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A REVIEW ON PHARMACOLOGICAL SCREENING OF ANTI ULCER AGENTS

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ABSTRACT: Ulcers are caused by imbalance between the gastro duodenal mucosal defensive factors such as bicarbonate, mucus versus aggressive factors like acid and pepsin secretion. The drug treatment of peptic ulcer has significantly brought down the morbidity and mortality and need of surgical interventions which may be attributed to the advent of H2 blockers and proton pump inhibitors. These symptoms frequently occur several hours following a meal, after the food leaves the stomach but while acid production is still high. Instead of pain, some patients experience intense hunger or bloating. Many animal models are using to induce ulcer to identify the antiulcer property of many new and existed drugs such as Pyloras ligated rat, Stress ulcers, Histamine induced gastric ulcers, Cysteamine induced duodenal ulcers and Dulcerozine induced duodenal ulcers.

KEYWORDS: Peptic ulcer, duodenal ulcer and inflammation.

INTRODUCTION:

Gastro-intestinal disorders [1] are one of the severe classes of human ailments causing maximum discomfort, morbidity and mobility. Peptic ulcer [2-3] is one such GIT disorder. Peptic ulcer is considered as a major health problem, both in terms of morbidity and mortality and it is very common in the present day life of industrialized and civilized countries. Available statistical reports indicate that10% or more of adult population are affected within their life time and peptic ulcer affects individuals invariably from 20 to 60 years of age with males being predominantly affected. Peptic ulcer is benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed acid and pepsin. There are several causes smoking, H.pylori infection, ingestion of drugs and chemicals. Especially consumption of alcohol for a prolonged period, smoking of Cigarette, or chronic consumption of NSAIDs are causing peptic ulcers. The peptic ulcer is mainly caused because of irregulated acid secretion in the body. The symptoms of peptic ulcer are: severe pain and irritation in the upper abdomen. If it is not treated properly, it may result in perforations in the wall of the gastrointestinal tract. Because of the severity of the problem, now world is awaiting for the treatment of it. Before going to do the treatment on the human, we need to check the effects of the

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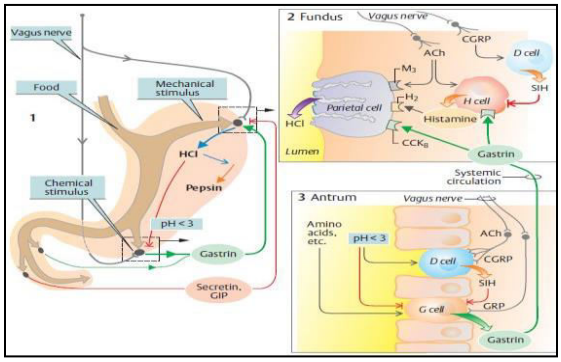
drugs on animal to safe the human life from disaster of the drugs. This review describes such animal screening models for anti-ulcer drugs.

PHYSIOLOGY OF GASTRIC ACID SECRETION [5-8]

- Gastric acid secretion is a complex, continuous process in which multiple central and peripheral factors contribute to a common endpoint: the secretion of H+ by parietal cells.
- Neuronal (acetylcholine (Ach)), paracrine (histamine), and endocrine (gastrin) factors all regulate acid secretion.
- Their specific receptors (M3, H2 and CCK2 receptors respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach.
- The H2 receptor is a GPCR that activates the Gs – adenyl cyclase - cyclic AMP-PKA pathway.
- ACh and gastrin signal through GPCRs that couple to the Gq protein-coupled - inositol 1,4,5-trisphosphate - Ca2+ pathway in parietal cells.
- In parietal cells, the cyclic AMP and the Ca^{2+} - dependent pathways activate H+, K+ - ATPase (the proton pump), which exchanges hydrogen and potassium ions across the parietal cell membrane.

REGULATION OF ACID SECRETION IN THE BODY [9]

Fig. 1: Regulation of acid secretion in the body



APPROACHES TO TREATMENT [10]

Reduction of gastric acid secretion
Neutralization of gastric acid
Ulcer protective
Anti H. Pylori drugs

PHYTO-CHEMICALS USED IN THE TREATMENT OF PEPTIC ULCER [11-15]

- **Allophylus serratus Kurz** is commonly known as Tippani. It belongs to the family Sapindaceae.
- **Aloe vera (L.) Burm.f.** is commonly known as Aloe. It belongs to the family Xanthorrhoeaceae.
- **Curcuma longa L.** is commonly known as Turmeric and also a household remedy for biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis which belongs to the family Zingiberaceae.
- **Butea frondosa Roxb**. is commonly known
- as Flame of the forest .The plant is distributed throughout India and belongs to the family Fabaceae.
- **Capsicum annuum L.** is commonly known as Chilli pepper and it is most widely cultivated throughout the world. It belongs to the family Solanaceae.
- **Carica papaya Linn.** is commonly known as Papaya. It belongs to the family Caricaceae.
- **Cissus quadrangularis L.** is a succulent plant of family Vitaceae.
- **Desmostachya bipinnata (L.)** Stapf is commonly known as Saved gram belongs to the family Gramineae.
- **Excoecaria agallocha L.** is commonly known as Milky mangrove belonging to the family Euphorbiaceae
- **Glycyrrhiza glabra L.,** is a sweet, moist, soothing, flavoring herb commonly known as Liquorice belonging to the family Fabaceae.

SCREENING OF ANTI ULCER AGENTS [12]

Requirements of an ideal model

- Should be simple, reproducible & AMP; allow for easy quantification of results.
- Should induce characteristic ulceration in specific locations.
- Should involve different mechanisms by which ulceration is produced.
- Ulcers produced should not spontaneously heal during observation period.

IDEAL ANIMAL FOR SCREENING ANTI ULCER AGENTS [16]

Majorly used animal model is rats because of continuous secretion of acid, glandular portion of rat stomach analogous to body of stomach in man both anatomically and functionally and being omnivorous resembles man nutritionally. Along with rats, Guinea pigs are used when histamine is used to induce ulcers.

ANIMAL MODELS FOR SCREENING [17-20]

- Anti-secretory activity screening
    - Isolated whole stomach preparation
    - GOSH and SHILD perfused rat stomach preparation
- Gastric anti-ulcer activity screening
    - Pylorus ligation induced gastric ulcers in rats (Shay rat)
    - Drug (NSAID) induced gastric ulcers in rats
    - Ethanol induced gastric ulcers in rats
    - Acetic acid induced gastric ulcers in rats
    - Stress induced ulcers in rats
- Duodenal anti-ulcer activity screening
    - Cysteamine induced duodenal ulcer in rats
    - Duclerozine induced duodenal ulcer in rats
    - Indomethacin and histamine induced duodenal ulcer in rats
    - Histamine induced duodenal ulcers in guinea pigs

ISOLATED WHOLE STOMACH PREPARATION

This method is used for evaluation of H2 – receptor antagonists.

PROCEDURE:

Immature Wistar rats weighing around 40 g are taken for the procedure. Anaesthetize the rats with 30 mg/kg pentobarbitone administered intra-peritoneally. The abdomen is opened and esophagus is ligated close to the stomach. An incision is made in the rumen of the stmach and the contents are washed out with warm Krebs-Henseleit solution. A second incision is made at the pyloric sphincter and polyethylene cannulae are inserted and tied into the stomach via these incisions. The stomach is dissected out. Place immediately into 10 ml organ bath containing Kerbs-Henseleit solution at 37°C. The lumen of the stomach is perfused at a rate of 1ml/min with modified Kerbs Henseleit solution (without Na_2Co_3 and KH_2PO_4) at 37°C. The effluent perfusate from the stomach is passed over a micro dual electrode. The change in pH is converted to a function of H^+ ion activity. The test compounds or secretogogues are added in a volume of 0.5 ml to the Kerb's Henseliet solution bathing the serosal surface of the stomach. After setting up the stomach preparation, the basal H^+ output is allowed to stabilize, both under control and treated. Then measure secretogogue response by measuring the amount of acid secreted at peat response above the predicting basal level.

The rate of acid secretion is measured and expressed as (H^+) moles * 108 per minute

Both solutions are gassed with carbogen (95% O2 and 5% CO2)

Compare the test and standard with that of the control to access the anti-ulcer activity of the drug.

GOSH AND SHILD PERFUSED RAT STOMACH PREPARATION

PRINCIPLE:

The anti-ulcer agent screening is done by continuous reading of acid secretion in the rat, which is stimulated by histamine, acetylcholine and gastrine and that acid secretions can be blocked by anti-ulcer drugs.

PROCEDURE:

Male Sprague Dawley or Wistar rats of weighing 180 g are taken for the procedure. Prior to the experiment, starved the animal overnight by withdrawing the food. Group the rats randomly as four rats in a group. Anaesthetize the animals with 25% urethane solution (0.6 ml/100 g, i.m.). The body temperature is artificially stabilized by means of a heating coil using a rectal thermometer and also trachea is exposed and cannulated for artificial respiration. The external jugular vein is exposed and cannulated with polythene tubes leveled at the tip. The abdomen is opened through midline incision, and pyloric end of the stomach is cannulated. A polythene tube is passed down the oesphagus and tied in the cervical region. The stomach is washed out thoroughly by passing distilled water to the tube. Perfuse the stomach with N/4000 sodium hydroxide at a uniform rate. The concentration of sodium hydroxide is adjusted so that the perfusate under basal conditions has a pH. The perfusate emerges out bathes the micro electrodes which are directly connected to the pH meter. Changes in acid secretion are accessed by pH changes. The gastric secretion is stimulated by continuous i.v. infusion of 100 microgram/kg/hr of pentagastrin or 3 mg/kg/h of histamine hydrochloride or 30 microgram/kg/h of carbachol. The test is injected either prior or after the infusion and measure the inhibition of acid secretion and compare the results with that of standard.

PYLORUS LIGATION INDUCED ULCERS IN RATS

This method is first demonstrated by Shay and co-workers in 1945. Pyloric ligation in rats leads to accumulation of gastric acid in the stomach leading to acute gastric ulceration.

REQUIREMENTS:

Albino Wistar Rats (150-200 g), Ether (Anesthetic), Saline (control), Omeprazole (standard), Test drug (3 different concentrations x, 2x, 4x), NaOH (0.01N), Topfer's reagent (dimethyl amino azo benzene) and Phenolphthalein.

PROCEDURE:

Wistar albino rats of either sex weighing 150 – 200 g are taken for the procedure. Rats fasted for 24 hrs prior to pyloric ligation.

Randomly divided into 5 groups of 10 animals each

Group I: Control vehicle
Group II: Standard drug (Omeprazole)
Group III: concentration of test drug
Group IV: concentration of test drug
Group V: concentration of test drug

Drugs administered once for 2 days and 30 mins prior to ligation. Rats anesthetized with ether. Pyloric ligation procedure:

- The abdomen is opened by a small midline incision.
- Pyloric portion of stomach is slightly lifted out & ligated avoiding traction to pylorus or damage to its blood supply.
- The stomach is replaced carefully and abdominal wall is closed by interrupted sutures.

The drugs are administered subcutaneously immediately after pyrolus. Rats placed in separate cages and allowed to recover. After 19 hrs to pyloric ligation, animals sacrificed by decapitation. Abdomen opened and stomach

dissected out. Contents of the stomach collected in a centrifuge tube. Stomach opened along greater curvature and ulcers observed under 10x magnification.

Ulcer index is calculated: 10/X (X = Total mucosal area/ total ulcerated area)

Intensity of ulcers is scored as below

- 0 -normal stomach
- 1 - superficial mucosal erosion
- 2 - deep ulcer
- 3 - penetrated or perforated ulcer

Contents of the stomach analyzed for Volume, pH, free acidity and total acidity (Titration of the solution against 0.01N NaOH done using Topfers reagent and phenolphthalein as indicators. Volume of NaOH which turns the solution to yellowish orange corresponds to free acidity. Titration is continued till solution turns pink. The total volume of NaOH used up corresponds to total acidity. Acidity (meq/l/100 g) = (Vol of

NaOH X Normality x 100)/0.1) and Mucin and prostaglandin levels (estimated to detect cytoprotective effects).

INFERENCE:

- Ulcer index of test drug compared with control group to detect anti-ulcer effect of test drug. If present, it is compared with that of standard group.
- Other parameters help to infer the mechanism of ulcer protection.
  Eg. Decrease in volume, free & AMP; total acidity: antisecretory action Rise in pH: acid neutralisng action Increase in mucin, PGs: cytoprotective effect.

DRUG INDUCED ULCERS IN RATs

Generally gastric ulceration is produced in rats by certain drugs. The ability of the test drug to protect against the ulceration is observed. Drugs used for the induction of ulcer are NSAIDs like Aspirin, Indomethacin and Ibuprofen. The inhibition of endogenous prostaglandin production leads consequent loss of gastric mucosal defense, which in turns causes the formation of ulcer. It is important model for identifying drugs that could be effective in NSAID induced gastropathy.

PROCEDURE:

Wistar Rats weighing 150 -200 g are taken for the procedure. Rats fasted for 24 hrs in separate cages and randomly divided into 5 groups. The control, standard, test drug are administered once daily for 2 days and 30 mins prior to administration of ulcerogenic agent. Ulcerogens administered by oral gavage. Rats sacrificed 4 - 6hrs later. Ulcer index and analysis of stomach contents have done.

- **Aspirin:** Aspirin is suspended in 1% carboxymethyl-cellulose in water(20mg/ml) and administered the drug with a dose of 500mg/kg orally.
- **Phenylbutazone:** It is administered in a similar fashion as aspirin in a dose of 100mg/kg, p.o.(suspension) or i.p.(solution).
- **Indomethacin:** Indomethacin is administered in a dose of 20mg/kg (4mg/ml dissolved in 0.1% Tween80 solution) p.o.

ETHANOL INDUCED GASTRIC ULCER IN RATS

PRINCIPLE:

Ethanol damages superficial epithelial layers & AMP; inhibits prostaglandin release. An agent that protects against ethanol induced ulcers might be cytoprotective & AMP; exert its action by stimulating release of endogenous prostaglandins & AMP; mucin. However, anti-secretory agents also are effective in this model.

ACETIC ACID INDUCED GASTRIC ULCERS IN RATS

It is the model mimics the chronic pattern seen with peptic ulcer.

PROCEDURE:

Male Donryv, Wistar or Sprague Dawley rats Weighing 250 – 300 g are taken for the procedure. Overnight fasted rats operated under ether anesthesia. Anterior & AMP; posterior walls of stomach clamped with forceps. 0.2 ml of 40% acetic acid injected into clamped portion. After 45 secs, acid removed. Deep round ulcers develop on the anterior & AMP; posterior walls. Respective treatments (control, standard and test) started from 3rd to 10 th day. Rats sacrificed on 10^{th} day. Ulcers respond well to most anti ulcer drugs like PPI, H2 blockers, cytoprotectives.

STRESS INDUCED ULCER IN RATS

Male Donryv, Wistar or Sprague Dawley rats Weighing 250 – 300 g are taken for the procedure. Drugs (control, standard, test) administered once daily for 2 days & AMP; 30 mins prior to applying restraint. Fasted & AMP; lightly anesthetized rats placed on galvanized steel window screen. Limbs are held together in pairs & AMP; tightened with adhesives. After 24 hrs, animal removed, sacrificed and degree of ulceration noted.

WATER IMMERSION INDUCED RESTRAINT ULCER

PRINCIPLE:

Generally exposure of rats to stress will decreases the acid secretion but there occur an increase in secretion towards the pre-stress hours when restrained animal is subjected to additional water immersion. It is important model for identifying drugs that could be effective in gastropathy.

PROCEDURE:

Wistar rats of either sex of weighing 150 – 200 g are taken for the procedure. Group the rats as each group contains 10 rats. The rats are fasted for 24 hrs before starting the test. After the oral administration of test drug or vehicle, the rats are immobilized in the stress cage and they are immersed vertically to the level of the process in a water bath at 22°C for 16 hrs. Remove the animal from the water immersion and dry it. Inject 30 mg/kg Evans Blue i.v. via tail vein. After 10 min sacrifice the animals and remove the stomach of the animal carefully. Filled it with the 1% formalin and stored overnight. In the next day, open the stomach with along a greater curvature, washed in warm water and examined under magnifying lens. Observe the longest diameters of the lesions, measure and summed up to give the total lesion score in mm for each animal, the mean count of each group is calculated. Inhibition of lesion is shown as a control score. Statistically compare the data obtained and give the results as such. The restrain case and immersion in water produce the stress in the rats that in turns increase the acid secretions in the rats and cause the ulcer to it.

CYSTEAMINE INDUCED DUODENAL ULCER IN RATS

PRINCIPLE:

Cysteamine inhibits the alkaline mucus secretion from the Brunner's glands in proximal duodenum and stimulated gastric acid secretion rate. Gastric emptying also delayed and in terms increases serum gastrin concentration, which leads to the formation of ulcer.

PROCEDURE:

Male Wistar or Sprague Dawley rats weighing around 200 g are taken for the procedure. Administer cysteamine Hcl of dose 280 mg/kg orally tree times in a day on the first day of

experiment to the fed rats. For the treated animals: Administer the drugs before 30 min of first dose and again after 24 hrs on the second day. The rats are sacrificed after 48hrs of the first dose of cysteamine Hcl. The duodenal ulcers are developed 2 -4 mm away from the pylorus on the anterior wall of the duodenum and frequently perforate the liver. A small ulcer present on the posterior wall (kissing ulcer) of the duodenum and it is invariably penetrates the pancreas.

The intensity of the duodenal ulcers is evaluated as 0 – No ulcer
1 – Superficial mucosal erosion
2 – Deep ulcer usually with transmural
3 – Perforated or penetrated ulcer

APPLICATIONS:

- Suitable method for studying the pathogenesis of duodenal ulcer
- An effective method for anti-ulcerogenic regimes detection.
- Since some of such chemicals might have a role in the etiology of human duodenal ulcers as well, the structure activity conclusions may helps in the identification of ulcerogenic chemicals in our diet and environment.
-

DUCLEROZINE INDUCED DUODENAL ULCER IN RATS

PROCEDURE:

Male wistar or Sprague dawley rats weighing around 200 g are taken for the procedure. Duclerozine 300 mg/kg, suspended in 5% gum acacia solution, is administered orally as a single dose. The drugs (test/standard) are given 30 min prior to the administration of Duclerozine. The animals are sacrificed after 18 hr of administration.

SCORING:

0 – No ulcer
1 – Superficial mucosal erosion
2 – Deep ulcer usually with transmural
3 – Perforated or penetrated ulcer

APPLICATIONS:

- The lesions developed are analogus to the clinical disease with respect to location and histology.
- The factors responsible for producing the pathological changes are similar in man and animal used.
- The drugs effective against experimental ulcer could be clinically useful.
- The method is dependable, reproducible and easy to perform and results are obtained with in 24hrs.

INDOMETHACIN AND HISTAMINE INDUCED DUODENAL ULCER IN RATS

PRINCIPLE:

A single administration of indomethacin and subsequent dosing with histamine consistently produce lesions at the opposite site of the mesenteric attached in the proximal duodenum of rats. The development of duodenum lesions by indomethacin + histamine induction in rats is due to both an increase in gastric secretion and an impairment of acid induced duodenal HCO_3 secretion.

PROCEDURE:

Wistar or Sprague Dawley rats weighing 150-200 g are taken for the procedure. Grouped rats as such 6-8 rats must in a group. Fast the rats for 24 hrs before the experiment with water ad libitum. Administered 5 mg/kg Indomethacin s.c and subsequently administered 40 mg/kg histamine dihydrochloride 3 times in a day at 2.5 hours interval, beginning after 30 min of the indomethacin injection. Sacrifice the animal after 24 hrs of the procedure and observe it for ulcers. Due to this combined treatment, two lesions are formed at the proximal duodenum and also few lesions at corpus and antrum of the stomach. Statistically compare the data of test and

standard then conclude the activity of the test. The standards for treating duodenum and antrum ulcers are oral cimetidine and 16, 16 – dimethylprostaglanin E2 in a dose dependent manner and also for corpus ulcer is cimetidine.

HISTAMINE INDUCED DUODENAL ULCERS IN GUINEA PIGS

PROCEDURE:

Guinea pigs fasted for 48 hrs are taken for the procedure. Drugs (control, standard and test) given once daily for 2 days & AMP; before 30 mins to drug, administrate histamine. Ulceration induced by injecting 1 ml of histamine solution intraperitoneally. Promethazine 5 mg injected intraperitoneally 15 mins before and after histamine. Animals sacrificed after 4 hrs. Degree of ulceration & AMP; gastric contents assessed.

ESTIMATION OF PARAMETERS:

Estimation of free radical generation: The fundic part of the stomach is homogenised (5%) in ice cold 0.9% saline with a Potter-Elvehzem glass homogeniser for 30 second. The homogenate is then centrifuged at 800× g for 10 min followed by centrifugation of the supernatant at 12000× g for 15 min and the obtained mitochondrial fraction is used for the following estimation. Statistical analysis was done by student's t-test.

Lipid peroxides (LPO): LPO product malondialdehyde (MDA) is estimated using 1, 1, 3, 3-tetraethoxypropane as the standard and is expressed as n mol/mg protein.

Super oxide dismutase (SOD) activity:

Inhibition of reduction of nitro blue tetrazolium (NBT) to blue coloured Formosan in presence of phenazine methasulphate (PMS) and NADH is measured at 560 nm using n-butanol as blank. One unit of enzyme activity is defined as the amount of enzyme that inhibits rate of reaction by 50% in one min under the define assay condition and the results have been expressed as unit (U) of SOD activity/mg protein.

Estimation of mucosal glycoprotein's:

Sample of gastric mucosal scraping is homogenised in distilled water and treated with 90% ethanol and are subjected for the estimation of carbohydrates and proteins using the methods described above for gastric juice contents. Statistical analysis was done by student's t-test.

Estimation of free acidity and total acidity:

One ml of gastric juice is pipette into 100 ml conical flask, added 2 to 3 drops of topfer's reagent and treated with 0.01 N sodium hydroxide until all traces of red colour disappears and the colour of the solution turns to yellowish orange. The volume of the alkali added was noted. This volume corresponds to free acidity. Then 2 to 3 drops of phenolphthalein solution is added and titration is continued until a definite red tinge reappears. Again the total volume of alkali added is noted. Acidity is calculated by: Acidity = Volume of NaOH × Normality of NaOH × 100 / 0.1 × meq/L/100 gm.

Estimation of DNA in gastric mucosa: DNA and protein are estimated in the gastric fundal mucosal scrap homogenised in 2.5 ml of ice cooled 0.6N perchloric acid (PCA). The concentration of DNA is expressed as µg DNA/mg protein.

Estimation of glandular weights of stomach: The weight of the glandular portion of stomach is calculated by subtracting the weight of the whole stomach minus rumen and is expressed as mg/100 g body weight of the animals. Statistical analysis was done by student's t-test.

Estimation of Ulcer index (Ui):

Ui = mean degree of ulceration × % group of ulceration /100

%inhibition = (ulcer index in control - ulcer index in test) ulcer index in control x 100

Estimation of gastrin: In order to determine the gastrin levels in plasma, blood is collected by cardiac puncture, centrifuged, and the plasma is analysed for gastrin levels with double-antibody liquid phase radioimmunoassay.

Histological studies:

Gastric tissue samples from each group were fixed in 10% formalin for 24 h. The formalin fixed specimens are embedded in paraffin and section (3-5µm) and stained with haematoxylin and eosin dye. The histochemical sections are evaluated by light microscopy.

Recent advances

- Gastrin transgenic mice
- H.pylori infected mice models: Mice
- infected with type I & AMP; II strains of H.pylori showed delayed healing of acetic acid induced chronic ulcers.

SUMMARY AND CONCLUSION:

The knowledge of the pathophysiology of gastric ulcer disease remains incomplete. Current pharmacological management of gastric ulceration is directed primarily at the reduction or neutralization of gastric acid secretion despite evidence that patients with this disease often exhibit normal gastric secretory activity [21]. A relatively new ulcerogenic procedure such Pyloras ligated rat, Stress ulcers, Histamine induced gastric ulcers, Acetic acid induced chronic gastric ulcers, Cysteamine induced duodenal ulcers, Dulcerozine induced duodenal ulcers, Dimaprite induced duodenal ulcers, Duodenal ulcers following Infusion of pentagastrin and carbacol, Indomethacin and histamine induced duodenal ulcers, MPTP induced duodenal ulcers is described. These procedures are simple, effective and produced a reliably high incidence of gastric glandular lesions in a variety of animal species. In some cases, these lesions penetrate the muscularis mucosa and as such may be called ulcers. It is suggested that the above mentioned all types of induced models procedure meets the established criteria for a useful experimental ulcer model and thus represents a viable research tool [22]. The natural and synthetic products can be scientifically evaluated to establish therapeutic efficacy by the above mentioned techniques.

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