing number of lesion counts and severity of ulcers[14].
- **Indomethacin-induced gastric ulcers:** Rats were fasted for 24 hours with water available ad libitum. Animals were weighed using a triple beam balance before the initiation of the experiment. Then, on experimental day, they were administered 0.9% normal saline at 50mg/kg/animal followed by administration of indomethacin at 50mg/kg [15]. After drug induction, the rats were maintained for 8 hours to permit ulcer development. Thereafter the rats were sacrificed using chloroform anesthesia in an airtight plastic chamber. The stomachs were dissected and opened along the greater curvature. The gastric contents were collected, and the stomach was rinsed thoroughly with distilled water. Histological confirmation of ulcer detection was performed[16].

Chemical Injury Model

- **Ethanol-Induced Ulcers**

Ethanol models of ulcers are too numerous to document here, but many have been used to assess the humanly relevant ulcer-healing properties of antioxidants andanti-inflammatory agents. Acetylcysteine was shown to be protective via reducing oxidative stress and maintaining cell membrane integrity [17]. Mesalazine, an anti-inflammatory drug was, shown to have ameliorative effects by decreasing cytokine activity and increasing mucosa restoration. [18]. In addition, sinapic acid was revealed to activate the Nrf_2/HO 1 pathway and inhibit NF B signaling in order to decrease apoptosis and oxidative insult [19]. The advantage of ethanol models is the ability to assess cytoprotective and antioxidant drugs, but the weakness comes from their acute, fast-healing lesions.

Principle: Ethanol administration is a well-established experimental model for producing acute gastric mucosal injury in laboratory animals. It is a widely used model, as the ulcer produced mimics human ulcer pathology and also provides reproducible results. Ethanol directly irritates the stomach lining, resulting in disruption of the protective mucus barrier due to which it reacts with corrosive factors and forms ulcers. Mechanistically, ethanol stimulates excessive secretion of gastric acid, which increases the aggressiveness of gastric juice against the mucosa. Ethanol also increases the synthesis of inflammatory mediators like leukotriene C4. This increases tissue injury. Ethanol also acts on parietal cells and causes histamine release [20].

Procedure: Ethanol-induced gastric ulceration is produced by administering 70% ethanol orally at a dose of 2 mL/kg to rats that have been fasted for 36 hours with water available. Administration of ethanol damage the gastric mucus and produces lesions [21]. After one hour of administration, the animals were sacrificed by the decapitation method. The stomach was dissected and opened along the greater curvature and rinsed to collect gastric content. Histopathology was done to get the desired results [22].

- **Acetic-acid induced ulcers**

The acetic acid model has been used in recent studies to test a wide range of pharmacological agents. It can demonstrate the pharmacological action of various agents on the production of free radicals and their impact on tissue [23]. An extract from Aspergillus awamori has been demonstrated to have an antioxidant, anti-inflammatory, and anti-apoptotic effect in acetic acid-induced colitis [23]. A drug with anti-inflammatory activity, gabapentin was shown to reduce cytokine production and mucosal damage [24]. Apocynin, an inhibitor of NADPH oxidase, was also able to prevent inflammation and oxidative stress in this model [25]. These are just some examples of the wide range of pharmacological agents that have been shown to have effects in this model. The acetic acid model recreates the chronic ulcer appearance seen in humans through inducing a rapid ulcer healing process. As such, it is suitable for research into drugs that are anti-inflammatory and therefore enhance the process of mucosal repair. The weakness of this model is the surgical intervention and the localized nature of the lesions created in this model, which means it is not as physiologically relevant as the other experimental models.

Principle: Acetic acid- induced gastric ulceration is a well-established experimental technique designed to replicate chronic ulcer pathology. When acetic acid is injected into the stomach, it corrodes the stomach lining, harming epithelial cells and provoking inflammation. It causes embolism of submucosal blood vessels, thereby restricting perfusion to adjacent mucosal regions. This results in persistent ischemia affecting both upper and lower mucosal parts and also prevents rapid ulcer healing [26].

Procedure: The ulcers were induced by the surgical intervention under anesthesia. A midline incision was made in the stomach, and 0.05 ml of 30% acetic acid was injected into the submucosal layer of the glandular region. The stomach was washed with saline before abdominal closure to prevent contamination. After two days of recovery, animals began feeding again and were given coral therapy each day for 10 days. On the day following the final dose, animals are sacrificed under anesthesia by cervical dislocation. The stomachs undergo dissection and are removed. The stomachs are opened along the greater curvature and rinsed thoroughly [27]. The ulcer inhibition is determined by:

Ulcer inhibition rate= Control (ulcer index) − Test (ulcer index)/Control (ulcer index)× 100%

- **Ferrous Iron-Ascorbic Acid-Induced Gastric Ulcers**

Principle: Ferrous iron plus ascorbic acid together acts as a potent drug for the induction of ulcers. It is a commonly employed model for research in experimental pharmacology where gastric mucosal injury mediated by oxidative stress is studied. While ferrous iron molecules take part in redox reactions, ascorbic acid molecules act as reductants and thus promote oxidative stress. This leads to an increase in lipid peroxidation in the gastric mucosa and the formation of ulcers. This model is based on the reaction between ferrous iron and ascorbic acid, whereby lipid peroxidation occurs in gastric tissues. In turn, the reactive oxygen species attack membrane lipids and so compromise epithelial integrity. Thus, protective functions are overwhelmed, including mucus production and control of the blood flow rate [28-29].

Procedure: Male albino rats weighing not less than 150g were used for the study. The animals are split into groups and fasted for 18 hours prior to experimentation, but water is still available. A solution of 25 µL of ferrous iron and ascorbic acid made in normal saline is administered for ulcer induction. Then this formulation is injected into the submucosa of the anterior gastric wall using a micro-syringe. After 4 hours following administration, the animals are sacrificed by using suitable anesthesia. Stomachs are removed or dissected and rinsed with saline to remove debris. The ulcer index is worked out based on how severe the lesions appear, how many are present, and the overall surface area. Gastric contents are gathered for determining acidity and pH. Finally, histopathological slides are prepared to inspect cellular changes and to confirm the pathophysiology that leads to ulceration [30].

Vascular/Oxidative Stress-Induced Ulcer Models

Ischemia-reperfusion models highlight the role of oxidative stress and vascular injury in ulcerogenesis. Eugenia punicifolia extract enhanced healing via antioxidant and anti-inflammatory pathways [31]. Phytol showed gastroprotective effects by modulating oxidative stress and inflammatory mediators [32]. Low-dose vanadium attenuated ischemia-reperfusion ulcers by reducing oxidative damage and preserving mucosal integrity [33]. These studies confirm the strength of this model in testing antioxidant and cytoprotective drugs, though its weakness lies in surgical complexity and limited clinical translation.

- **Gastric Ischemia-Reperfusion Injury in Rats**

Principle: Ischemia/reperfusion (I/R) injury is a well-recognized mechanism for producing gastric mucosal damage in experimental models. Such an approach models conditions where interruption and reperfusion initiate oxidative stress and subsequent inflammatory pathways resemble clinical conditions. The process of reperfusion causes production of excessive oxygen and nitrogen radicals. These radicals disrupt cellular membranes and facilitate necrosis, which causes tissue injury and ulcers to form. An increase in the gastric acid leads to the disruption of the protective barrier. This principle comprises combining oxidative stress, immune activation, and acid imbalance [34-35].

Procedure: Wistar rats were used for the study and were weighed prior to the experiment. The rats were anesthetized by the administration of ketamine (70 mg/kg) along with xylazine hydrochloride (10 mg/kg) intraperitoneally. A homeothermic surgical table is used to maintain the temperature at 37°C for the maintenance of physiological stability. The abdominal surface was disinfected with povidone iodine solution. A midline laparotomy was done by clamping the artery atraumatically for about 45 minutes to restrict blood flow. Successful ischemia is confirmed by the absence of arterial pulsations and the pale appearance of gastric tissue. The clamp was removed to allow tissue for reperfusion for about one hour. Animals were sacrificed under anesthesia, and stomachs were dissected and rinsed with cold heparinized saline to collect the gastric mucosa. One part of the sample was treated with 10% buffered formalin, and the other part will be stored at -80°C for biochemical investigation [36].

Acid/Secretagogue Base Models

- **Histamine-Induced Acid Secretion**

Histamine models are reliable models for testing hyperacidity and for screening of anti-secretory or cytoprotective drugs. Fluoxetine was found to delay and inhibit histamine and serotonin-mediated mucosal damage through reduction of ulcer indices in experimentally induced ulcers in rats [37]. Similarly, a study carried out by Narayanamurthy, U., et al. (2019) found that pretreatment with quercetin in guinea pigs reduced histamine-induced gastric ulcers through inhibition of acid secretion and by its antioxidant property. However, the weakness of this model is that it produces acute lesions through excessive acid secretion and is not able to reflect other factors involved in human peptic ulcers [38].

Principle: Histamine is a potent secretory agent which directly influences gastric acid production. When histamine enters into the stomach, it targets H_2 receptors, which are present on the parietal cells of the stomach. This stimulation enhances the activity of the H+/K+ ATPase pump, leading to hydrogen ion exchange and excessive hydrochloric acid release. An overproduction of acid disrupts the protective barrier of the stomach and causes injury to the stomach lining, leading to ulcers[39].

Procedure: Male Wistar rats were used for the study. The rats should be weighing between 200-250 g. Prior to the experiment, animals were kept in hygienic, climatic-controlled rooms with free access to water. Then for the induction of physiological stress in the rats, they were placed in restraint cages. Due to the restricted movement, the physiological stress was induced in the rats. After that, animals were immersed in water maintained at 23 °C for 3.5 hours. After that, rats were administered 2mg/kg of histamine phosphate to induce ulceration by acting on the H_2 receptors present on the parietal cells. After 3.5 hours, animals were anaesthetised and sacrificed. The stomach was exposed by making a midline incision on the stomach and opened along the greater curvature to determine the histopathological studies[40].

Cysteamine-Induced Duodenal Ulcer

Cysteamine is a potent inducer of duodenal ulcers, widely used to study oxidative stress and mucosal injury. Captopril, an ACE inhibitor, showed protective effects by reducing cysteamine-induced duodenal ulcer severity, suggesting a role for modulation of oxidative and vascular pathways [41]. More recently, (–)-fenchone prevented cysteamine-induced ulcers and accelerated healing through antioxidant and immunomodulatory mechanisms, promoting re-epithelialization of gastric mucosa [42]. These findings highlight the strength of this model in evaluating antioxidants, immunomodulators, and cytoprotective drugs, though its weakness lies in producing acute lesions with limited chronic relevance compared to human duodenal ulcer disease.

Principle: The cysteamine-induced duodenal ulcer model is frequently employed in pharmacological research to study the mechanisms of ulcerogenesis and to evaluate the efficacy of antiulcer drugs. Cysteamine acts primarily in the duodenum, where it activates the release of reactive oxygen, which induces oxidative stress. Cysteamine elevates endothelin 1 levels. This causes mucosal changes such as reduced perfusion and oxidative imbalance [43].

Procedure: Ulcers are induced in experimental animals after fasting for 24hours with free access to water. Ulcers are generated with two oral doses of cysteamine hydrochloride (450mg/kg in 10% aqueous solution) at a four-hour interval [44]. Duodenal lesions arise within 24hours on this regimen. Animals are euthanised with an ether overdose 24 hours after the last administration of cysteamine or vehicle. The duodenum, about 5cm long, is delicately cutwhile making sure not to cause any mechanical injury. In other words, the duodenum, roughly 5 cm in length, is carefully excised so as to avoid mechanical damage. The tissue is then incised along

the antimesenteric edge and rinsed with saline in order to wipe away debris and blood clots. After that, the lesions are checked under fivefold binocular magnification, which helps with a crisp view of mucosal injury [44-45].

Reserpine-induced gastric ulcers

To understand the role of neurotransmitter depletion in ulcer formation, the reserpine model is used. Recent studies show that Tadalafil, known as a phosphodiesterase-5 inhibitor, is used against the reserpine- induced gastric ulcer model by showing strong protective effects in ulcer recovery [46], [47]. Its protective actions were linked to- increased mucosal blood flow, antioxidant activity, and modulation of nitric oxide pathways. This demonstrates the value of the reserpine model for testing drugs that target neurotransmitter balance and vascular mechanisms. A limitation, however, is that the lesions induced by this model are acute lesions through artificial neurotransmitter depletion, which may not fully mimic the multifactorial nature of human peptic ulcers.

Principle: Reserpine, which is obtained from the total alkaloid extract of Rauwolfia serpentina, is an effective ulcerogenic agent in experimental animals. The ulcerogenic work is mostly done due to the depletion of neurotransmitters, and especially dopamine. Dopamine plays a critical role in how gastric acid secretion gets regulated, plus it also helps keep the mucosal protection sort of intact. So essentially when reserpine reduces dopamine this increases acid secretion by the stomach and ends up upsetting mucosal balance. Hypersecretion of gastric acid occurs, overwhelming the mucosal barrier, also causes impaired prostaglandin synthesis, diminished cytoprotective mechanisms such as mucus and bicarbonate secretion. This has a dual effect too much acid is produced and very few gastric protective factors driving erosion of the mucosal layer [48-49].

Procedure: Adult albino male rats (120–170g body of weight) are grouped and acclimatized under controlled laboratory conditions to perform the experiment. All experiments are preceded by fasting for 24 h (to sensitize the gastric mucosa), and water is removed 2 h before administering the drugs. The ulcerogenic group gave reserpine (8mg/kg p.o) in Tween 80. Tween 80 has been used as a solubilizing adjuvant used to improve the solubilisation and absorption. Eighteen hours after drug administration, animals are sacrificed by cervical dislocation. The stomachs are removed, opened along the greater curvature, and fixed in 10% formaldehyde saline solution. Macroscopic Observation is made to look for ulcerative lesions. The number of ulcers scored is indicative of severity of ulcerative lesions; and index of ulcers indicates percent damage [50-51].

Conclusion

Models used to study ulcer disease have traditionally been multifactorial, due to the multifactorial nature of peptic ulcer disease itself. Each ulcer model better represents certain aspects of ulcer disease pathogenesis than others. Inducing stress through experimental ulcer models better represents ulcer disease due to oxidative stress and inflammation, ulcer disease due to vascular/compromise and hyperacidity, etc. With their ability to generate acute lesions very uniformly, chemical models are highly beneficial for dissecting the precise pathways through which investigated drugs operate. Their strength lies in reproducibility and mechanistic clarity, making them valuable for investigation of- quercetin, sinapic acid, N acetylcysteine, mesalazine, gabapentin, apocynin, fluoxetine, fenchone, and tadalafil's roles in ulcer healing, for instance, was conducted using chemical models. Limitations of these models include, but are not limited to producing acute lesions only, being very surgical or technically difficult, causing massive amounts of damage not seen in normal human disease, or lack of chronic models. Overall, these models allow for greater understanding of ulcer disease pathogenesis and potential therapeutics.

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