

Ulcer - Review on Types, Anti-ulcer Drugs, Anti-ulcer Medicinal Plants, Anti-ulcer Drug Market, Diagnostics and Current Global Clinical Trials Status

Devansh Mehta^{1*}

Abstract: An ulcer is disease of epithelial cells of body or organ which represents an open sore in the lining of epithelial cells or deep lesion in the specific region resulting into its degradation thus disrupting the normal physiology of the organ affected. The damage can be to the extent of bleeding, which is commonly known as bleeding sore. Ulcer is known to exist in pre-historic era with, published cases around 3000 BC. Hippocrates the “father of medicine”, (460 - 370 BC), defined ulcer when he first demarcated cancer terming it as *carcinomas* and *carcinoma* and mentioned it as non-ulcer forming and ulcer forming tumors. The present review focuses on history of ulcer, its types, pathophysiology, Anti-ulcer drugs, Anti-ulcer medicinal plants, diagnostic tests for ulcers and current status of global clinical trials conducted on ulcers. The review is drafted via an exhaustive literature review from popular scientific search engines mainly, pubmed, science-direct, google scholar as well as articles present in google search. Author strongly believes in maintaining proper balanced diet to ward off or restrict the occurrence of ulcer in humans. He also believes that traditional medicines should be researched more and more, followed by inculcating it into modern medical practice for the benefit of *homo-sapiens*. Traditional medicines or to point out clearly, the medicinal plants have wider range of therapeutic advantages in the proper management of disease, as they have better pharmacological activity along with low incidence of side effects or the adverse effects. Anti-ulcer therapeutics has wider market globally citing the fact of prevalence of ulcers in humans and animals. Medicinal plants also thus have huge market for themselves in our ultimate goal of providing healing touch to the diseases person. Clinical trials are happening around the globe, including India, in their effort to come up with specific therapeutic strategies to deal with ulcers and occurrence of other diseases. Time will be no far, when clinical trials conducted, would help in bringing out clear therapeutic goal to reduce the occurrence of ulcers and better management of this disease to serve the mankind.

INTRODUCTION

An Ulcer is disease of skin both which is lining the human body externally and its internal viscera which can be demarcated as an open sore in the lining of epithelial cells or deep lesion in the specific region which vitiates and would lead to bleeding and turn out as bleeding sore or bleeding ulcers. ^[1]

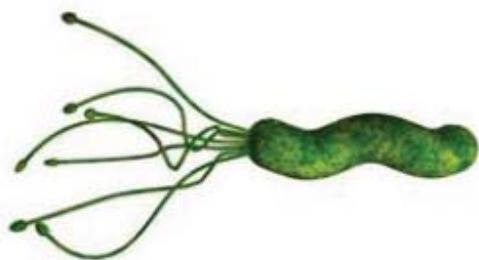
HISTORY

The earlier description of ulcer dates back to an era of 3000 BC and even before that. *Hippocrates* (460-360 BC) known as “father of medicine”, described an ulcer while defining, Cancer and termed it as *carcinomas* and *carcinoma* referring them as non-ulcer forming and ulcer forming tumors. ^[2] In pre-16th century Hippocrates himself described gastric ulcer and symptoms related to it. He even described the management of ulcer, which could be seen in *Corpus Hippocraticum*, a compilation of Hippocrates work by his followers. ^[3] The great Arabic physician Avicenna (980-1037) studied the relationship between gastric pain and the mealtimes. ^[4] The first recorded case of gastric ulcer was described by the Italian physician named Marcello Donati (1538-1602) who reported the case in 1586. During that age it was clear that gastric pain and ulcer had very close relationships and often depended upon the lifestyle and eating habits of the person. The first clear description of the symptoms and morbid anatomy of gastric ulcers was attributed to an English physician, Matthew Baillie in the

year 1793 followed by his first publication on ulcer in the year 1799. In 1875, G Bottcher and M Letulle hypothesized that ulcer was caused by a bacteria, however, no one believed them at that time. As it was thought that bacteria couldn't survive the acidic conditions and the use of antibiotics was deemed as quackery. T Schwann (1810-1882) discovered Pepsin in 1834 and it was clear to the scientific fraternity as another known cause of peptic ulcer. During the age 1889 spiral-shaped bacteria had been identified in both mucosa and gastric contents of ulcer patients, this was followed by observation of *Helicobacter pylori* by Howard steer in the biopsies of patient with the ulcer in the year 1971. Revolution in the medical science came in the year 1982, when *Helicobacter pylori* was first identified and cultured separately and was revealed as one of the known cause for peptic ulcer by John Robin Warren and Barry Marshal the two Australian physicians, for which they were also awarded Nobel prize in 2005, which proved Koch's 3rd postulate that the pathogenesis of ulcer and many diseases including cancer lied in the presence of a bacteria. As we look at the dawn of history related to ulcer, the scientific investigations were followed by treatment methodologies applied by medical practitioners, the treatment goals and management of diseases have seen drastic changes including proper management and cure of ulcer. During 1920's, milk was thought to cure gastritis and problems associated with gastric region. During that time it was thought that giving milk through nasal-gastric tube could cure or heal the ulcer. Soon this was changed to surgical options during 1930's to 1960's when vagotomy or surgical removal of parts of stomach were thought to be the treatment options to eradicate ulcer from the diseased individual. During 1980's cimetidine was found to cure

¹I. E. S. Management College and Research Centre, Bandra West, Near Lilavati Hospital, Mumbai-400050, Maharashtra, India.
E-mail: devanshm84@gmail.com

*Corresponding author



A drawing of the *H. pylori* organism. The Gram-negative spirillum measures about 3.0 by 0.5 micrometers. Its four to six flagella power it. Source: Concrete Bob Software.

Figure 1: *Helicobacter pylori* [6]

gastric ulcer and with more knowledge on the pathogenesis of ulcer i.e. due to acid, cimetidine and ranitidine were introduced to cure ulcer as by then it was clear that acid was the main culprit in causing ulcer in most of the cases. After the revolutionary discovery of pathogen i.e. *Helicobacter pylori* the treatment goals changed to the use of antibiotics and bismuth followed by use of acid blockers. [5] After the discovery of *Helicobacter pylori* during the age of 1995, almost 75 % patients with ulcer were treated with anti-secretory agents or medications and only 5 % received antibiotic therapy. This was followed by national campaign to educate the masses about the known cause of ulcer i.e. *H. pylori* and changed the treatment options available with the medical fraternity. [5]

It took two decades to understand that *H. pylori* was causative agent for an ulcer, numerous investigations and animal models were established to come up with the mechanism via which *Helicobacter pylori* establishes itself in gastric environment and is responsible for the pathogenesis of gastric ulcer. More than half of the population of world is affected by *H. pylori*, only 5-10 % develop ulcer. [5]

ULCERS TYPES

Different types of ulcers have been demarcated by medical scientists and are known by the origin or place of occurrence in human body. Ulcer types known till now are Pressure ulcers, Genital ulcers, Ulcerative dermatitis (*itis* means inflammation), Anal fissure, Diabetic foot ulcer, Corneal ulcer (based on specific region of occurrence), Mouth ulcer also known as Aphthous ulcer (Canker sores), Peptic ulcer, Venous ulcer, Stress ulcer, Ulcerative sarcoidosis, Ulcerative lichen planus, Ulcerative colitis, Ulcerative disposition. However, the most common types of ulcers are:

1. Peptic Ulcer: This type of ulcer is related to pepsin and can occur at different regions.

2. Gastric Ulcer: Ulcer happens in the stomach region and is often known as Stomach ulcer.

3. Duodenal Ulcers: This type of Ulcer occurs in the duodenal region of the GIT tract or Gastro-intestinal tract.

The other less common forms of ulcers are:



Figure 2: Peptic ulcer [9]

1. Esophageal Ulcer

Esophageal Ulcer usually occurs in the lower end of a patient esophagus. Esophageal ulcers as other types of Ulcers are caused by the harmful bacteria.

2. Bleeding Ulcer

Sometime internal bleeding is caused by a peptic ulcer if that ulcer has been left untreated for a long time. When this occurs, it is now referred to as a bleeding ulcer and is the most dangerous type of ulcer. It requires an immediate treatment.

3. Refractory Ulcer

Simple peptic ulcers that have not healed after at least 3 months of treatment are called refractory ulcers.

4. Stress Ulcer

Stress ulcers consist of a group of lesions and usually found in the esophagus, the stomach or the duodenum. Stress Ulcer is normally present in the people who have other illness or are critically ill.

5. Chronic Leg Ulcer

It affects around 1 % of world population. Leg ulceration is often regarded as a disease of elderly people. Since it is a chronic disorder the age distribution is heavily weighted towards the elderly and with an aging population this trend is likely to continue. It is, however, notable that a substantial proportion of the patients were under age 60 at the time of the survey. More revealing is the age at the onset of the first episode of ulceration. More than one third of the patients had ulcers before they turned to 50 and more than two thirds before the age of 65. [7]

Peptic Ulcer

Peptic ulcer or Peptic ulcer disease (PUD's) are ulcers associated with the Pepsin (An enzyme which occurs in stomach, which breaks down proteins), which can occur both in Gastric or Duodenum region. Treatment of Peptic ulcer was revolutionized after the discovery of H₂ receptor antagonists, which led to, the principle of acid suppression therapy, for peptic ulcer an alternative to the followed

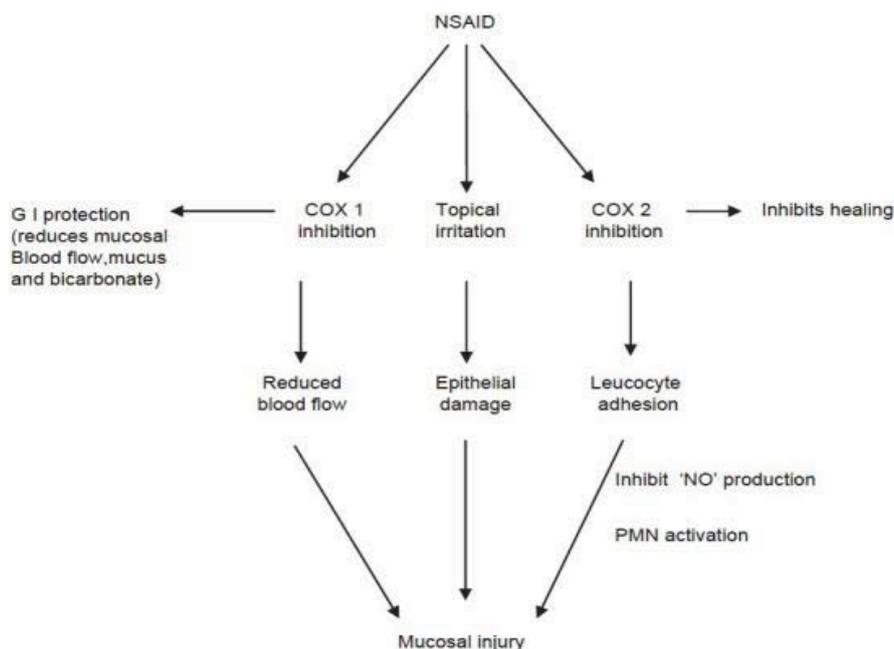


Figure 3: NSAID's causing PUD's [10]

practice of surgical intervention in the form of gastric resection, vagotomy, etc. After the discovery of *Helicobacter pylori* organism as the causative factor, a triple drug regime was identified to treat peptic disease which was further modified to sequential therapy to avoid antibiotic resistance. The management of peptic ulcer disease and its complications remain a surgical challenge.

Peptic ulcer or PUD's occurs because of an imbalance between aggressive factors (gastric acid and pepsin) and defensive factors (gastric mucus, bicarbonate, prostaglandins). About 25 percent of patients with this disease have a serious complication such as hemorrhage, perforation, or gastric outlet obstruction. Peptic ulcer can be diagnosed either by direct visualization using an endoscope or by using contrast radiography. Various class of drugs are used in the treatment of this disease like H_2 antagonists, Proton pump inhibitors, Prostaglandin analogues, Antacids, Ulcer protectives and Anti-*H. pylori* drugs. History of Peptic ulcer dates back to 350 BC, when it was first acknowledged by Diocles of carystos, Celsius and Galen (131-201 AD). It was also noted in history the direct relation between acid and ulcer and common understanding was, no acid, no ulcer. Medical science had studied peptic ulcer in detail and postulated different types of Peptic ulcer depending upon its location in human body and pathophysiology associated with it. Types of peptic ulcers are gastric ulcer, duodenal ulcer, acute peptic ulcer and chronic peptic ulcer. [8]

1. Pathophysiology of Peptic Ulcer

The pathogenesis of peptic ulcer disease is understood through examination and involves an imbalance between defensive factors (mucus bicarbonate layer, prostaglandins, cellular regeneration, mucosal blood flow) and aggravating factors (hydrochloric acid, pepsin, ethanol, bile salts, drugs). NSAIDs play an important role in the pathogenesis. Pathogenesis of Peptic ulcer also lies in the imbalance of

Endogenous and Exogenous factors. Among the Endogenous factors are visceral neurotransmitters, hormones (Acetylcholine, Gastrin, Histamine, Somatostatin, Choleosystokinin), Second messengers Ca^{+2} and Genetic factors and the Exogenous factors are bacterial infection i.e. *Helicobacter pylori*, NSAID's, Alcohol, Psychogenic factors and dietary habits. Figure 3 describes the pathophysiology related to NSAID's causing peptic ulcer disease. The size of Peptic ulcer may range from several millimeters to several centimeters. During the age from history till present, the occurrence of peptic ulcer has changed from maximum cases in males compared to females to the rate of equal prevalence in both men and female. Reason behind occurrence of peptic ulcer range from, infections due to *Helicobacter pylori*, to genetic reasons, use of Anti-inflammatory drugs commonly NSAID's (*Non-steroidal anti-inflammatory drugs*), Alcohol dependence, smoking or occurrence of (bile and pancreatic) enzymes in stomach. [10]

Pressure Ulcers

Pressure ulcers are type of ulcers on the derma region of the body. It is called as pressure ulcer as the certain degree of pressure on the skin, which, leads to obstruction of blood flow to skin, causes a severe condition of ulcer. The prevalence of pressure ulcers is high for the bed ridden patients and patients who are accustomed to spinal injury and at on wheelchair. Pressure ulcer can happen at any area of body, which is under the pressure. The pathophysiology of pressure ulcer lies in the fact that certain degree of pressure causes obstruction of skin nature. The blood vessels are not able to nourish the skin at the area of pressure and leads to development of ulcer. Thus pressure ulcer is disease of soft tissue and mostly affects the bed ridden or wheel chair person, who is either dealing with chronic disease, coma, paralysis, or spinal cord injury. Pressure ulcers are high for the hospitalized patients. Pressure ulcers are also responsible for high rate



Figure 4: Pressure ulcer [12]



Figure 5: Genital ulcer [14]

of morbidity and mortality for the hospitalized patients. Depending upon the extent of damage to the skin or area or occurrence, Pressure ulcers have been classified into different stages, i.e., Stage 1 - Non-blanchable erythema, Stage 2 - Partial thickness, Stage 3 - Full thickness skin loss, Stage 4 - Full thickness tissue loss, Unstageable and suspected deep tissue injury. It is very important for proper management of bed-ridden patients as, if appropriate care is not given to patient, apart from Chronic illness, the patient may develop ulcer at the specific area under pressure or under constant friction. [11]

1. Pathophysiology of Pressure Ulcers

Pressure ulcers are ulcers which develop at the specific area where blood vessels are damaged and lead to obstruction of blood to the specific region. If proper blood supply is restricted at the specific region, it will hamper the proper nourishment of skin and will lead to ulcer. [11]

2. Occurrence of Pressure Ulcer

Pressure Ulcers are more prevalent to the elderly people, as they have limited mobility due to age factor and have ageing skin. As the person ages his degree of mobility gets limited and would lead to development of ulcer at the specific region under pressure and will lead to Pressure ulcer.

Proper management and prevention guidelines would help in dealing and restricting the occurrence of pressure ulcer. The treatment option includes scraping the dead skin in the wound developed or region of ulcer. Proper dressing and cleaning of wound follows next and regularly changing the site of pressure by adjusting the patient in different positions points out the proper management of pressure ulcers. [11]

Genital Ulcers

Genital ulcers represent ulcer in the genital areas like scrotal ulcers, of both men and female. It's known to cause due to sexually transmitted diseases such as Genital herpes, Syphilis, Chancroid or chlamydia trachomati, Granuloma inguinale, Lymphogranuloma venereum. The causes may be attributed due to chronic skin diseases, or skin cancer. Around 70 % to 80 % of Genital ulcers are to infection from HSV-1 (Herpes simplex virus) or HSV-2. [13]

Ulcerative Dermatitis

It is a skin disorder leading to degradation of skin area and may transform to painful and at times bleeding. The main organism causing Ulcerative dermatitis is *Staphylococcus aureus*. Ulcerative colitis caused by bacteria could also result to stress and patient may develop stress ulcer and disease complications. [15]

Diabetic Foot Ulcer

Diabetic foot ulcer, is ulcer of foot region and mainly is one of the complication of diabetes. During diabetes many complication occur in patient's body, like, mechanical changes in conformation of the bony architecture of the foot, peripheral neuropathy and arteriosclerotic peripheral arterial disease. All these factors occur in high degree among diabetes patients. Thus as the name suggests, its diabetic foot ulcer. [16]

Stress Ulcer

Stress ulcers are deep, focal mucosal damage penetrating the submucosa with high risk for gastro-intestinal bleeding. Stress may be physical stress or psychological stress. Stress ulcers mainly occur in Chronic disease patients, like those who are suffering from Cancer, Spinal injury, respiratory diseases. Stress ulcers occur in almost 75 % of hospitalized patients. [17]

CHEMOTHERAPY OF ULCER

Ulcer is a chronic remitting and relapsing disease lasting several years. The goals of anti-ulcer therapy therefore are, Relief of pain, Ulcer healing, Prevention of Complications and prevention of relapse. Anti-ulcer drugs are classified as, 1) Agents which help in reduction of gastric acid secretion, 2) Agents which neutralize the gastric acid, 3) Ulcer protective agents and 4) Anti-helicobacter pylori agents. Table 1 describes the chemotherapeutic options available for medical practitioners in dealing with ulcer and proper management of ulcer. [18]

As *Helicobacter pylori* has been known as reason behind the pathogenesis of Ulcer, new treatment therapies are available for proper management of *Helicobacter pylori* induced ulcers. [18]

It includes, Triple therapy for 14 days: Proton pump inhibitors + clarithromycin 500 mg plus metronidazole 500

Table 1: Anti-Ulcer Drugs Classification [18]

Classification	Drugs
1. Reduction of Gastric acid secretion H ₂ Histamines Proton Pump Inhibitors Anticholinergic drugs Prostaglandin analogue	Cimetidine, Ranitidine, Famotidine, Roxatidine Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Dexrabeprazole Pirenzepine, Propantheline, Oxyphenonium Misoprostol
2. Neutralization of Gastric acid Systemic Non-systemic	Sodium bicarbonate, Sod. Citrate Magnesium hydroxide, Mag. Trisilicate, Aluminium hydroxide Gel, Magaltrate, Calcium carbonate
3. Ulcer Protectives	Sucralfate, Colloidal bismuth subcitrate
4. Anti-H.pylori drugs	Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

Table 2: Medicinal Plants having Anti-ulcer Property [17-25]

Common Name	Botanical Name	Parts Used	Effects	Reference
Tulsi	<i>Ocimum sanctum</i>	All parts	Anti-ulcer, Antibacterial	[23]
Tippani	<i>Allophylus serratus</i>	Leaves	Antiulcer	[24]
Shaparni	<i>Desmodium gangeticum</i>	Root Extract	Inflammation, typhoid, Anti-ulcer	[25]
Neem	<i>Azadirachta indica</i>	Dried Bark	GIT disorders	[26]
Indian Sarsaparilla	<i>Hemidesmus indicus</i>	Extract of Leaves	Antidiarrheal, Anti-ulcer	[27]
Satavari	<i>Asparagus racemosus</i>	Root extract	Anti-diarrheal, Anti-ulcer	[28]
Triphala	<i>Terminalia pallida</i>	Plant extract	Anti-ulcer	[29]
Aamla	<i>Embilica officinalis</i>	Fruit extract	Anti-ulcer	[30]
Gotu Kola	<i>Centella asiatica</i>	Fresh juice	Anti-ulcer	[31]
Brahmi	<i>Bacopa monniera</i>	Fresh juice	Anti-ulcer	[32]
Apple Bananas	<i>Musa sapientum</i>	Fruits	Anti-ulcer	[33]
Pappeta	<i>Carica papaya</i>	Seeds	Anti-amoebic, Anti-ulcer	[34]
Pausanto	<i>Kielmeyera coriacea</i>	Stem	Anxiolytic, Anti-ulcer	[35]
Brindle Berry	<i>Garcinia cambogia</i>	Fruit extract	Anti-ulcer	[36]
Winter melon	<i>Banincasa hispida</i>	Fruits	Anti-ulcer, epilepsy	[37]
Wild pipal	<i>Ficus arnottiana</i>	Fruits	Anti-ulcer, Demulcent	[38]
Indian devil tree	<i>Alstonia scholaris</i>	Whole plant	Anti-ulcer	[39]
Indian mulberry	<i>Morinda citrifolia</i>	Fruit	Anti-ulcer, Anti-diabetic	[40]
Indian borage	<i>Plectranthus amboinicus</i>	Whole plant	Diuretic, Anti-ulcer	[41]
Babul	<i>Acacia Arabica</i>	Leaves, Gums	Ulcer, Wound	[42]
Garlic	<i>Allium sativum</i>	Bulb juice	Antiulcer	[43]
Boabab	<i>Adansonia digitate</i>	Leaves and Bark	Antiulcer, syphilitic ulcer, irritable inflammatory ulcer disease	[44]
Bael tree	<i>Aegle marmelos</i>	Fruits	Antiulcer	[45]
Kattalai	<i>Aloe vera</i>	Leaves and powder	Anti-ulcer	[46]
Custard apple	<i>Annona squamosal</i>	Leaves	Anti-ulcer	[47]
Kanchanara/ Orchid tree	<i>Bauhinia variegata</i>	Bark and roots	Anti-ulcer	[48]
India or Nepal barberry	<i>Berberis aristata</i>	Root and wood	Anti-ulcer	[42]
Beetroot	<i>Beta vulgaris</i>	Roots	Anti-ulcer	[49]
Slow match tree	<i>Careya arborea</i>	Leaves, stem and bark	Anti-ulcer	[50]
Arasha-maram	<i>Ficus religiosa</i>	Bark and Leaves	Anti-ulcer	[51]

mg or Amoxicillin 1 g twice a day (tetracycline 500 mg can be substituted for amoxicillin or metronidazole). [19]

Quadruple therapy for 14 days: Proton pump inhibitors twice a day + metronidazole 500 mg three times daily plus bismuth subsalicylate 525 mg + tetracycline 500 mg four times a day. [19]

The control of acid-peptic disease represents a major triumph for modern medical fraternity and pharmacology. Out of the many classification of Anti-ulcer regimens, it has been proved that proton pump inhibitors are in superior class and have great advantage in terms of proper management of the peptic ulcer diseases. These agents largely have replaced the use of misoprostol and sucralfate, although the latter still is a low-cost alternative for

prophylaxis against stress ulcers. The delay in maximal inhibition of acid secretion with the PPI's (Proton pump inhibitors) i.e. 3 to 5 days, makes them less suited for use on an as-needed basis for symptom relief. In such scenario use of H₂ receptor antagonists, although less effective than proton pump inhibitors in suppressing acid secretion, have a more rapid onset of action that makes them useful for patient-directed management of mild or infrequent symptoms. [19]

NEWER ANTIULCER DRUGS

AN5; A 4-phenyl-tetrahydroisoquinoline derivative has been found through research as an effective Anti-ulcer agent. Upon comparison studies with cimetidine and

Table 3: Current CT Status [56]

Clinical Trial	Status and Region
A pilot trial of the use of ReCell Autologous cell harvesting device for venous leg ulcers Helicobacter eradication Aspirin Trial (HEAT)	Recruiting, Active, UK Active, recruiting, UK
Evaluation of lightweight fiberglass heel casts in the management of ulcers of the heel in diabetes	Active, recruiting, UK
Misoprostol for small bowel ulcers and obscure bleeding due to Aspirin Or NSAID's	Active, recruiting, UK
A clinical study of Vranari guggulu and Vrana lepa in the management of diabetic foot ulcer	Active, recruiting, INDIA
Effect of herbal medicine Vranari Guggulu and Vrana Iepa for diabetic foot wound	Active, recruiting, INDIA
Comparison of two treatment regimens, sequential therapy and concomitant therapy for treatment of Helicobacter pylori in patients with perforated duodenal ulcer.	Active, recruiting, INDIA
Clinical Study on Diabetic foot and its management with Katupila and blood letting	Active, recruiting, INDIA
A clinical trial to study the evaluation of exudate management and adhesion of Aquacel A foam adhesive dressing in pressure ulcer	Active, recruiting, INDIA
An open clinical trial to determine the efficacy of Manjitti kudineer and Manjitti nei in chronic non-healing ulcers, burns and scalds	Active, recruiting INDIA
Efficacy and safety of troxipide extended release tablet in patient with gastritis and/or gastric ulcer	Not recruiting, INDIA
A clinical trial to study effectiveness and safety of Revaprazan tablets in comparison with Omeprazole capsules in patients suffering from Peptic ulcer or Acute Gastritis	Not recruiting, INDIA

ranitidine it was found that AN5 had higher antiulcer activity with maximal antiulcer activity shown at the dose of 1 mg/ kg. [20] A new parasympatholytic agent, Ba-5473 has been researched upon to find an effective anti-ulcer agent. Through the clinical studies it was found to have potent Antiulcerant property in the cases. [21]

HERBAL REMEDIES (TRADITIONAL MEDICINES)

Traditional system of medicine has been in use by *Homo sapiens* since years, man started learning from the nature and depending upon the nature for his mundane actions. Gradually and slowly a fundamental knowledge (in other words traditional system of medicines) got developed via accidental experiments or chance discoveries. The first record of practice of traditional medicine by humans comes from the tablet around 2600 B.C. old. The tablet mentions the significance and use of oils from *Cedrus species* (cedar), *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora species* (myrrh) and *Papaver somniferum* (poppy juice). No matter how much advance in allopathic medicine or chemotherapy is there, the changes of adverse effects or side-effects cannot be ruled out. Therefore there is need to find an alternative therapy for the cure of disease which has negligible adverse impact on the patient. The answer lies in the use of traditional medicines and herbal remedies citing their low-incidence of side-effects. Table 2 describes the medicinal plants having antiulcer effects. [22]

DIAGNOSTIC TESTS FOR ULCER

The diagnosis of ulcer depends first investigating the history of the patient. The investigations are carried forward only after thorough examination of ulcerants which are responsible for causing ulcer, like mainly, history of smoking, NSAID's intake, Stress if any, alcoholic or not. A routine examination through endoscopy lays one of the strategies to diagnose ulcer. After the revolutionary discovery of *Helicobacter pylori*, there are many tests

available to tests its examination. Urea breath test, test for presence of *Helicobacter pylori* antigen, Stool antigen tests to check presence of *H. pylori*. There may be normal test conducted like Complete blood count test, to check whether there has been blood loss or not, like in case of bleeding ulcers. These are the main strategies to come up with proper diagnosis of ulcer. [52] Diagnosis for Pressure ulcers depend upon physical examination of site of occurrence followed by routine test for blood like Complete blood count or also known as CBC and tissue culture as directed by the healthcare practitioner. Tissue culture is necessary to examine the growth of any kind of bacterial or fungal infections. If found the treatment would include antiulcer drugs along with antibiotics. [53]

GLOBAL MARKET FOR ANTI-ULCER DISEASES

During literature survey it was found that anti-ulcer drugs have huge market in the global drug industry. Gastro-intestinal tract drugs contribute 11 % of the global pharmaceutical market. In Indian scenario, the Indian pharmaceutical market is at present \$ 20 billion dollar market. 11 % of \$ 20 billion drug market accounts for \$ 2.2 billion dollar market. Another study projects that Anti-ulcer market which falls under Gastro-intestinal drug market is around Rs. 8413 crore as per IMS 2015 report. It is estimated that Indian pharmaceutical market would reach \$ 55 billion dollar market by 2035, which, makes the total GIT (Gastro-intestinal tract) market to \$ 6.05 billion dollar market by 2035. [54]

CLINICAL TRIAL STATUS

Clinical trials are part of drug development process and include the study or examination of the lead compound on humans. There are different phases under which clinical trials are conducted. The companies have to take prior permission from the heading body to initiate the trials. Only when the lead compound has potential of significance to wide range of population the clinical trials are conducted.

In the present review the current clinical trials which are conducted across globe have been included. Table 3 highlights some of the clinical trials happening across globe. [55]

CONCLUSION

Ulcer has a known history for morbidity and mortality in humans. Ever since the age of Hippocrates and till present times, drastic changes were seen in disease pathophysiology and treatment goals. Chemotherapy has evolved to great extent and continues to do so with newer findings by the scientist across globe. No matter how much research is done to find an effective molecule, the chances of side effects or adverse effects cannot be ruled out. Thus, the prime focus on developing traditional medicines or herbal cure shall be carried out. There are lots of clinical developments happening across the globe. The author feels the times will change the whole or complete management of ulcer and other diseases and we will become more advance in treatment strategic terms.

REFERENCES

1. Ulcers digestive [online]. 2006 [cited 2016 january 29]; available from url: <http://www.encyclopedia.com/topic/ulcer.aspx>.
2. A brief history of cancer: age old milestones underlying our current knowledge database [online]. 2014 april 22 [cited 2016 january 29]; available from: url: https://www.researchgate.net/publication/264675408_a_brief_history_of_cancer_age-old_milestones_underlying_our_current_knowledge_database.
3. Hippocratic corpus [online]. 2015 november 23 [cited 2016 january 29]; available from: url: https://en.wikipedia.org/wiki/hippocratic_corpus.
4. Avicenna [online]. 2016 [cited 2016 january 29]; available from: url: [https://books.google.co.in/books?hl=en&lr=&id=w1sthfc4wsc&oi=fnd&pg=pa1&dq=avicenna+\(9801037\)+studied+the+relationship+between+gastric+pain+and+the+mealtimes.&ots=31uaqr3wqp&sig=wkbgozww0tn1vhjfbqak5qex-dy#v=onepage&q&f=false](https://books.google.co.in/books?hl=en&lr=&id=w1sthfc4wsc&oi=fnd&pg=pa1&dq=avicenna+(9801037)+studied+the+relationship+between+gastric+pain+and+the+mealtimes.&ots=31uaqr3wqp&sig=wkbgozww0tn1vhjfbqak5qex-dy#v=onepage&q&f=false).
5. Kidd M, Modlin I M. A century of helicobacter pylori. Digestion, 59:1-5, 1998.
6. Helicobacter pylori [online]. 2016 [cited 2016 january 29]; available from: url: http://www.helico.com/images/o_helicobacter-pylori.png.
7. Types of peptic ulcer-topic overview [online]. 2014 november 14 [cited 2016 january 29]; available from: url: <http://www.webmd.com/digestive-disorders/tc/types-of-peptic-ulcers-topic-overview>.
8. What is peptic ulcer disease [online]. 2016 [cited 2016 january 29]; available from: url: <http://www.webmd.com/digestive-disorders/digestive-diseases-peptic-ulcer-disease>.
9. Peptic ulcer [online]. 2016 [cited 2016 january 29]; available from: url: <https://www.carilionclinic.org/sites/default/files/164748951.jpg>.
10. Mertz H R, Walsh J H. Peptic ulcer pathophysiology. Med Clin North Am, 75(4):799-814, 1991.
11. Pressure ulcers [online]. 2014 september 10 [cited 2016 january 29]; available from: url: <http://www.nhs.uk/conditions/pressure-ulcers/pages/introduction.aspx>.
12. Pressure ulcer [online]. 2016 [cited 2016 january 29]; available from url: <http://www.polariswoundcare.com/images/pressure-ulcer-a.jpg>.
13. Genital ulcer disease [online]. 2013 february 01 [cited 2016 january 29]; available from: url: <http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-4-3-eng.php>.
14. Genital ulcer [online]. 2016 [cited 2016 january 29]; available from: url: http://images.rheumatology.org/image_dir/album75674/md_99-12-0045.tif.jpg.
15. Ulcerative colitis [online]. 2013 july 04 [cited 2016 january 29]; available from: url: https://en.wikipedia.org/wiki/ulcerative_dermatitis.
16. Diabetic ulcers [online]. 2015 september 08 [cited 2016 january 29]; available from: url: <http://emedicine.medscape.com/article/460282-overview>.
17. Prophylaxis and management of stress ulceration [online]. 2001 [cited 2016 january 29]; available from: url: <http://www.ncbi.nlm.nih.gov/books/nbk6992/>.
18. Tripathy K D. Essentials of medical pharmacology. Jaypee Brothers Publishers, New Delhi, 17th edition, 647, 2014.
19. Goodman and Gilman's. The pharmacological basis of therapeutics, McGraw Hill, NY, 12th edition, 1307-1320, 2011.
20. Ivanova N. A new class of antiulcer drugs. I. Antiulcer effect of an5, a 4-phenyl-tetrahydroisoquinoline derivative, on different experimental models of ulcer in rats. Methods Find Exp Clin Pharmacol, 12(6):401-10, 1990.
21. Manimekalai K. Evaluation of protective effect of delonix elata on chronic inflammation and comparison of its ulcerogenic potential with ibuprofen. Int J of Pharm Bio, 2(2):237-243, 2011.
22. Mehta Devansh. An insight on traditional system of medicine in pharmaceutical industry, with pharmacological profile reporting on Devadaru and Indian Rhubarb: Vital to Pharmaceutical Research Endeavor. Inventi Impact: Ethnopharmacology, 2012(4):200-211, 2012.
23. Ghangale G R, Mahale Tushar and Jadhav N D. Evaluation of antiulcer activity of *Ocimum sanctum* in rats. Veterinary World, 2(12):465-466, 2009.
24. Dharmani P, Mishra P K, Maurya R, Singh Chauhan V, Palit G. *Allophylus serratus*: a plant with potential anti-ulcerogenic activity. J Ethnopharmacol, 99(3):361-6, 2005.
25. Dharmani P. *Desmodium gangeticum*: A potent anti-ulcer agent. Indian Journal of Experimental Biology, 43:517-521, 2005.
26. Chattopadhyay I, Nandi B, Chatterjee R, Biswas K, Bandyopadhyay U, Banerjee R K. Mechanism of antiulcer effect of Neem (*Azadirachta indica*) leaf extract: effect on H⁺-K⁺-atpase, oxidative damage and apoptosis. Inflammopharmacology, 12(2):153-76, 2004.
27. Shalini R, Rajan S. Antiulcer activity of *Hemidesmus indicus* root on ethanol-HCl induced ulcer in rats. Indo Am J Pharm Res, 5(05):1995- 2001, 2015.
28. Bhatnagar M, Sisodia S S. Antisecretory and antiulcer activity of *Asparagus racemosus* Wild against indomethacin plus phyloric ligation-induced gastric ulcer in rats. J Herb Pharmacother, 6(1):13-20, 2006.
29. Gupta M, Mazumder U K. Anti-ulcer activity of ethanol extract of *Terminaliapallida Brandis*. In Swiss albino rats. J Ethnopharmacol, 97(2):405-8, 2005.
30. Sairam K. Antiulcerogenic effect of methanolic extract of *Emblica officinalis*: an experimental study. J Ethnopharmacol, 82(1):1-9, 2002.
31. Abdulla M A. Antiulcer activity of *Centella asiatica* leaf extract against ethanol-induced gastric mucosal injury in rats. Journal of Medicinal Plants Research, 4(13):1253-1259, 2010.

32. Dorababu M, Prabha T, Priyambada S, Agrawal V K, Aryya N C, Goel R K. Effect of *Bacopa monniera* and *Azadirachta indica* on gastric ulceration and healing in experimental NIDDM rats. *Indian J Exp Biol*, 42(4):389-97, 2004.
33. Prabha P, Karpagam T, Varalakshmi B, Packiavathy A S. Indigenous anti-ulcer activity of *Musa sapientum* on peptic ulcer. *Pharmacognosy Res*, 3(4):232-8, 2011.
34. Oloyede H O, Adaja M C, Ajiboye T O, Salawu M O. Anti-ulcerogenic activity of aqueous extract of *Carica papaya* seed on indomethacin-induced peptic ulcer in male albino rats. *J Integr Med*, 13(2):105-14, 2015.
35. Goulart Y C F. Evaluation of gastric anti-ulcer activity in a hydro-ethanolic extract from *Kielmeyera coriacea*. *Braz Arch Biol Technol*, 48(2), 2005.
36. Mahendran P, Vanisree A J, Shyamala Devi C S. The antiulcer activity of *Garcinia cambogia* extract against indomethacin-induced gastric ulcer in rats. *Phytother Res*, 16(1):80-3, 2002.
37. Rachchh M A. Gastro-protective effect of *Benincasa hispida* fruit extract. *Indian J Pharmacol*, 40(6):271-275, 2008.
38. Gregory M. Anti-ulcer (ulcer-preventive) activity of *Ficus arnottiana* Miq. (Moraceae) leaf methanolic extract. *American Journal of Pharmacology and Toxicology*, 4(3):89-93, 2009.
39. Bhano P. Complete Aspects of *Alstonia Scholaris*. *International Journal of Pharmtech Research*, 5(1):17-26, 2013.
40. Muralidharan P, Srikanth J. Antiulcer activity of *Morinda citrifolia* Linn fruit extract. *J Sci Res*, 1(2):345-352, 2009.
41. Devi M R. Anti-gastric ulcer activity of *Plectranthus amboinicus* (Lour) in wistar albino rats. *J Chem Pharm Res*, 2(3):374-380, 2010.
42. Vimala G, Shoba F G. A Review on Antiulcer activity of few Indian medicinal plants. *Int J of Microbio*, 2014: 1-14, 2014.
43. Azamthulla M. Anti-ulcer activity of *Allium sativum* Bulb juice. *Saudi Pharm J*, 17(1):70-77, 2009.
44. Karumi Y. Gastroprotective effects of aqueous extract of *Adansonia digitata* leaf on ethanol-induced ulceration in rats. *Journal of Biological Sciences*, 8(1):225, 2008.
45. Shenoy A M. Evaluation of anti-ulcer activity of *Aegle marmelos* leaves extract. *IJPSR*, 3(05):1498-1501, 2012.
46. Gopinathan S. Anti-ulcer activity of *Aloe vera* juice and *Aloe vera* and amla fruit combined juice in ethanol induced ulcerated rats. *Int J of Pharmacy and Pharm Sci*, 6(6):190-197, 2014.
47. Saha Rajsekhar. Pharmacognosy and Pharmacology of *Annona squamosa*: A review. *Int J of Pharm and Life Sci*, 2(10):1183-1189, 2011.
48. Snafi A E A. The pharmacological importance of *Bauhinia variegata*. A Review. *Int J of Pharma Sci and Res*, 4(12):160-164, 2013.
49. Evaluation of anti-ulcer activity of *Beta vulgaris* in rats [Online]. 2015 [Cited 2016 January 30]; Available from: URL: https://www.researchgate.net/publication/286856138_Evaluation_of_anti_ulcer_activity_of_beta_vulgaris_in_rats.
50. Goyal K K. Phytochemical and Anti-ulcer activity of *Careya arborea* Roxb. Lap Lambert Publishing, Germany, 2013.
51. Gregory M. Anti-ulcer activity of *Ficus religiosa* leaf ethanolic extract. *Asian Pac J Trop Biomed*, 3(7):554-556, 2013.
52. Test and diagnosis [Online]. 2013 July 26 [Cited 2016 January 30]; Available from: URL: <http://www.mayoclinic.org/diseases-conditions/peptic-ulcer/basics/tests-diagnosis/con-20028643>.
53. Diabetic foot ulcers [Online]. 1998 Mar15 [Cited 2016 January 30]; Available from: URL: <http://www.aafp.org/afp/1998/0315/p1325.html>.
54. Global Pharmaceutical Market [Online]. 2011 Jun 02 [Cited 2016 January 30]; Available from: URL: <http://www.pharmtech.com/global-pharma-market-expected-reach-1-trillion>.
55. Clinical trial market [Online]. 2011 July 07 [Cited 2016 January 30]; Available from: URL: http://www.pharmatimes.com/article/11-07-07/Over_50_growth_to_2015_seen_in_global_clinical_trials_market.aspx.
56. Peptic ulcers [Online]. 2016 [Cited 2016 January 30]; Available from: URL: <http://www.nhs.uk/Conditions/Peptic-ulcer/Pages/clinical-trial.aspx>.

Cite this article as: Devansh Mehta. Ulcer - Review on Types, Anti-ulcer Drugs, Anti-ulcer Medicinal Plants, Anti-ulcer Drug Market, Diagnostics and Current Global Clinical Trials Status. *Inventi Rapid: Pharmacy Practice*, 2016(2):1-8, 2016.