A REVIEW ON THE POTENTIAL OF FULVIC ACID IN GASTRIC ULCER MANAGEMENT: A HOLISTIC APPROACH

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ABSTRACT:

Gastric ulcers are a very common gastric disorder characterized by damage to the lining and making ulcers. Millions of folks across the world get afflicted with this disorder. Current treatment options often have limited efficacy and significant side effects, emphasizing the need for alternative approaches. Fulvic acid, a naturally occurring compound with antioxidant, anti-inflammatory, and antimicrobial properties, has shown promising potential in managing gastric ulcers. This review peeks into how fulvic acid might play a role in dealing with ulcers in the stomach and takes an integrated approach. Looking closely at the anatomy and physical structure of stomachs, we are also studying how fulvic acid affects the health of the inner lining of the stomach, reduces inflammation and also stops ulcers from forming. Our study aims to provide insight into the therapeutic benefits of fulvic acid in preventing and treating gastric ulcers, offering a potential alternative to conventional treatment options. This review is bringing forward exciting new methods for managing ulcers in the stomach, and these methods are natural and really effective. The approach upholds outstanding digestive health and general wellbeing greatly.

KEY WORDS: Gastric ulcer, fulvic acid, NSAIDS, Cyclooxygenase (COX-1 &COX-2 enzymes), Antiulcerogenic activity.

I. INTRODUCTION:

ANATOMY OF STOMACH:

1. DIVISIONS:

On the top left side of the abdomen is a muscular organ called the stomach[1].The stomach is divided in five regions: the cardia, the fundus, the body, the pyloric antrum, and the pylorus. Proximal to the cardia is the lower esophagus, and the two blend together.The pylorus connects the stomach with the duodenum [2].

2. MORPHOLOGY AND GLANDULAR ORGANIZATION:

The wall of the stomach is covered by a peritoneal layer which forms the serosa.Underneath the serosa, three layers of smooth muscles make up the muscular layer or muscular propria.

- The middle, circular layer creates the pyloric sphincter.
- The outer layer is made of longitudinal muscle fibers.
- The inner layer is made of oblique muscle fibers.

The gastric mucosa consists of columnar glandular epithelium. The composition of the glandular epithelium varies with the different regions of the stomach. In the cardia the epithelium mostly produces mucous via mucus producing cells. The body of the stomach contains most of the parietal cells and chief cells.Parietal cells mostly produce acid, ghrelin, and leptin. Chief cells produce pepsin and leptin. Enterochromaffin- like cells (ECL cells) which produce histamine are mostly in the body of the stomachwhile G cells which produce gastrin are in the antrum. D cells producing somatostatin are found both in the body and the antrum of the stomach.

3. BLOOD SUPPLY:

The stomach receives its blood supply from the celiac artery with the right and left gastric arteries supplying the lesser curvature, and the left and right gastroepiploic arteries supplying the greater curvature[2].

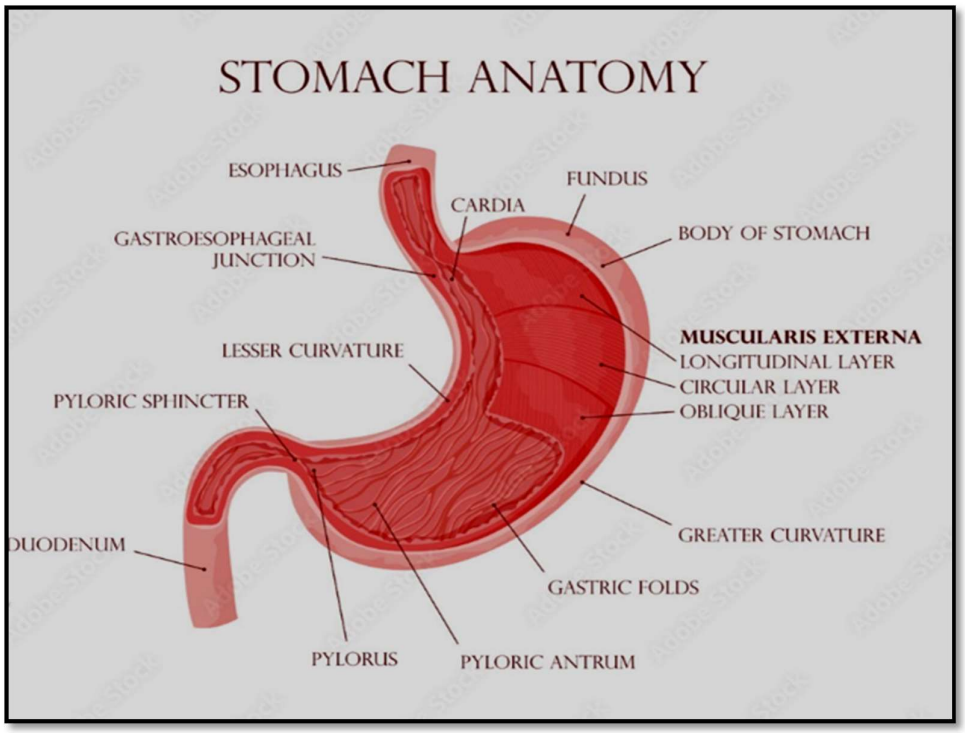


Figure no. 01- Anatomy of stomach

PHYSIOLOGY OF STOMACH:

In addition to the stomach's secretary function, the stomach also has a muscular component, as do all structures within the alimentary canal.The muscularis externa is composed of smooth muscle cells that orient in three directions: oblique layer, a circular muscle layer, and the longitudinal layer. Together these three muscle layers are responsible for the gastric movements needed to break the food bolus into smaller components[3].The receptive relaxation phase is mediated from a vasovagal response that occurs when oral and pharyngeal mechanoreceptors are stimulated, and consists of a brief relaxation during chewing and swallowing[4] . A food bolus, which consists of partially digested food from the mouth and the esophagus, is processed by the stomach into chyme, which is a more readily absorbable substance by the small intestine. The stomach accomplishes this food processing through forceful back-and-forth churning motions by the inner oblique layer of the muscularis externa[3] .Acid secretion is a very important non-immunological defence against invading pathogens as well as being an important mechanism for vertebrates to have more complex diets.The means by which this is regulated and effected is Stimulation of acid secretion involves the translocation of H+/K+-ATPases to

the apical membrane of the parietal cell. When the cell is resting (not stimulated), H+/K+-ATPases are located in vesicles inside the cell. When the cell is stimulated, these vesicles fuse with the plasma membrane, thereby increasing the surface area of the plasma membrane and the number of proton pumps in the membrane. The regulation of acid secretion is a complex milieu of neurological, endocrine and paracrine factors to maintain an optimal acid output[4].

TYPES OF ULCERS:

1. GASTRIC ULCER:
   When a Gastric ulcer occurs in the stomach, it is called a gastric ulcer. The bacterium called H. pylori cause this type of ulcer. Antacids are used as a treatment option for gastric ulcers; the patient usually starts to feel well after two or three weeks of using antacids. Also, ulcer patients are advised not to use too much oily and greasy food and also asked to limit the consumption of acidic foods[1].
2. DUODENAL ULCER:
   A duodenal ulcer is a sore in the membrane of the duodenum.Duodenal ulcers are more common than gastric ulcers, and are caused by increased gastric acid secretion as opposed to gastric ulcers. Duodenal ulcers are commonly found anteriorly, and rarely thereafter[5].

3. ESOPHAGEAL ULCERS:
   Esophageal ulcers are lesions that occur in the esophagus (food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Oesophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs and smoking.

4. BLEEDING ULCER:
   Internal bleeding is caused by a Gastric ulcer that has been left untreated. When this happens, it is referred to as a bleeding ulcer, this is the most dangerous type of ulcer and it requires immediate treatment.

5. REFRACTORY ULCER:
   Simple Gastric ulcers that have not healed after at least 3 months of treatment are called refractory ulcers.

6. STRESS ULCER:
   A series of lesions (or lacerations) known as stress ulcers can develop in the esophagus, stomach, or duodenum. These are typically only seen in people who are seriously unwell or under a lot of stress(1) .

II. GASTRIC ULCER:

Gastric ulcers are defined as open sores or lesions that develop within the mucosal lining of the stomach, characterized by a breach in the gastric mucosa extending into the deeper layers of the stomach wall. These ulcers typically exhibit a round or oval shape and can vary in size from small erosions to larger defects[(6)].In every case of chronic benign gastric ulceration two factors are present: hydrochloric acid, and progressive erosion of an area of mucosa by the digestive action of the gastric juices[(7)].Sometimes, people feel that upper abdominal pain may increase after lunch or dinner, and sometimes people vomit materials which looks like coffee grounds,blood comes with stool, have black or tarry stools, all these symptoms cause severe abdominal pain. The gastric ulcer pain may increase with eating and we feel burning-like sensation in ourstomach[(8)].Most patients with a gastric ulcer do not feel symptoms when their stomach is empty, as eating produces stomach acid. This can lead to food avoidance when undiagnosed, which becomes easier since the bacteria also affects appetite. Despite never feeling hungry the patient begins to lose weight. Gastric ulcers can be hard to diagnose. The symptoms may be confused for other common digestive system ailments from acid reflux to gallstones, depending on the location of the ulcer. There are just three ways to confirm there is an ulcer:

• Treat the patient, and hope to improve the symptoms. This is not recommended for patients who are sensitive to potent antibiotics, however, and treatment takes at least one week.

• Do an endoscopy there. This is, however, considered an invasive procedure and can normally only be done on an empty stomach.

• Carry out a test on carbon-14. That is to take a patient's breath sample and then give them a cap[(5)].

PATHOPHYSIOLOGY OF GASTRIC ULCER:

1. *ACID SECRETION:*

The parietal cell present in the oxyntic glands of the fundus and of the stomach is the source of the production of gastric acids. The parietal cell is the clear winner among all epithelial cells in its ability to produce a gradient in the concentration of hydrogen ions. The pH of the gastric lumen is often as low as 1 to 2, as opposed to a blood pH of 7.4. For example, this difference in concentration of 6 logs is much greater than the average difference in concentration of hydrogen ions between the urine and the blood .

2. *REGULATION OF ACID SECRETION:*

Histamine is released in the gastric mucosa from advanced mast cells and possibly diffuses to the parietal cell where it interacts with a particular receptor, the H2 receptor. Histamine's interaction with the H2 receptor is inhibited by antagonists of the H2 receptors such as cimetidine, ranitidine or famotidine[(5)].

3. *MUCOSAL PROTECTION:*

The gastrointestinal mucosa was protected by the powerful effects of digestive of pepsin and acid is a vitally important in biologic . When luminal pH is low 1.5, maintain the above pH 6 of duodenal mucosa and gastric. The epithelial cell affects peptic destruction and resists acid. The connection between gastric epithelial cells with tight junctions was assisted to prevent penetration of acid[(9)].

4. *NSAID'S:*

The pathophysiology of these complications has mostly been ascribed to NSAID's action on the cyclooxygenase (COX) inhibition and the subsequent prostaglandin (PG) deficiency . Due to their high chemical reactivity and the existence of uncoupled electrons inside their molecules, reactive oxygen species (ROS) play a role in the pathophysiology of gastric mucosal injury. As a result, there is tissue damage, which is mostly caused by increased lipid peroxidation. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are the products of the metabolism of lipid peroxides. The local rise in MDA and 4-HNE levels indicate ROS-dependent tissue damage[(1)].

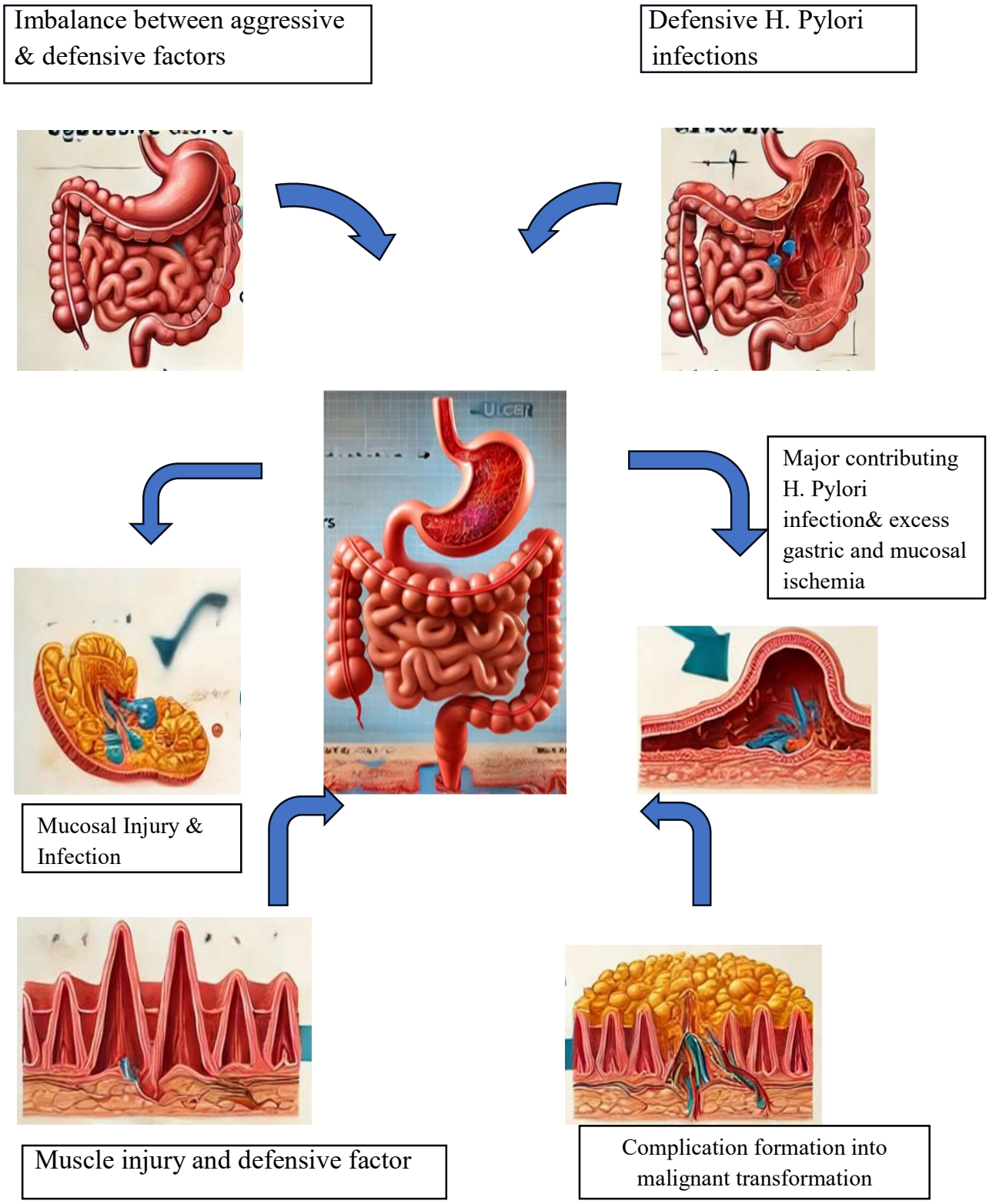


Figure no.02- Pathophysiology of gastric ulcer

CAUSES OF GASTRIC ULCER:

Table no.01- Causes of Gastric ulcer

ACUTE ULCERATION	CHRONIC ULCERATION	BOTH ACUTE & CHRONIC ULCERATION
✓ Extensive burns ✓ Head injuries ✓ Encephalitis ✓ Intracranial tumors ✓ Cerebrovascular lesions	✓ Chronic dyspepsia ✓ Chronic hypoxia ✓ Zollinger-Ellison syndrome ✓ Renal failure ✓ Daily vomiting with dehydration with weight loss	✓ Chronic-iron deficiency anaemia ✓ Massive haemorrhage ✓ Use of wide range of drugs including, Acetylsalicylic acid, Phenylbutazone, Indomethacin or Corticosteroids.

FACTORS AFFECTING GASTRIC ULCER:

Table no.02- Factors affecting gastric ulcer

S.NO	THE FACTOR RESPONSIBLE FOR ULCER
1.	Drug-induced injury: NSAID, Aspirin, chemotherapy
2.	Infection-induced inflammation: CMV, H-pyloric, HSV-1, Syphilis, TBC
3.	Physical-mechanical trauma: balloon, Cameron, Nissen
4.	vascular compromise: tobacco, vasculitis, ischemia
5.	caustic injury: damage radiation
6.	post-mucosal ablation
7.	Inflammatory condition Idiopathic: Behcet's Crohn's
8.	Aggravation through smoking

DRUGS USED IN GASTRIC ULCER:

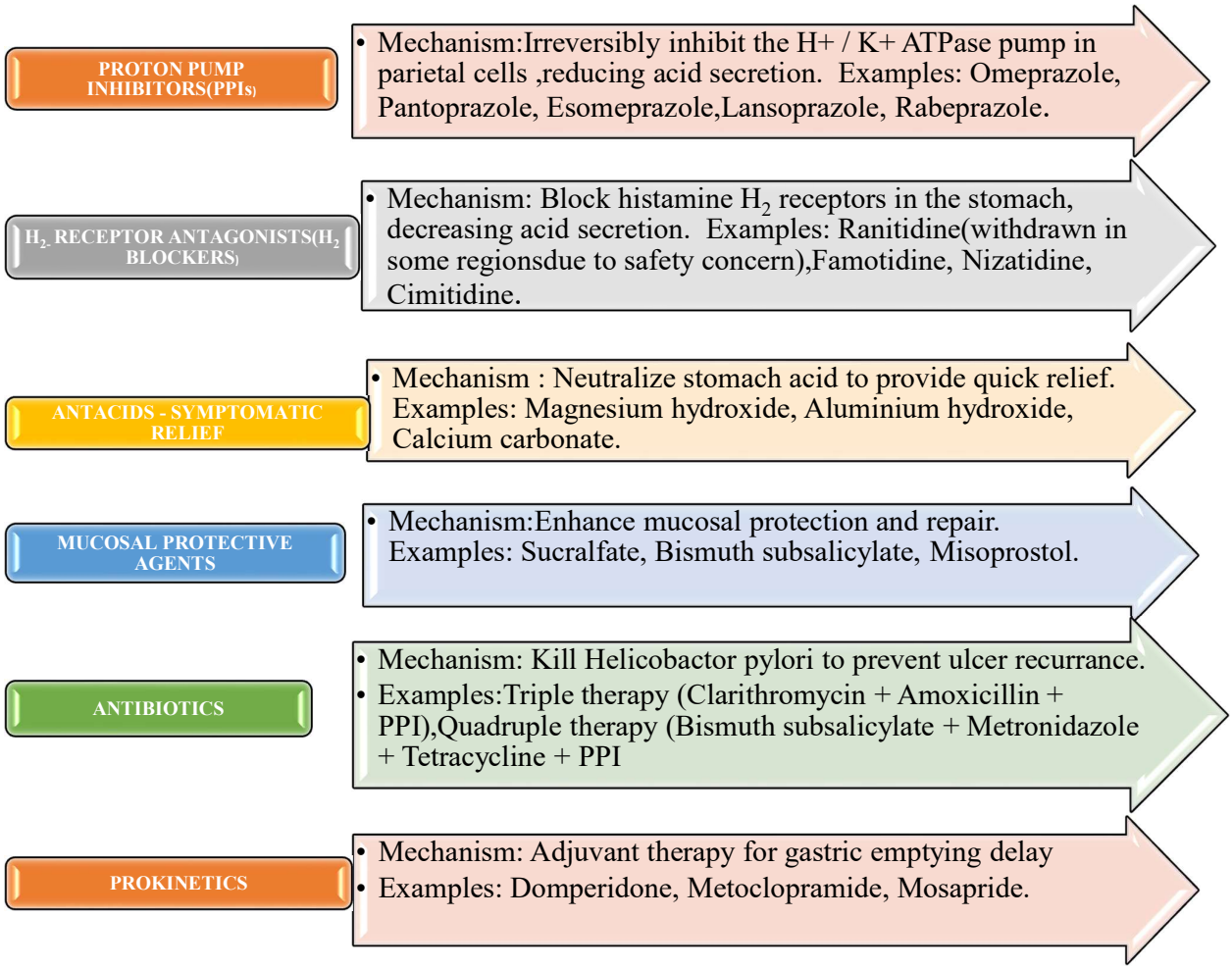


Figure no.03-Drugs used in gastric ulcer

NOVEL THERAPEUTIC APPROACHES:

Gastric ulcers remain a significant health concern globally, necessitating continuous exploration of novel therapeutic approaches beyond conventional treatments. This note provides an overview of emerging pharmacological agents, innovative endoscopic techniques, and integrative medicine approaches for the management of gastric ulcers, highlighting their potential benefits and clinical implications. They focusing three novel approaches for gastric ulcer in emerging pharmacological action, Innovative endoscopic techniques, Integrative medicine approaches. Various alternative therapies, such as acupuncture, acupuncture, and traditional Chinese medicine (TCM), offer adjunctive approaches to ulcer management. These therapies focus on restoring

balance and harmony within the body, addressing underlying imbalances contributing to ulcer pathogenesis. Novel therapeutic approaches hold promise for advancing the management of gastric ulcers, offering innovative strategies to promote healing, reduce recurrence, and improve patient outcomes. Emerging pharmacological agents, innovative endoscopic techniques, and integrative medicine approaches represent exciting avenues for further research and clinical application, fostering a comprehensive and personalized approach to ulcer management[6] .

III. FULVIC ACID:



Figure no.04- Fulvic acid

- Fulvic acid (FA) is an organic compound extracted from peat and various forms of coal, such as lignite and worn coal, which is created as a result of the breakdown of microbial matter, animal and plant leftovers, as well as the buildup of processes . FA is a low-molecular-weight molecule with high biological activity dissolved in alkali and acid liquids. In addition, FA has been shown to be compatible with all aquatic creatures. Numerous reactive functional groups are included in fulvic acids, such as hydroxyl, quinine, phenol, and carboxyl groups which confer the following beneficial activities on Fulvic acid antioxidant activity, anti viral activity

,anti – inflammatory effects, stimulation of immunity, and metal chelation[11] .

- Fulvic acid has various useful effects due to its functional groups. Studies on the physiological actions of Fulvic acid exerted on the living body are gradually being carried out. The possible application of coal-derived Fulvic acid as an antimicrobial and antioxidant substance has been described and the inflammatory property of coal-derived Fulvic acid has been also reported . It has been used externally to treat haematoma, phlebitis, desmorrhexis, myogelosis, arthrosis, polyarthritis, osteoarthritis and osteochondrosis. Likewise, Fulvic acid has been taken orally as a therapy for gastritis, diarrhoea, stomach ulcers, dysentery, colitis and diabetes mellitus. Fulvic acid and humic substances isolated from soil and water reservoirs have been reported to stimulate neutrophil and lymphocyte immune function . It is especially reactive with metals, forming strong complexes with Fe3+, Al3+ and Cu2+ 9, 10. FA and its related compounds have no toxic compounds . Humic and Fulvic acid are commonly used as a soil supplement in agriculture and as a human nutritional supplement [12] .

- Medically important humic substances such as humic acid, fulvic acid and humin are found abundantly in peat, weathered coal, and other humified sources. Humic substances are used in medicine as antimicrobial, anti-inflammatory, and antitumor agents, as liver stimulants, as remedies for gastric ulcers to stop bleeding, and for the treatment of skin burns.Natural humification products have been used to develop pharmacologic agents with diverse applications in vivo[13] . Fulvic acid is the bioactive component of shilajit, which is recognized to have immunomodulatory and hallucinogenic effects. Typically, a humic substance is composed of this bioactive ingredient [14] .

- A preliminary clinical study exists which investigates the efficacy of probiotics in combination with fulvic acid in gastrointestinal (GI) disorders. Unfortunately though, all groups including ones with fulvic acid see no improvement in Gastrointestinal Quality of Life Index (GIQLI) and Visual Analogue Scale (VAS) scores for GI symptoms. This study does showcase the safety of fulvic acid intake over a 12-week

period. Even though fulvic acid is not shown to have an effect in the previous study, fulvic acid isolated from Shilajit shows promise to be anti ulcerogenic during several battery tests in albino rats (15).

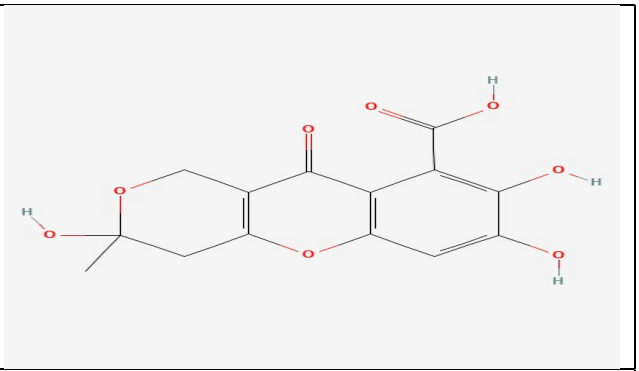
HISTORY :

Vedic Age: Hindu culture is the world's oldest and is preserved in the Vedas, which are a treasure trove of knowledge. Ayurveda is a branch of the Atharva Veda, which is the knowledge of living well. There are differing viewpoints about the Vedic era. There is no inscription of Shilajit during the time of the Vedic period, according to Bala Gangadhar Tilak.

Pauranic Age: The author of Brihat Rasaraja Sundara cites Shilajit, which is listed in Puranas as a mineral ore and a material of Mandarachala Parvat. Gods and Demons utilised Mandarachala and Vasuki Naga for churning purposes during the Samudra Manthana period. Shilajit Promsing Ayurvedic Molecule Some minerals were created in Mandarachala Parvata due to friction, one of which being Shilajit, the precise date of which was unknown[6].

STRUCTURE & ORIGIN:

Table no.03- Structure & origin of Fulvic acid

STRUCTURE	
MOLECULAR FORMULA	$C_{14}H_{12}O_8$
MOLECULAR WEIGHT	308.242 g / mol.
IUPAC NAME	Acide 3, 7,8,- trihydroxy -3- methyl – 10-oxo-4,10 – dihydro-1H, 3H, - pyrano [4, 3 – b]chromene – 9 –carboxylique.
CATEGORY	Anti ulcerogenicactivity,Anti – microbial activity, Anti- oxidant activity, Cardioprotective effects.

PHYSICAL PROPERTIES	Fulvic acid is a yellowish – brown amorphous powder.
SOLUBILITY	Soluble in water for all PH levels and also soluble in chloroform and methanol.
ADVERSE DRUG REACTIONS	Allergic reactions: Skin rashes, itching. Fatigue and weakness. Mineral deficiencies.

Fulvic acids are therefore the component which is soluble in water under all pH conditions and is, in general, lower in molecular size and weight. This means that fulvic acids have higher oxygen but lower carbon contents than the high molecular-weight humic acids. In addition, fulvic acids contain more functional groups of an acidic nature (COOH) and its total acidities are considerably higher than for humic acids [(20)] . Another important difference is that the oxygen molecules found in fulvic acids is contained in mainly known functional groups (COOH, OH, C=O) where as with humic acids, the oxygen occurs as a structural component of the nucleus . It is further distinguished in that it is light yellow in colour as compared to the dark brown/black colour of the humic acids . It is apparent that humic substances consist of a heterogeneous mixture of compounds and as such, no single structural formula is possible[(17)].

MEDICINAL PROPERTIES:

Among the many indications for which these humic acid type compounds are used include: burns, injuries, bone fractures, dislocations, disease of the skin, neuralgia, arthritis, poisoning and as an anti inflammatory, antibacterial, anticancer, a diuretic and an immune stimulating agent. Other diverse conditions claimed to respond to these compounds are diabetes, cholesterolemia, eczema, amnesia, epilepsy, asthma, dysmenorrhoea and digestive disorders - including ulcers (17) .

PHARMACOLOGICAL ACTIVITIES:(14,16,15,18)

- Immuno modulatory activity
- Anti - microbial activity
- Anti - diabetic activity
- Anti - oxidant activity
- Anti - viral activity
- Cardioprotective effects
- Anti - stress effects

- Anti - ulcerogenic & Inflammatory effects.

FULVIC ACID USED IN GASTRIC ULCER:

Studies were carried out on fulvic acid(shilajit) samples collected from different locations to evaluate their possible role as antiulcerogenic and antiinflammatory agents. It was found that fulvic acid (shilajit) increased the carbohydrate/protein ratio and decreased the gastric ulcer index, indicating an increased mucus barrier[21]. Shilajit has reduced the stomach ulcer index and raised the carb/protein ratio, all of which point to an enhanced mucus barrier . Fulvic acids have been demonstrated in a study to decrease the occurrence of duodenal ulcers in an animal model when combined with 4′-methoxy-6′ carbomethoxy biphenyl [14] .Shilajit was also found to have potent antiinflammatory activity in all three models of acute, subacute and chronic inflammation. Shilajit, at a dose of 50 mg/kg was also found to significantly reduce carrageenan-induced hind paw oedema in rats, having an effect comparable to phenylbutazone (100 mg/kg, i.p.) and betamethasone (0.25 mg/kg, i.p.). Shilajit is perhaps the first agent to possess both antiulcerogenic and antiinflammatory activities and this unique property of shilajit can be safely utilized in clinical practice[18] .Shilajit's phenolic and triterpenoid components, as well as its fulvic acids, have shown to be effective against ulcers caused by constraint stress. The combinations offered strong resistance to ulcerogens' effects on mucosa, as well as preventing mucosal cell shedding. Shilajit also improved the carbohydrate/protein ratio and reduced the stomach ulcer score, indicating a stronger mucus barrier [21]. Non-steroidal anti-inflammatory medications (NSAIDs) limit the synthesis of prostaglandins, which reduces pain and edoema. This is accomplished by suppressing the activity of the cyclooxygenase (COX)-1 and -2 enzymes. However, since prostaglandins are important mediators of multiple components of GI mucosal defence, inhibiting their production with NSAIDs decreases the mucosa's resilience to damage while also interfering with healing processes. Selective COX-2 inhibitors, which were predicted to decrease prostaglandin production at sites of inflammation but not in the GI tract, were supposed to be the answer to this problem. Shilajit is unusual in this regard since it has both antiulcerogenic and antiinflammatory properties and may be safely used in clinical settings as GI sparing anti-inflammatory medicines[16] .

APPLICATION:

BIOMEDICAL APPLICATION:

fulvic acid produced on a commercial scale are used in veterinary and human medicine. Several studies of the medicinal properties of materials fulvic have been reported .It was found that fulvic acids administered prophylactically to rats decreased significantly the extension of gastric damage induced by ethanol. TPP administered to rats with experimental gastric and duodenal ulcers significantly accelerated the healing process. The main reason for the increasing attention devoted to fulvic acids can be explain by their antiviral, profibrinolytic, anti-inflammatory and estrogenic activities . The potential of fulvic substances to form chelate complexes with heavy metals (such as cadmium) enable them to be used for the elimination of heavy metals from living organisms. Fulvic materials in aquatic systems and water sediments have been observed to be closely connected with efficacy of hydrotherapy [(19)] .

IV. CONCLUSION:

Gastric ulcers pose a significant burden on public health worldwide, with varying prevalence rates across different regions. In India, the prevalence of gastric ulcers remains a concern, influenced by factors such as H. pylori infection, lifestyle habits, and access to healthcare services. Epidemiological studies in India have reported varying prevalence rates, highlighting the need for further research to understand the regional disparities and develop targeted interventions[(6)].Fulvic acid also improved the carbohydrate/protein ratio and reduced the stomach ulcer score, indicating a stronger mucus barrier. Non-steroidal anti-inflammatory medications (NSAIDs) limit the synthesis of prostaglandins, which reduces pain and edoema. This is accomplished by suppressing the activity of the cyclooxygenase (COX)-1 and -2 enzymes. However, since prostaglandins are important mediators of multiple components of GI mucosal defence, inhibiting their production with NSAIDs decreases the mucosa's resilience to damage while also interfering with healing processes. Selective COX-2 inhibitors, which were predicted to decrease prostaglandin production at sites of inflammation but not in the GI tract, were supposed to be the answer to this problem. Shilajit is unusual in this regard since it has both antiulcerogenic and antiinflammatory properties and may be safely used in clinical settings as GI sparing anti-inflammatory medicines [(16)]. A multifaceted

approach integrating pharmacological and non-pharmacological interventions, guided by individual patient characteristics, is essential for optimizing ulcer management. Continued research and innovation are imperative to enhance treatment efficacy, minimize adverse effects, and improve patient care in the realm of gastric ulcer management [6].

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