Evaluation of Anti-ulcer and Anti-inflammatory activity of Ethanolic extract of *Solanum pubescens willd* leaves on experimental animals

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY,

Chennai-32

In Partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACOLOGY

Submitted by

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TAMIL NADU.

MAY-2012

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"Evaluation of Anti-ulcer and Anti-inflammatory activity of Ethanolic extract of *Solanum pubescens willd* leaves on experimental animals"** submitted by the student bearing **Reg. No:26103092** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACOLOGY** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation "**Evaluation of Anti-ulcer and Anti-inflammatory activity of Ethanolic extract of *Solanum pubescens willd* leaves on experimental animals",** submitted to "The Tamil Nadu Dr.M.G.R. Medical University", Chennai, was carried out by **Mr. Bharadwaja yanamadala [Reg.No: 26103092],** for the Partial fulfillment of degree of **MASTER OF PHARMACY** in Department Of Pharmacology under direct supervision of **Mrs. M. SUDHA, M.Pharm.,** Assistant Professor**,** Department Of Pharmacology, J.K.K.Nattaraja College of Pharmacy, Komarapalayam, during the academic year 2011-2012.

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DECLARATION

The work presented in this dissertation entitled **"Evaluation of Anti-ulcer and Anti-inflammatory activity of Ethonolic extract of *Solanum pubescens willd* leaves on experimental animals",** was carried out by me, under the direct supervision of **Mrs. M. SUDHA, M.Pharm.,** Assistant Professor, Department Of Pharmacology, J.K.K.Nattaraja College of Pharmacy, Komarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university.

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ACKNOWLEDGEMENT

I acknowledge first of all, the almighty, for his goodness and grace, which have brought me this far successfully. Without his kindness and blessings, I could not have made this far.

I take this opportunity with pride and enormous gratification to express the deeply embedded feeling of thanks and gratefulness to all the persons who backed me directly or indirectly throughout the materialization of this research work.

I am swollen with pride to dedicate my humblest regards and deep sense of gratitude and heart felt thanks to late **Thiru. J.K.K. NATARAJAH CHETTIAR, founder** of our college. I wish to express my sincere thanks to our respectful correspondent **Smt. N. SENDAMARAAI** and our Managing Director **Mr. S. OMM SHARRAVANA,** B.Com., LLB., and Executive director **Mr. S. OMM SINGARAVEL,** B.E., M.S., for enabling us to do the project work.

I take this opportunity in expressing my deep sense of gratitude to my respectable and beloved guide **Mrs. SUDHA,** M.Pharm.,Department of Pharmacology, **J.K.K. Nataraja College of Pharmacy,** whose active guidance, innovative ideas, constant inspiration, untiring efforts help encouragement and continuous supervision has made the presentation of dissertation a grand and glaring success to complete this research work successfully.

I express my heartful thanks to our beloved **Dr.P.PERUMAL, M.Pharm., Ph.D., A.I.C., Principal, J.K.K. Nattaraja College of Pharmacy, Komarapalayam f**or his indispensable support which enabled us to complete this task with success.

My glorious acknowledgement to **Dr.K.SENGODAN, M.B.B.S.,** administrative officer for encouraging us in a kind and generous manner to complete this work.

My sincere thanks to **Mr.V.Rajesh,** M.Pharm., Professor and Head., Dr. **P. Ashok kumar,** Ph.D**,** Professor, **Mrs. R. Krishnaveni,** M.Pharm., Lecturer, Department of Pharmacology, for their valuable help during my project.

My sincere thanks to **Mr. V.Shekar,** M.Pharm., Ph.D, **S. Jayaseelan,** M.Pharm., Asst.Professor, **Mr.Boopathy,** M.Pharm., Ph.D, Assistant Professor, **Mr.Senthilraja,** M.Pharm., Ph.D, Asst.Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

I expresses my sincere thanks to **Mr.R.Sambathkumar,** M.Pharm., Ph.D, Professor &Head, **Mrs.S.Bhama,** M.Pharm., Lecturer, **Mr.Jaganathan,** M.Pharm., Lecturer, **Mr. R. Kanagasabai,** B.Pharm., M.Tech., Asst. Professor, Department of Pharmaceutics, for their valuable help during my project.

I express my sincere thanks to **Dr. P.Sivakumar,** M.Pharm**.,** Ph.D, **Mr.M.Vijayabaskaran,** M.Pharm., Asst. Professor, Ph.D, **Mrs.Vijayanthimala,** M.Pharm. Lecturer, **Mrs. Mahalakshmi**, M.Pharm., Lecturer, Department of Pharmaceutical Chemistry, for their valuable suggestion and inspiration.

My sincere thanks to **Dr.S.Sureshkumar,** M.Pharm., Ph.D., Professor & Head Department of Pharmacognosy and **Mr.M.K.Senthilkumar,** M.Pharm., Ph.D, Asst.Professor, Department of Pharmacognosy for their valuable suggestions.

I express my sincere thanks to **Mr.N.Venkateswara Murthy,** M.Pharm., Ph.D, Asst Professor & Head, **Mr. Raja Rajan,** M.Pharm., Lecturer. **Ms.S.Thangamani**, M.pharm.,Lecturer, Department of Pharmacy practice for their Valuable suggestions.

My sincere thanks to **Mr.N.Kadhiravel,** M.C.A., for his help during the project. I am delighted to thank **Mr. Ramesh**, Lab Assistant, **Mrs.Gandhimathi,** M.A., M.L.I.S., Librarian., **Mrs.S.Jayakala,** B.A., Asst.Librarian, **Mahalingam**, Asst.librarian, for providing necessary facilities from Library at the time of Work. I extend my thanks to **Mr.Venkatesan**, Storekeeper, **Mr.Manikandan**, computer lab Assistant, for their help during the project.

I am thankful to all my Classmates, Friends and Juniors.

Last but not the least, I pay **tribute** to **my endearing parents Mr. China kondaih, my Father**, **Mrs. Seshamma, my Mother** for lifting me up till this phase of life. I sincerely thank them for the colossal support they granted me with and also for their love, trust, patience and bearing all kinds of stress to make me what I am.

It is very difficult task to acknowledge the services to thank all those gentle people. So I would like to thank all those people who have helped me directly or indirectly to complete this project work successfully.

Mr. BHARADWAJA YANAMADALA

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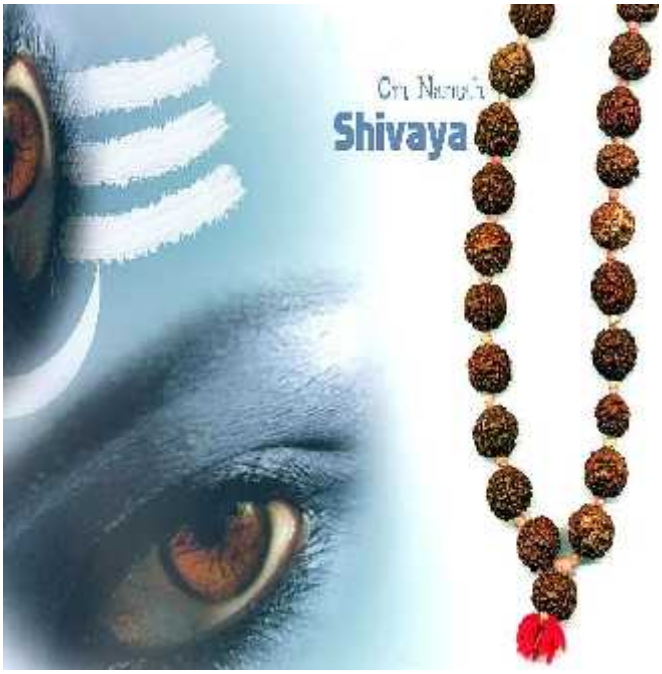
“DEDICATED TO ALMIGHTY GOD LORD SHIVA, MY GUIDE AND MY BELOVED PARENTS”



CONTENTS

ABBREVATIONS

ABBREVATION	EXPANSION
ANOVA	Analysis of Variance
b.w	Body Weight
BALF	Bronchoalveolar Lavage Fluid
cm	Centimeter
CMC	Carboxy Methyl Cellulose
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclo oxygenase
ECL	Entero Chromaffin cells
EGD	Esophagogastroduodenoscopy
ft	Feet
GERD	Gastro Esophagal Reflux Disease
gms	Grams
Hcl	Hydrochloric Acid
HCO_3^-	Carbonate ion
hrs	Hours
in.	Inches
IPF	Idiopathic Pulmonary Fibrosis
K^+	Pottasium ion
kgs	Kilograms

lt	Litre
LT	Leukotriene
EESP	Ethanolic Extract of *solanum pubescens willd*
mEq/lt	Milli Equivalents per Litre
mg/kg	Milligrams per kilogram
ml	Milli Litre
Mm	Millimeter
N	Normality
NaOH	Sodium Hydroxide
NSAIDs	Non Steroidal Anti Inflammatory Drugs
p	Probit value
PG	Prostaglandin
PL	Pyloric ligation
PPI	Proton Pump Inhibitor
ROS	Reactive oxygen species
rpm	Revolutions per Minute

1. INTRODUCTION

1.1 **HERBS**

Herbs are staging a comeback and herbal 'renaissance' is happening all over the globe. The herbal products today symbolise safety in contrast to the synthetics that are regarded as unsafe to human and environment. Although herbs had been priced for their medicinal, flavoring and aromatic qualities for centuries, the synthetic products of the modern age surpassed their importance, for a while. However, the blind dependence on synthetics is over and people are returning to the naturals with hope of safety and security. Over three-quarters of the world population relies mainly on plants and plant extract for health care. More than 30% of the entire plant species, at one time or other were used for medicinal purposes.

Human being appears to be afflicted with diseases more than any other animal species. Thus he very early sought to alleviate his sufferings from injury and disease by taking advantage of plants around him. Today a vast store of knowledge concerning therapeutic properties of different plants has amassed. All phyla of plants contain species that yield official and unofficial products of medicinal importance. By far the greatest number of these are derived from plants **(Kokate C.K., 1995).**

In India, drugs of herbal origin have been used in traditional systems of medicines such as *Unani* and *Ayurved since* ancient times. The *Ayurveda* system of medicine uses about 700 species, *Unani* 700, *Siddha* 600, Amchi 600 and modern medicine around 30 species. The drugs are derived either from the whole plant or from different organs, like leaves, stem, bark, root, flower, seed, etc. Some drugs are prepared from excretory plant product such as gum, resins and latex. Even the Allopathic system of medicine has adopted a number of plant-derived drugs which form an important segment of the modern pharmacopoeia. Some important chemical intermediates needed for manufacturing the modern drugs are also obtained from plants (Eg. diosgenin, solasodine, b-ionone). Not only, that plant-derived drug offers a stable market worldwide, but also plants continue to be an, important source for new drugs.

Traditional systems of medicine continue to be widely practiced on many accounts. Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several allopathic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments.

Ayurveda, Siddha, Unani and Folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, Ayurveda is most developed and widely practiced in India. Ayurveda dating back to 1500-800 BC has been an integral part of Indian culture. The term comes from the Sanskrit root *Au* (life) and *Veda* (knowledge). As the name implies it is not only the science of treatment of the ill but covers the whole gamut of happy human life involving the physical, metaphysical and the spiritual aspects. Ayurveda recognises that besides a balance of body elements one has to have an enlightened state of consciousness, sense organs and mind if one has to be perfectly healthy. Ayurveda by and large is an experience with nature and unlike in Western medicine, many of the concepts elude scientific explanation. Ayurveda is gaining prominence as the natural system of health care all over the world. Today this system of medicine is being practiced in countries like Nepal, Bhutan, Sri Lanka, Bangladesh and Pakistan, while the traditional system of medicine in the other countries like Tibet, Mongolia and Thailand appear to be derived from Ayurveda.

Phytomedicines are also being used increasingly in Western Europe. Recently the US Government has established the “Office of Alternative Medicine” at the National Institute of ealth at Bethesda and its support to alternative medicine includes basic and applied research in traditional systems of medicines such as Chinese, Ayurvedic, etc. with a view to assess the possible integration of effective treatments with modern medicines. The development of systematic pharmacopoeias dates back to 3000 BC, when the Chinese were already using over 350 herbal remedies. Ayurveda, a system of herbal medicine in India, Sri Lanka and South-East Asia has more than 8000 plant remedies and using around 35,000-70,000 plant species. China has demonstrated the best use of traditional medicine in providing the health care. China has pharmacologically validated and improved many traditional herbal medicines and eventually integrated them in formal health care system.

Green plants synthesise and preserve a variety of biochemical products, many of which are extractable and used as chemical feed stocks or as raw material for various scientific investigations. Many secondary metabolites of plant are commercially important and find use in a number of pharmaceutical compounds. However, a sustained supply of the source material often becomes difficult due to the factors like environmental changes, cultural practices, diverse geographical distribution, labour cost, and selection of the superior plant stock and over exploitation by pharmaceutical industry.

Plants, especially used in Ayurveda can provide biologically active molecules and lead structures for the development of modified derivatives with enhanced activity and /or reduced toxicity. The small fraction of flowering plants that have so far been investigated have yielded about 120 therapeutic agents of known structure from about 90 species of plants. Some of the useful plant drugs include vinblastine, vincristine, taxol, podophyllotoxin, camptothecin, digitoxigenin, gitoxigenin, digoxigenin, tubocurarine, morphine, codeine, aspirin, atropine, pilocarpine, capscicine, allicin, curcumin, artemesinin and ephedrine among others. In some cases, the crude extract of medicinal plants may be used as medicaments. On the other hand, the isolation and identification of the active principles and elucidation of the mechanism of action of a drug is of paramount importance. Hence, works in both mixture of traditional medicine and single active compounds are very important. Where the active molecule cannot be synthesised economically, the product must be obtained from the cultivation of plant material. About 121 (45 tropical and 76 subtropical) major plant drugs have been identified for which no synthetic one is currently available (table 1). The scientific study of traditional medicines, derivation of drugs through bioprospecting and systematic conservation of the concerned medicinal plants are thus of great importance.

The history of medicines is as old as human civilization. The documents reveal that plants were used medicinally in India, china, Egypt and Greece long before the beginning of the Christian era. One of the most famous surviving remnants is the *Papyrus Beers*. The text of document is dominated by more than 800 formulae and 700 different drugs. Most of the medicinally active substances identified in the nineteenth and twentieth century were used in the form of crude

extract. Indians also worked to examine and classify the herbs which they came across, into groups called Guans. Charaka made 50 groups of ten herbs each of which would suffice an ordinary physician's need. Similarly Sushruta arranged 760 herbs in 7 different sets based on some of their common properties. A large portion of the Indian population even today depends on the Indian system of medicine- **Ayurveda (Gratus *et al*., 2009).**

Table 1. Major plant drugs for which no synthetic one is currently available (Kumar *et al*, 1997).

Drug Plant Use

Vinblastine	Catharanthus roseus	Anticancer
Ajmalacine	Catharanthus roseus	Anticancer, hypotensive
Rescinnamine	*Rauvolfia serpentine*	Tranquilizer
Reserpine	*Rauvolfia serpentine*	Tranquilizer
Quinine	*Cinchona sp.*	Antimalarial,amoebic dysentery
Pilocarpine	*Pilocarpus jaborandi*	Antiglucoma
Cocaine	*Erythroxylum coca*	Topical anesthetic
Morphine	*Papaver somniferum*	Painkiller
Codeine	*Papaver somniferum*	
Atropine	*Atropa belladonna*	Spasmolytic, cold
Atropine	*Hyoscyamus niger*	Spasmolytic, cold
Cardiacglycosides .	*Digitalis sp*	For congestive heart Failure
Artemisinin	*Artemesia annua*	Antimalarial,
Taxol	*T. brevifolia* *Taxus baccata*	Breast and ovary cancer , antitumour
Berberine	*Berberis*	For leishmaniasis

Diospyrin	*Diospyros Montana*	Antibacterial, antifungal
Gossypol	*Gossypium sp.*	Antispermatogenic
Allicin	*Allium sativum*	Antifungal, amoebiasis
Ricin	*Ricinus communis*	Emetine
	Cephaelis ipecacuanha	Amoebiasis
Glycyrrhizin	*Glycyrrhizia glabra*	Antiulcer
Nimbidin	*Azadirachta indica*	Antiulcer
Catechin	*Acacia catechu*	Antiulcer
Sophoradin	*Sophora subprostrata*	Antiulcer
Magnolol	*Magnolia bark*	Peptic ulcer
Forskolin	*Coleus forskohlii*	Hypotensive, cardiotonic
Digitoxin,Digoxin	*Digitalis, Thevetia*	Cardio tonic
Thevenerin,	*Thevetia*	Cardio tonic
Nerrifolin	*Thevetia*	Cardio tonic
Podophyllin	*Podophyllum emodi*	Anticancer
IndicineN-oxide	*Heliotropium indicum*	Anticancer
Elipticine	*Ochrosia*	Anticancer
Homoharringtonine	*Cephalotaxus*	Anticancer
Camptothecine	*Camptotheca acuminate*	Anticancer

A major lacuna in Ayurveda is the lack of drug standardisation, information and quality control. Most of the Ayurvedic medicines are in the form of crude extracts which are a mixture of several ingredients and the active principles when isolated individually fail to give desired activity. This implies that the activity of the extract is the synergistic effect of its various components. In the absence of pharmacopoeia data on the various plant extracts, it is not possible to isolate or standardise the active contents having the desired effects. Ayurvedic pharmacopoeia compiled on modern lines and updated periodically is an urgent requirement.

A combination therapy integrating Ayurveda and allopathy whereby the side effects and undesirable reactions could be controlled can be thought of. Studies can

show that the toxic effects of radiations and chemotherapy in cancer treatment could be reduced by Ayurvedic medications and similarly surgical wound healing could be accelerated by Ayurvedic medicines. Modern science and technology have an essential role to play in the process. An integrated approach for the cultivation, conservation and preservation of important plant species through plant molecular biology, plant tissue culture; research on the rationale and methodology of Ayurvedic medical practice; isolation of active constituents and their development into new therapeutics; standardisation and validation of known herbal medicines and other related aspects need to be focused upon (Sharma, 1997).

Despite the diverse nature of crops grown in the country and the existence of a fast-growing pharmaceutical sector, the share of India in world trade is quite insignificant considering the large geographical area. However, this is bound to rise rapidly with better research inputs and efficient management of the farm sector. So far, India has been involved in the export of only large volume raw material. To achieve competitive advantage we need to resort to low volume high cost (value) trade through value addition to the raw and unfinished products. It is therefore, necessary to develop genetically superior planting material for assured uniformity and desired quality and resort to organized cultivation to ensure the supply of raw material at grower's end. Post harvest storage and process technologies need to be developed to produce the value added finished products that may be directly utilised by the industry

Inventorisation of herbal drugs used in traditional and modern medicines for acountry like India, appears to be a stupendous task, where a number of well established indigenous or traditional systems, including Ayurveda, Unani, Siddha, Homoeopathy, Tibetan, Amchi, Yoga and Naturopathy are practised along with modern medicine for the management of total health care system. In all these systems a large number of plant drugs are used, although there may be some common plants. Another problem in correct identification of plants is that the plant drugs in those systems of medicine are known by their classical, Shastriya or vernacular names. It is not easy to correlate these names with acceptable scientific names. One plant species can have many vernacular classical names and one name may refer to different plant species. Chinese, Indian, Arabian and other traditional

systems of medicines make extensive use of about 5000 plants. India is proud to be rich in biological diversity and tenth among the plant rich countries of Asia, sixth as far as centres of diversity especially agrodiversity are concerned. Nearly three fourth of the drugs and perfumery products used in the world are available in natural state in the country. India possesses almost 8% of the estimated biodiversity of the world with around 1, 26,000 species. It is one of the 12 mega biodiversity centres with 2 hot spots of biodiversity in western Ghats and north-eastern region.

The sacred groves are a miniature ecosystem conserving biodiversity in its pristine form. There are about 400 families in the world of flowering plants; at least 315 are represented in India. According to WHO, around 21,000 plant species have the potential for being used as medicinal plants? About 5000 species have been studied. There are at least 121 major plant drugs of known structure, but synthetic means. For developing phytomedicines as a major area of concern, it would be essential to adopt a holistic interdisciplinary approach, have a scientific basis of the understanding of the plant systems, new innovations and their conservation for utilization in future on a sustainable basis (Sharma, 1997).

- Plant species with therapeutic value under different plant groups(Jiaxiang, 1997).

  Halophytes 230

  Bryophytes 39

  Pteridophytes 382

  Gymnospermae 55

  Angiospermae:

  A)Monocotyledones 676

  b) Dicotyledones 3495

  Total 4877

Table No. 2. List of Anti-ulcer plants

Plant	Family	Plant part used
Alpinia allughas	Zingiberaceae	Rhizome
Alpinia galangal	Zingiberaceae	Rhizome
Alpinia calcarata	Zingiberaceae	Rhizome
Glycyrrhiza glabra	Liquorice	Stem, root
Azadirachta indica	Meliaceae	Bark, leaves, flower
Acacia catechu	Mimosaceae	Bark
Sophora subprostrata	Leguminaceae	Root
Magnolia bark	Magnoliaceae	Bark
Gloriosa superb	Liliaceae	Roots, rhizome
Phyllanthus emblica	Euphorbiaceae	Root, bark
Aegle marmelos	Rutaceae	Leaf
Indigofera tinctoria	Papillonaceae	Leaf, fruit
Pongamia pinnata	Papillonaceae	Whole plant
Eclipta prostate	Asteraceae	Root
Terminalia arjuna	Combretaceae	Bark
Terminalia alata	Combretaceae	Bark
Terminalia chebula	Combretaceae	Powdered fruit
Coleus vettiveroides	Lamiaceae	Whole plant
Punia granatum	Puniaceae	Fruit
Murraya koenigii	Rutaceae	Leaf
Solanum melongina	Solanaceae	Fruit

Solanum nigram	Solanaceae	Plant
Bauhinia variegate	Caesalpiniaceae	Bark
Bauhinia purpurea	Caesalpiniaceae	Bark
Gymnema sylvestre	Asclepiadaceae	Whole plant
Balospermum montanum	Euphorbiaceae	Root
Saraca asoca	Caesalpiniaceae	Bark
Andrographis paniculata	Acanthaceae	Whole plant
Aristolochia bracteolata	Aristolochiaceae	Whole plant
Ficus microcarpa	Moraceae	Bark, leaf
Mimusops elengi	Sapotaceae	Flower
Lagenaria vulgaris	Curcubitaceae	Fruit
Mormodica charatia	Curcubitaceae	Fruit, seed
Citrullus colocynthis	Curcubitaceae	Fruit, root

The modern life style in terms of food, daily working pressure and use of medicine for common causes has been increased. All three has impact on GIT (gastrointestinal tract) causes many problem, one of them is gastric ulcer. It is an open discontinuation on the mucous membrane causes pain and usually inflamed called peptic ulcer.

The two most common types of peptic ulcer are called “gastric ulcers” and “duodenal ulcers”. These names refer to the location where the ulcer is found. Gastric ulcers are located in the stomach. Duodenal ulcers are found at the beginning of the small intestine known as the duodenum. A person may have both gastric and duodenal ulcers at the same time. People infected with *H. pylori* are at increased risk of developing peptic ulcers. When a person is diagnosed with an ulcer, testing

for H. *pylori* is often done. There are a number of tests to diagnose H. *pylori*. Which test is used depends on the situation.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are a group of medications typically used to treat pain. People, who take NSAIDs for a long time, at high doses or both, have a higher risk of developing ulcers. 5 - 10% of the world's population suffers at least once in their life from a peptic ulcer. Infection with *H. pylori* is the major cause of peptic ulcer disease and also a risk factor for cancer of the stomach.

It is well established that diet rich in vegetables and fruits can reduce disturbances in gastrointestinal system. Moreover, large number of populations today uses herbal therapies and home remedies along with conventional medications. However, concurrent use of these remedies with modern medications may cause either potentially dangerous side effects or enhanced therapeutic efficacy.

In traditional medicine, several plants and herbs have been used to treat gastrointestinal disorders, including gastric ulcers. The first drug effective against gastric ulcer was carbenoxolone, discovered as a result of research on a commonly used indigenous plant, *Glycyrrhiza glabra*. Studies on cabbage previously employed as an antiulcer agent in folk medicine, which acts by enhancing the gastric mucosal strength. Banana fruit has also been found to inhibit peptic ulceration. It is reported the antiulcer activity of species of the Campanulaceae in experimental models, while Kanturek et al found solon, a flavonoid, to be effective against ulcer in experimental animals. *Meliaazedarach* has been observed to inhibit stress-induced ulcer in rats. Santalum album stem is also used as an anti ulcer agent in traditional medicine

1.2 PEPTIC ULCER

The acid-peptic diseases are those disorders in which gastric acid and pepsin are necessary, but usually not sufficient, pathogenic factors. While inherently caustic, acid and pepsin in the stomach normally do not produce damage or symptoms because of intrinsic defense mechanisms. Barriers to the reflux of gastric contents into the esophagus comprise the primary esophageal defense. Peptic ulcers

are craters or open sores in the lining of the upper gastrointestinal tract (GIT). They include duodenal ulcers (those that are located in the top of the small intestine or duodenum) and gastric ulcers (those found in the stomach). Peptic ulcers are common and usually occur singly. But it is possible to have two or more, or even both duodenal and gastric ulcers at the same time.

Although the pathogenesis of peptic ulcer disease is not fully understood, three major factors are recognized: infection with gram-negative *H. pylori*, increased hydrochloric acid secretion, and inadequate mucosal defense against gastric acid. Treatment approaches include (1) eradicating *H. pylori* infection, (2) reducing secretion of gastric acid or neutralizing the acid after it is released, and (3) providing agents that protect the gastric mucosa from damage.

Digestive system: Cross-section of the alimentary tube has four layers the mucosa, submucosa, external muscle layer, and serosa. Each layer has a specific structure, and its functions contribute to the functioning of the organs of which it is a part.

Esophagus: The esophagus is a muscular tube that takes food from the pharynx to the stomach. No digestion takes place here. Peristalsis of the esophagus propels food in one direction and ensures that food gets to the stomach even if the body is horizontal or upside down. At the junction with the stomach, the lumen (cavity) of the esophagus is surrounded by the lower esophageal sphincter (LES or cardiac sphincter), a circular smooth muscle. The LES relaxes to permit food to enter the stomach, and then contracts to prevent the backup of stomach contents. If the LES does not close completely, gastric juice may splash up into the esophagus this is a painful condition we call heartburn, or gastroesophageal reflux disease (GERD). Most people experience heartburn once in a while, and it is merely uncomfortable, but chronic GERD is more serious. The lining of the esophagus cannot withstand the corrosive action of gastric acid and will be damaged, perhaps resulting in bleeding or even perforation. Medications are available to treat this condition.

MUCOSA: The mucosa, or lining, of the alimentary tube is made of epithelial tissue, areolar connective tissue, and two thin layers of smooth muscle. In the esophagus the epithelium is stratified squamous epithelium; in the stomach and intestines it is simple columnar epithelium. The epithelium secretes mucus, which

lubricates the passage of food, and also secretes the digestive enzymes of the stomach and small intestine. Just below the epithelium, within the areolar connective tissue, are lymph nodules that contain lymphocytes to produce antibodies, and macrophages to phagocytize bacteria or other foreign material that get through the epithelium. The thin layers of smooth muscle create folds in the mucosa, and ripples, so that all of the epithelial cells are in touch with the contents of the organ. In the stomach and small intestine this is important for absorption.

SUBMUCOSA: The submucosa is made of areolar connective tissue with many blood vessels and lymphatic vessels. Many millions of nerve fibers are also present, part of what is called the enteric nervous system, or the "brain of the gut," which extends the entire length of the alimentary tube. The nerve networks in the submucosa are called Meissner's plexus (or submucosal plexus) and they innervate the mucosa to regulate secretions.Parasympathetic impulses increase secretions, whereas sympathetic impulses decrease secretions. Sensory neurons are also present to the smooth muscle (a stretched or cramping gut is painful), as are motor neurons to blood vessels, to regulate vessel diameter and blood flow.

SEROSA : Above the diaphragm, for the esophagus, the serosa, the outermost layer, is fibrous connective tissue. Below the diaphragm, the serosa is the mesentery or visceral peritoneum, a serous membrane. Lining the abdominal cavity is the parietal peritoneum, usually simply called the peritoneum. The peritoneum-mesentery is actually one continuous membrane.

The serous fluid between the peritoneum and mesentery prevents friction when the alimentary tube contracts and the organs slide against one another. The preceding descriptions are typical of the layers of the alimentary tube. As noted, variations are possible, and any important differences are mentioned in the sections that follow on specific organs.

STOMACH: The stomach is located in the upper left quadrant of the abdominal cavity, to the left of the liver and in front of the spleen. Although part of the alimentary tube, the stomach is not a tube, but rather a sac that extends from the esophagus to the small intestine. Because it is a sac, the stomach is a reservoir for food, so that digestion proceeds gradually and we do not have to eat constantly. Both

mechanical and chemical digestion takes place in the stomach. The parts of the stomach are shown in Fig 1. The cardiac orifice is the opening of the esophagus, and the fundus is the portion above the level of this opening. The body of the stomach is the large central portion, bounded laterally by the greater curvature and medially by the lesser curvature. The pylorus is adjacent to the duodenum of the small intestine, and the pyloric sphincter surrounds the junction of the two organs. The fundus and body are mainly storage areas, whereas most digestion takes place in the pylorus. When the stomach is empty, the mucosa appears wrinkled or folded. These folds are called rugae; they flatten out as the stomach is filled and permit expansion of the lining without tearing it. The gastric pits are the glands of the stomach and consist of several types of cells; their collective secretions are called gastric juice. Mucous cells secrete mucus, which coats the stomach lining and helps prevent erosion by the gastric juice. Chief cells secrete pepsinogen, an inactive form of the enzyme pepsin. Parietal cells produce hydrochloric acid (HCl); these cells have enzymes called proton pumps, which secrete H+ ions into the stomach cavity. The H ions unite with Cl^- ions that have diffused from the parietal cells to form HCl in the lumen of the stomach. HCl converts pepsinogen to pepsin, which then begins the digestion of proteins to polypeptides, and also gives gastric juice its P_H of 1 to 2. This very acidic P_H is necessary for pepsin to function and also kills most microorganisms that enter the stomach. The parietal cells also secrete intrinsic factor, which is necessary for the absorption of vitamin B_{12}. Enteroendocrine cells called G cells secrete the hormone gastrin. Gastric juice is secreted in small amounts at the sight or smell of food. This is a parasympathetic response that ensures that some gastric juice will be present in the stomach when food arrives. The presence of food in the stomach causes the G cells to secrete gastrin, a hormone that stimulates the secretion of greater amounts of gastric juice.

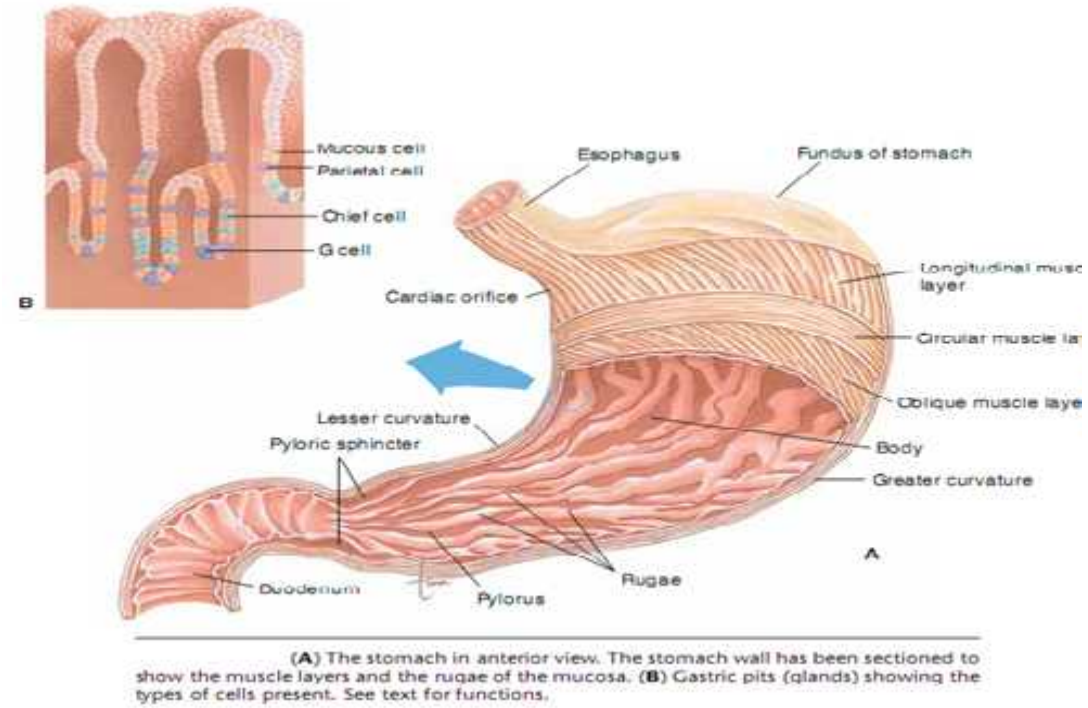


Fig: 01: Stomach anterior view and gastric pits

The external muscle layer of the stomach consists of three layers of smooth muscle circular, longitudinal, and oblique layers. These three layers are innervated by the enteric plexuses of the enteric nervous system. Stimulatory impulses are carried from the CNS by the vagus nerves (10th cranial) and provide for very efficient mechanical digestion to change food into a thick liquid called chyme. The pyloric sphincter is usually contract when the stomach is churning food; it relaxes at intervals to permit small amounts of chyme to pass into the duodenum. This sphincter then contracts again to prevent the back up of intestinal contents into the stomach.

Regulation of Pepsinogen Secretion

Regulation of pepsinogen secretion by the peptic cells in the oxyntic glands is much less complex than regulation of acid secretion; it occurs in response to two types of signals: (1) stimulation of the peptic cells by acetylcholine released from the vagus nerves or from the gastric enteric nervous plexus, and (2) stimulation of peptic cell secretion in response to acid in the stomach. The acid probably does not stimulate the peptic cells directly but instead elicits additional enteric nervous

reflexes that support the original nervous signals to the peptic cells. Therefore, the rate of secretion of pepsinogen, the precursor of the enzyme pepsin that causes protein digestion, is strongly influenced by the amount of acid in the stomach. In people who have lost the ability to secrete normal amounts of acid, secretion of pepsinogen is also decreased, even though the peptic cells may otherwise appear to be normal.

History

John Lykoudis, a general practitioner in Greece, treated patients for peptic ulcer disease with antibiotics, beginning in 1958, long before it was commonly recognized that bacteria were a dominant cause for the disease.

Helicobacter pylori was rediscovered in 1982 by two Australian scientists, Robin Warren and Barry J. Marshall as a causative factor for ulcers. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before.

The *H. pylori* hypothesis was poorly received, so in an act of self-experimentation Marshall drank a Petri dish containing a culture of organisms extracted from a patient and soon developed gastritis. His symptoms disappeared after two weeks, but he took antibiotics to kill the remaining bacteria at the urging of his wife, since halitosis is one of the symptoms of infection. This experiment was published in 1984 in the Australian Medical Journal and is among the most cited articles from the journal.

In 1997, the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about the link between *H. pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection, and that health can be greatly improved and money saved by disseminating information about *H. pylori*.

In 2005, the Karolinska Institute in Stockholm awarded the Nobel Prize in Physiology or Medicine to Dr. Marshall and his long-time collaborator Dr. Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease". Professor Marshall continues research related to *H. pylori* and runs a molecular biology lab at UWA in Perth, Western Australia.It was a previously widely accepted misunderstanding that the use of chewing gum resulted in gastric ulcers. The medical profession believed that this was because the action of masticating on gum caused the over-stimulation of the production of hydrochloric acid in the stomach. The low (acidic) P_H (P_H 2), or hyperchlorhydria was then believed to cause erosion of the stomach lining in the absence of food, thus causing the development of the gastric ulcers. On the other hand, in the recent past, some believed that natural tree resin extract, mastic gum, actively eliminates the *H. pylori* bacteria. However, multiple subsequent studies have found no effect of using mastic gum on reducing *H. pylori* levels.

Epidemiology

The lifetime risk for developing a peptic ulcer is approximately 10%. In Western countries the prevalence of *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80 etc). Prevalence is higher in third world countries. Transmission is by food, contaminated groundwater, and through human saliva (such as from kissing or sharing food utensils). A minority of cases of Helicobacter infection will eventually lead to an ulcer and a larger proportion of people will get non-specific discomfort, abdominal pain or gastritis.

Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. The reason why the rates of peptic ulcer disease decreased is thought to be the development of new effective medication and acid suppressants and the discovery of the cause of the condition, *H. pylori*.

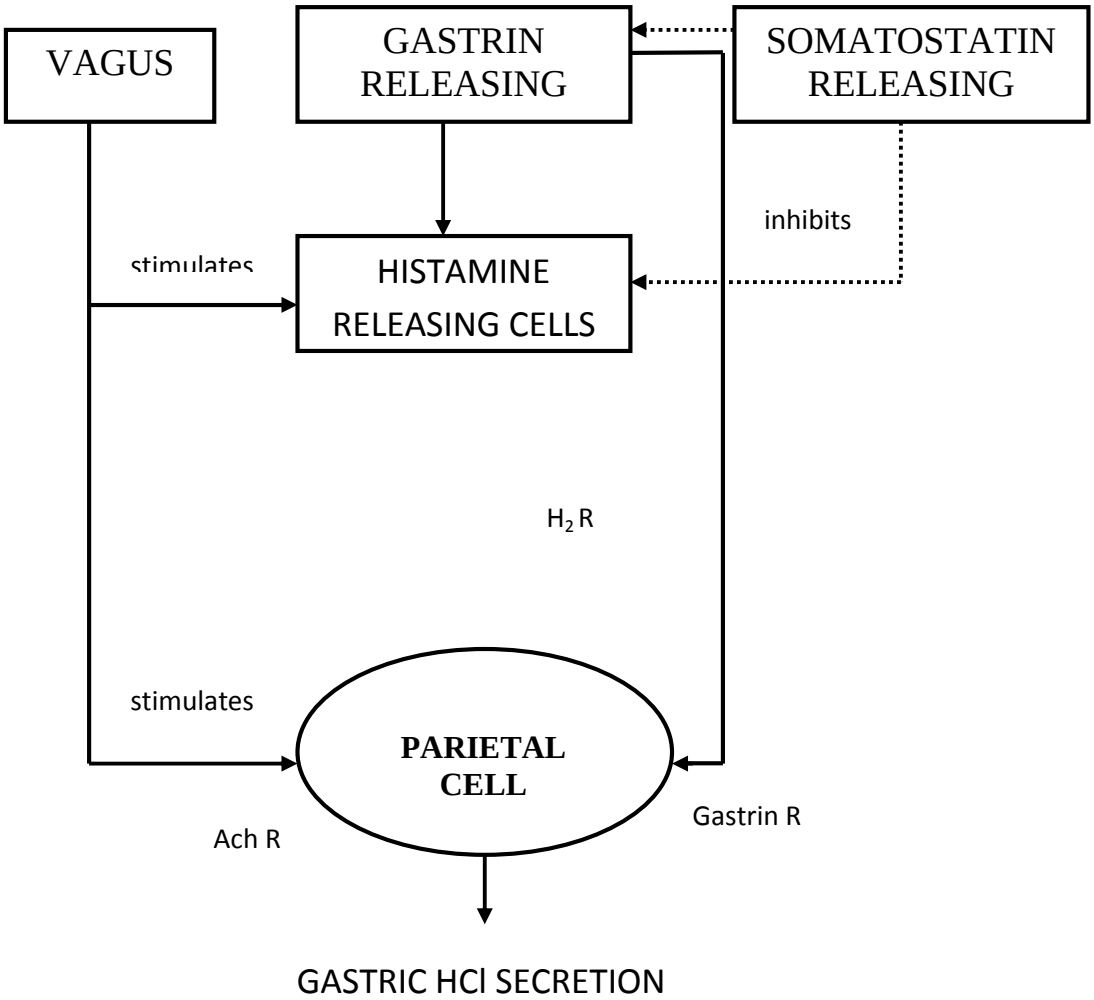
In the United States about 4 million people have active peptic ulcers and about 350,000 new cases are diagnosed each year. Four times as many duodenal

ulcers as gastric ulcers are diagnosed. Approximately 3,000 deaths per year in the United States are due to duodenal ulcer and 3,000 to gastric ulcer.

Synthesis of gastric HCl

H^+ and K ATPase. The enzyme is stimulated by protein kinases, activated by histamine and by acetylcholine and gastrin.

The two ions H^+ and Cl^- unite within the canaliculus of parietal cell to form HCl and HCl form in to the gastric lumen.



1.3 THE REGULATION OF ACID SECRETION

The regulation of acid secretion by parietal cells is especially important in the pathogenesis of peptic ulcer, and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a P_H less than 1, the concentration of hydrogen ions being more than a million times higher than that of the plasma. The Cl^- is actively transported into canaliculi in the cells that communicate with the lumen of the gastric glands and thus with the stomach itself. This Cl^- secretion is accompanied by K^+, which is then exchanged for H^+ from within the cell by a K^+/H^+ ATPase and bicarbonate ions. The latter exchanges across the basal membrane of the parietal cell for Cl^-.

The principal stimuli acting on the parietal cells are:

- Gastrin (a stimulatory hormone)
- Acetylcholine (a stimulatory neurotransmitter)
- Histamine (a stimulatory local hormone)
- Prostaglandins E_2 and I_2 (local hormones that inhibit acid secretion).

Gastrin is a peptide hormone synthesized in the mucosa of the gastric antrum and duodenum, and secreted into portal blood. Its main action is stimulation of the secretion of acid by the parietal cells. These receptors are blocked by *proglumide* which inhibits gastrin action. Gastrin also indirectly increases pepsinogen secretion, stimulates blood flow and increases gastric motility. Release of this hormone is controlled both by neuronal transmitters and blood- borne mediators.

Acetylcholine is released from neurons and stimulates specific muscarinic receptors on the surface of the parietal cells and on the surface of histamine-containing cells

Histamine: Within the stomach, mast cells (or histamine-containing cells similar to mast cells) lying close to the parietal cell release a steady basal release of histamine, which is further increased by gastrin and acetylcholine. The hormone acts on parietal cell H_2 receptors, which are responsive to histamine concentrations that are below the threshold required for vascular H_2 receptor activation.

The parietal cell itself has H_2 receptors for histamine and muscarinic M_2 receptors for acetylcholine, as well as receptors for gastrin itself. Acid secretion follows after the synergistic stimulation of H_2 receptors (which increases cAMP), and M_2 and gastrin receptors (which increase cytosolic Ca^{2+}).

Prostaglandins (mainly E_2 and I_2), synthesized in the gastric mucosa mainly by cyclo-oxygenase-1, stimulate mucus and bicarbonate secretion, decrease acid secretion and cause vasodilatation, all of which serve to protect the stomach against damage. This probably explains the ability of many non-specific non-steroidal anti-inflammatory drugs to cause gastric bleeding and erosions. More selective cyclo-oxygenase-2 inhibitors such as celecoxib and rofecoxib appear to cause less stomach damage. Other notable factors influencing HCl secretion include

1. Calcium
2. Alcohol
3. Coffee
4. Acidity of gastric content
5. Food fat

1.4 Peptic Ulcer Disease pathophysiology

The pathophysiology of peptic ulcer disease is best viewed as an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide, and other peptides and growth factors) and injurious factors (acid and pepsin). On average, patients with duodenal ulcers produce more acid than do control subjects, particularly at night (basal secretion). Although patients with gastric ulcers have normal or even diminished acid production, ulcers rarely if ever occur in the complete absence of acid. Presumably, a weakened mucosal defense and reduced bicarbonate production contribute to the injury from the relatively lower levels of acid in these patients. *H. pylori* and exogenous agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) interact in complex ways to cause an ulcer. Up to 60% of peptic ulcers are associated with *H. pylori* infection of the stomach. This infection may lead to impaired production

Treatment of *Helicobacter pylori* Infection

H. pylori, a gram-negative rod, has been associated with gastritis and the subsequent development of gastric and duodenal ulcers, gastric adenocarcinoma, and gastric B-cell lymphoma. Because of the critical role of *H. pylori* in the pathogenesis of peptic ulcers, to eradicate this infection is standard care in patients with gastric or duodenal ulcers. Provided that patients are not taking NSAIDs, this strategy almost completely eliminates the risk of ulcer recurrence. Eradication of *H. pylori* also is indicated in the treatment of mucosa-associated lymphoid tissue lymphomas of the stomach, which can regress significantly after such treatment.

Many regimens for *H. pylori* eradication have been proposed. Evidence-based literature review suggests that the ideal regimen in this setting should achieve a cure rate of at least 80%. Five important considerations influence the selection of an eradication regimen. First, single-antibiotic regimens are ineffective in eradicating *H. pylori* infection and lead to microbial resistance. Combination therapy with two or three antibiotics (plus acid-suppressive therapy) is associated with the highest rate of *H. pylori* eradication. Second, a proton pump inhibitor or H_2-receptor antagonist significantly enhances the effectiveness of *H. pylori* antibiotic regimens containing *amoxicillin* or *clarithromycin.*

Third, a regimen of 10 to 14 days of treatment appears to be better than shorter treatment regimens; in the United States, a 14-day course of therapy generally is preferred. Fourth, poor patient compliance is linked to the medication-related side effects experienced by as many as half of patients taking triple-agent regimens, and to the inconvenience of three- or four-drug regimens administered several times per day. Packaging that combines the daily doses into one convenient unit is available and may improve patient compliance.

Finally, the emergence of resistance to clarithromycin and *metronidazole* increasingly is recognized as an important factor in the failure to eradicate *H. pylori.* Clarithromycin resistance is related to mutations that prevent binding of the antibiotic to the ribosomes of the pathogen and is an all-or-none phenomenon. In contrast, metronidazole resistance is relative rather than absolute and may involve several adaptations by the bacteria. In the presence of *in vitro* evidence of resistance to metronidazole, amoxicillin should be used instead. In areas with a high frequency

of resistance to clarithromycin and metronidazole, a 14-day, quadruple-drug regimen (three antibiotics combined With a proton pump inhibitor) generally is effective therapy.

NSAID-Related Ulcers

Chronic NSAID users have a 2% to 4% risk of developing a symptomatic ulcer, gastrointestinal bleeding, or perforation. Ideally, NSAIDs should be discontinued in patients with an ulcer if at all possible. If continued therapy is needed, selective COX-2 inhibitors may be considered, although this does not eliminate the risk of subsequent ulcer formation and the possible association of these drugs with adverse cardiovascular events mandates caution. Healing of ulcers despite continued NSAID use is possible with the use of acid-suppressant agents, usually at higher doses and for a considerably longer duration than standard regimens (*e.g.*, 8 weeks or longer). Again, proton pump inhibitors are superior to H_2-receptor antagonists and misoprostol in promoting the healing of active ulcers (healing rates of 80% to 90% for proton pump inhibitors *versus* 60% to 75% for the H_2-receptor antagonists), and in preventing recurrence of gastric and duodenal ulcers in the setting of continued NSAID administration.

Stress-related ulcers

Stress ulcers are ulcers of the stomach or duodenum that occur in the context of a profound illness or trauma requiring intensive care. The etiology of stress-related ulcers differs somewhat from that of other peptic ulcers, involving acid and mucosal ischemia. Because of limitations on the oral administration of drugs in many patients with stress-related ulcers, intravenous H_2-receptor antagonists have been used extensively to reduce the incidence of GI hemorrhage due to stress ulcers. Now that intravenous preparations of proton pump inhibitors are available, it is likely that they will prove to be equally beneficial. However, there is some concern over the risk of pneumonia secondary to gastric colonization by bacteria in an alkaline milieu...

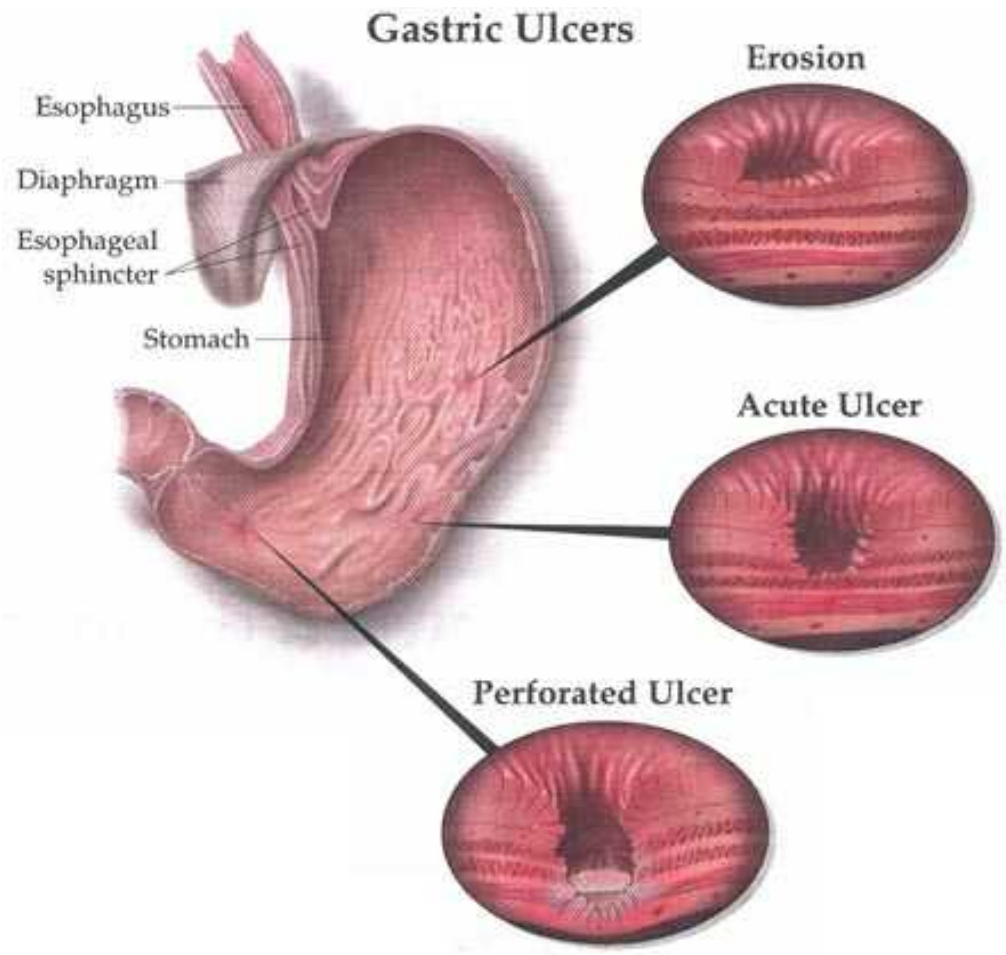


Fig. 02: Gastric ulcers

Zollinger-Ellison Syndrome

Patients with this syndrome develop pancreatic or duodenal gastrinomas that stimulate the secretion of very large amounts of acid, sometimes in the setting of multiple endocrine neoplasia, type I. This can lead to severe gastroduodenal ulceration and other consequences of uncontrolled hyperchlorhydria. Proton pump inhibitors clearly are the drugs of choice, usually given at twice the routine dosage for peptic ulcers with the therapeutic goal of reducing acid secretion to 1 to 10 mmol/h.

Nonulcer Dyspepsia

This term refers to ulcer-like symptoms in patients who lack overt gastroduodenal ulceration. It may be associated with gastritis (with or without *H. pylori*) or with NSAID use, but the pathogenesis of this syndrome remains

controversial. Although empirical treatment with acid- evidence of their benefit in controlled trials suppressive agents is used routinely in patients with nonulcer dyspepsia, there is no convincing.

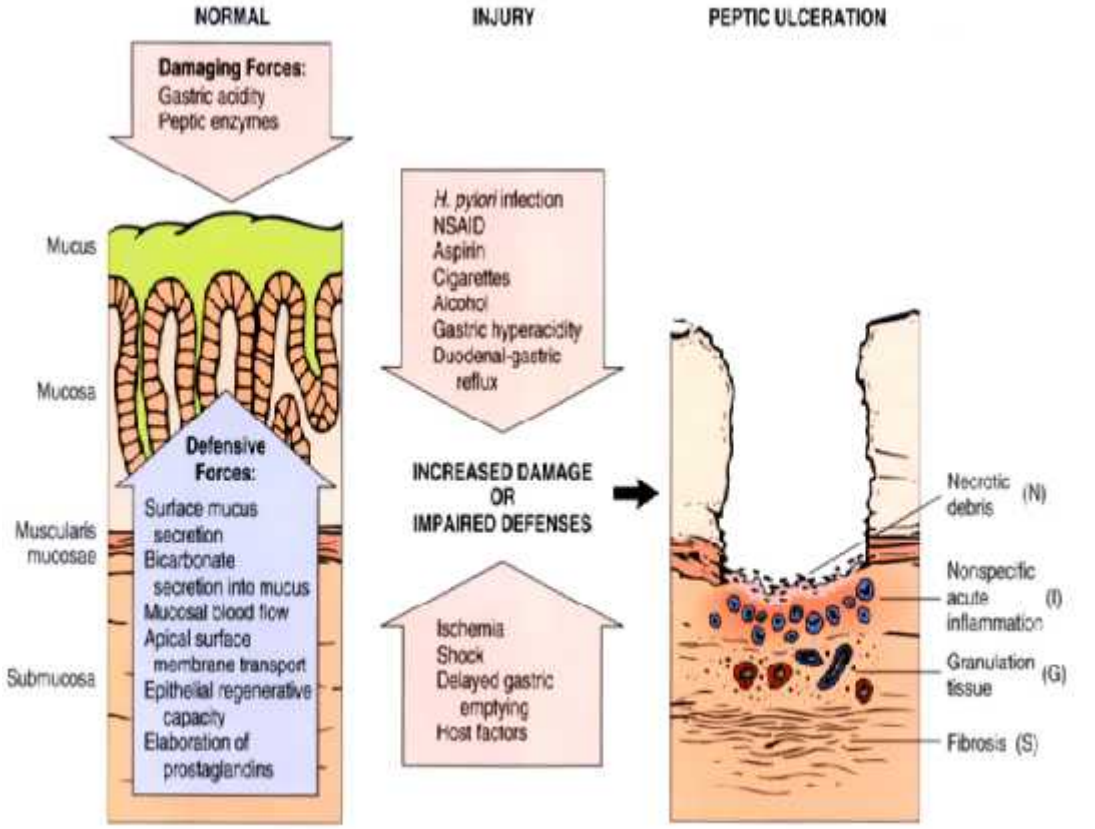


Figure 17-18 Peptic ulcer of the duodenum. Note that the ulcer is small (2 cm) with a sharply punched-out appearance. Unlike cancerous ulcers the margins are not elevated. The ulcer base is clean. *(Courtesy of Roode Foss, University of Florida, Gainesville, FL.)*

Fig.03: Peptic ulcer of duodenum

1.5 Peptic ulcer

First part of your small intestine. If peptic ulcers are found in the stomach, they're called gastric ulcers. If they're found in the duodenum, they're called duodenal ulcers. You can have more than a peptic ulcer is a sore in the lining of your stomach or duodenum. The duodenum is the One ulcer. Many people have peptic ulcers. Peptic ulcers can be treated successfully. Seeing your doctor is the first step. Peptic ulcers occur in the wall of the stomach and duodenum.

Acute ulcer

- Usually associated with sepsis, injection (cytomegalo-virus) [CMV], Candida, tuberculosis [TB], syphilis), surgery/trauma, central nervous system (CNS) injury or disease (Cushing's disease), extensive burns (Curling's ulcer), use of drugs (aspirin, steroid), or after radiation therapy
- If superficial, involving mucosa only (erosion), can heal completely
- If deep, fibrosis replaces muscle and perforation may occur

Microscopic

- Marked epithelial atypia

Chronic ulcer

- Cardinal symptom is nocturnal epigastric pain
- Associated with achlorhydria
- 95% along the lesser curvature
- 95% accuracy with endoscopic and 70% accuracy with radiographic diagnosis
- Questionable risk of malignancy Macroscopic
- 5% multiple
- Sharp delineation.

Stage of Microscopic Description

Stage	Microscopic Description
Chronic superficial gastritis	Inflammation limited to foveolae; no glandular atrophy; epithelial changes, including decreased cytoplasmic mucin, nuclear/nucleolar enlargement, and mitotic activity
Chronic atrophic gastritis*	Extensive inflammation; glandular atrophy (glands more widely spaced)
Gastric atrophy	Thin mucosa; no inflammatory changes; cystically dilated glands

** Note: risk of gastric carcinoma*

Causes of peptic ulcers

Peptic ulcers occur in 5-20% of longterm NSAID use.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are a group of medications typically used to treat pain. There are many drugs in this group. A few of these include: aspirin, oxaprozin . NSAIDs are also included in some combination medications, such as Alka-Seltzer, Acetaminophen and is therefore the preferred non-prescription treatment for pain in patients at risk for peptic ulcer disease.

Because NSAIDs are so common, and because many are available over the counter without a prescription, they are a very common cause of peptic ulcers. NSAIDs cause ulcers by interrupting the ability of the stomach and the duodenum to protect themselves from naturally occurring stomach acid. NSAIDs also can interfere with blood clotting. This has obvious Importance when ulcers bleed.
People, who take NSAIDs for a long time, at high doses or both, have a higher risk of developing ulcers. These people should discuss preventing ulcers with their physician. A PPI can prevent or significantly reduce the risk of an ulcer being caused by NSAIDs.

Helicobacter pylori

A bacterium called Helicobacter pylori (H. pylori) is a major cause of peptic ulcers.

1. Duodenal Ulcer: 90-100% Prevalence

2. Gastric Ulcer: 70-90% Prevalence .

H. pylorus causes more than half of peptic ulcers worldwide.

The bacterium causes peptic ulcers by damaging the mucous coating that protects the stomach and duodenum Damage to the mucous coating allows powerful stomach acid to get through to the sensitive lining beneath. Together, the stomach

acid and H. pylori irritate the lining of the stomach or duodenum and cause an ulcer. Yet, most people infected with H. pylori never develop ulcers. Why the bacterium causes ulcers in some people and not in others is not known. Most likely, development of ulcers depends on characteristics of the infected person; the type, or strain,of H. pylori present; and factors researchers have yet to discover.

Acid Induced Ulcers

1. Idiopathic
2. Zollinger-Ellison Syndrome.

Other medication

Steroids, bisphosphonates, potassium chloride, chemotherapeutic agents (e.g., intravenous fluorouracil)

Rare

Acid-hypersecretory states(e.g.,Zollinger-Ellison syndrome)	Multiple gastroduodenal, jejunal, or esophageal ulcers
Malignancy	Gastric cancer, lymphomas, lung cancers
Stress	After acute illness, multiorgan failure, ventilator support, extensive burns (Curling's ulcer), or head injury (Cushing's ulcer).
Genetic factors	People with blood group ‘O’ appear to be more prone to develop peptic ulcers than those with other blood groups. Genetic influences appear to have greater role in duodenal ulcers as evidenced by their occurrence in families, monozygotic twins and association with HLA-B5 antigen.

1.6 MEASURE TO CONTROL GASTRIC ACIDITY

- Neutralizing gastric acid using antacids.
- Inhibiting the gastric acid secretion with drugs
- Cessation of smoking
- Withdrawal of gastric acid secretion stimulants such as alcohol, caffeine and
- Soft cola drinks
- Surgical treatment such as partial gastrectomy or vagotom.

1.7 PEPTIC ULCER THERAPY

PRINCIPLES OF PEPTIC ULCER THERAPY

As the precise cause of peptic ulcer is not known, therapy is still empirical it consists of

- Controlling gastric acidity, hyper motility & sperm, thus relining the associated pain
- Promoting ulcer healing
- Prevention of complications & recurrence
- Treatment of H pylori infections

Reduction of gastric acid secretion

1. **Proton pump inhibitors:** Pantoprazole, Omeprazole, lansoprazole, Rabeprazole.
2. **H_2-Receptor antagonists:** Cimetidine, Ranitidine, Famotidine, Nizatidine.
2. **Anticholinergics**: Pirenzepin, propantheline, Oxyphenonium.
3. **Prostaglandin Analogs:** Misoprostol.

Neutralization of gastric acid (Antacid)

1. **Antacids:** Sodium bicarbonate, Sodium citrate, Magnesium hydroxide, Calcium carbonate.
2. **Ulcer protectives**: Sucralfate, Colloidal bismuth subcitrate.

3. **Ulcer healing drugs:** Carbenoxolone sodium
4. **Anti-H. pylori drugs**: Amoxicillin, Clarithromycin, Metronidazole, Tetracycline.

1.8 INFLAMMATION

Inflammation is the protective response of the living individual to get rid of the cause and effect of injury (microbes, toxins, necrotic tissues).

A free-living cell, whether prokaryotic or eukaryotic, must establish structural and functional barrier between its internal and hostile environment.

Unicellular organisms (amoeba) selectively admit some and exclude or extrude others.

Multicellular organisms protect themselves by different cells to perform different functions.

Example:

- Storage of nutrients (liver cells)

- Communication (neurons)

- Contractile activity of muscles (heart)

- Synthesis of proteins and peptides from exports (liver, pancreas, endocrine cells)

- Absorption (intestine)

- Defense against foreign invaders (neutrophils, lymphocytes, macrophages) . Inflammation is described in the Egyptian papyrus (3000BC).

In the first century, the Roman writer Celsus described 4 cardinal signs of inflammation (rubor, tumor, calor, and dolor). The fifth cardinal sign, the functio laesa was added by Virchow.In 1793, John Hunter noted that inflammation is not a disease but is a beneficial response of the host The detail vascular changes in inflammation was recorded by Julius Cohnheim (1839- 1884).In 1882, Elie Metchnikoff described that phagocytes engulf the offending agents to destroy and

remove them (hence phagocytes accumulate in inflammation). Paul Ehrlich described that factors in the serum is needed to neutralize the infective agents. It soon became clear that both cellular (phagocytes) and serum factors (antibodies) are important defense against microorganisms. Thomas Lewis established that chemical substances such as histamine locally induced by injury mediate the vascular changes in inflammation. Thus, at the present century, knowledge of inflammation has reached from cellular age to the chemical and molecular age

Definition: Inflammation of prolonged duration (weeks and months), in which active inflammation, tissue destruction and healing occur simultaneously.

Acute inflammation is characterized by vascular changes, edema and neutrophilic infiltration, where as chronic inflammation is characterized by infiltration of mononuclear cells i.e. macrophages, lymphocytes and plasma cells along with tissue destruction and repair by fibrosis.

Causes

1. Following acute inflammation due to persistence of the injurious agent or interference of healing. Example: Acute osteomyelitis
1. Repeated bouts of acute inflammation. Example: duodenal ulcer. Peptic Ulcer
2. Low intensity injurious agents:
   (i) Intracellular low toxicity microbes. Example: Mycobacterium Tuberculosis, T. pallidum, virus, fungi etc. Infectious Disease Online-India.
   (ii) Toxic agents. Example: Silica , asbestosis. Visit: Silicosis ;
   (iii) Immune reactions. Example: autoimmune diseases

Granulomatous Inflammation

It is a distinctive pattern of chronic inflammation, in which the predominant cells are activated macrophages, which are enlarged, oval or elongated with indistinct cell boundary and called epithelioid cells. Diagnosis of granuloma rests on the identification of epithelioid cells. Epithelioid cells may coalesce to form multinucleated giant cells (Visit: Tuberculosis).

Two types of granuloma

(i) Foreign body: Incited by inert foreign bodies. Example: suture materials, splinter, breast prosthesis, silica, asbestos etc. foreign body granuloma ; Silicone granulomas

(ii) Immune granulomas: It is Type IV hypersensitivity and mediated by T-cells, typically seen in tuberculosis.

Microscopically, granuloma is characterized by aggregation of epithelioid cells surrounded by lymphocytes. Epithelioid cells often fuse to form multinucleated giant cells. Giant cells with nuclei dispersed to the periphery of the cells are called Langhans type of giant cells.

Examples of Granulomatous inflammations:

Bacteria: Tuberculosis (Mycobacterium Tuberculosis) ; Leprosy (Mycobacterium Leprae); Syphilitic Gumma (T. pallidum); Cat Scratch Disease (gram-negative bacillus).

Parasite: Schistosomiasis.

Fungus: Histoplasma Capsulatum ; Blastomycosis ; Cryptococcus neoformis; Coccidioides immitis.

Inorganic metals and dusts: Silicosis ; Berylliosis. (Pneumoconiosis ; Silicosis ; Asbestosis ; Coal Pneumoconiosis ; Talcosis)

Foreign body: Suture materials ; Breast prosthesis ; Splinters. Foreign body granuloma ; Silicone granuloma

Acute inflammation is the immediate and early response to injury, characterized mainly by vascular changes with delivery of leucocytes to the site of injury to clear the invaded bacteria and damaged tissue.

(i) **Cardinalsigns**

1. Rubor (redness) due to dilatation of arterioles
2. Calor (heat)
3. Dolor (pain) due to pressure on nerve endings by edema fluid and chemical mediator bradykinine
4. Tumor (swelling) due to edema.
5. Functio laesa (loss of function) due to inhibition of movement by pain and tissue necrosis.

Sequence of vascular changes

1. Transient vasoconstriction of arterioles may be due to:

i) direct mechanical stimulation of capillaries

ii) Local axon reflex (vasoconstrictor fibers).

2. Persistent vasodilation - first arterioles, followed by opening of capillary beds, caused by chemical mediators.

3. Increased blood flow mainly due to arteriolar dilatation and opening of capillary beds.

4. Slowing of the circulation (Stasis) due to

i) Increased viscosity of blood due to fluid loss

ii) Swollen capillary endothelium due to toxin.

5. Flow of protein-rich fluid into extra-vascular space called inflammatory exudates.

Inflammatory Exudates: due to:

(i) increased intra-vascular hydrostatic pressure.
(ii) Increased permeability due to endothelial contraction with increased inter cellular gaps, of the venules.
(iii) Direct endothelial injury and detachment, involving venules, capillaries and arterioles.
(iv) Increased tissue osmotic pressure.

6. Margination and immigration of leucocytes

Normally red and white cells flow intermingled in the center of the vessel forming axial stream, separated from vessel wall by a clear cell-free plasmatic zone. Due to slowing of the circulation, leucocytes fall out of the axial stream and come to plasmatic zone known as margination of leucocytes. Leucocytes gradually adhere to the vessel wall known as pavementing of the leucocytes. Leucocytes squeeze between the endothelial cells by the process of diapedesis and migrate through the vessel wall into the interstitial tissue, a process known as emigration of leucocytes (first neutrophils followed by monocytes and lymphocytes). Emigrated leucocytes move towards the site of injury under the influence of chemo tactic agents & the process is called chemotaxis.

Termination of Acute Inflammation

1. Complete resolution- when minimal or no tissue damage and the involved tissues regenerate, there is restitution to normal structure. Example: Lobar pneumonia, acute infective hepatitis.
2. Healing by fibrosis - when there is substantial tissue destruction and the involved tissues do not regenerate. Example: Acute rheumatic carditis
3. Dissemination - cellulites, septicemia.
4. Progression to chronic inflammation-Example: Acute osteomyelitis

Types of acute inflammation

1**. Catarrhal type-** Mild inflammation in mucous membrane and is characterized by copious outpouring of mucus along with desquamated epithelial cells and a few leucocytes. Example: Common cold, catarrhal appendicitis etc.

2. **Serous type**- Mild inflammation in serous surface such as pleural cavity joint cavity etc with accumulation of low protein containing fluid (effusion). Example: Tuberculosis pleurisy. It is also seen due to repeated mild trauma. Example: Common blisters.

3**. Fibrinous type**- Characterized by outpouring of exudates with high protein and less volume. Commonly seen in serous surface such as pleura, peritoneum, and

pericardium. Two contiguous surfaces covered in fibrin tend to stick together and if not lysed scar tissue is formed with permanent loss of function - Example: Adhesive and constrictive pericarditis. Lobar Pneumonia due to Streptococcus pneumoniae is associated with massive fibrinous exudates in the lung alveoli. Visit: Pericardial Disease

Lobar pneumonia shows massive fibrinous inflammatory exudates in alveoli.

4. **Membranous type**- Fibrinous inflammation in which network of fibrin entangling inflammatory cells and bacteria forms pseudo-membrane. Example: Diphtheria , Bacillary dysentery. Pseudomembranous inflammation in diphtheria showing network of fibrin entangling inflammatory cells. Bacteria forming pseudo-membrane (left).

5. **Suppurative or purulent type**- Usually caused by pyogenic bacteria and is characterized by pus formation Example: Abscess.

Abscess

Abscess is the localized collection of pus, commonly seen solid block of tissue - Example: dermis, liver, kidney, brain etc. Pus consists of partly or completely liquified dead tissue mixed with dead or dying neutrophils and living or dead bacteria, Pyemic abscess in myocardium. Abscess containing necrotic cell debris, colonies of bacteria, and large number of neutrophils, many of them degenerate.Myocardium is on the right.

Microscopic feature

Central purulent zone is surrounded from inside outwards by, pus cells, living neutrophils and granulation tissue known as pyogenic membrane. This last layer represents the repair process and serves as a barrier to the spread of inflammation. It also prevents the discharge of pus from the abscess without which healing cannot occur. When pus is drained the granulation tissue proliferates to replace the necrotic tissues and repair is done.

6. **Phlegmonous type**- (Phlegmon means fire): Characterized by woody hardness of the inflamed area due to low resistance of the body and high virulence of the bacteria - Example: Erysipelas, pelvic cellulites etc.

Function of chemotactic agents

1. *Recognition* and engulfment of microorganisms by covering it with serum protein (opsonin).
2. Activation of leucocytes causing liberation of oxygen metabolites, enzymes etc. which kills the engulfed microorganisms.
3. These liberated toxic metabolites and proteases also cause tissue damage.

Different mediators are discussed separately but they are intimately related and their actions start in sequence.

Once started, they are quickly inactivated or destroyed by enzymes or other substances, so that inflammation may not persist.

Chemical mediators may be

1. Exogenous - microbial products

2. Endogenous.

Endogenous chemical mediators

Early phase

Vasoactive amines

1. Histamine - Source: mast cells, basophils, platelets. Action: increases vascular permeability.

2. Serotonin (5HT) - Source: platelets. Action: similar to histamine.

Intermediate Phase

1. Kinin system

Kallikrein (Plasma substrate): i) Plasma - Bradykinin ; ii) Tissue - Kallidin. Action: i) Pain and increased vascular permeability ; ii) Chemotaxis of neutrophils and monocytes.

2.Compliment derivatives : Action: acts by increasing vascular permeability and chemotaxis of neutrophils monocytes (3a and 5a called anaphylatoxin).

3. Permeability globulin : Present in plasma. Action: similar to compliment.

4. Leukotrienes: present in all leukocytes. Action: similar to compliment.

Late phase

1. Prostaglandins : Liberated from all leukocytes and platelets. Action: (i) Vasodilation, pain and fever (ii) Potentiates actions of other chemical mediators.

2. Slow Reacting Substance of Anaphylaxis (SRS- A): Liberated from mast cells, basophils and neutrophils. Action: potentiates the actions of other chemical mediators.

2. PLANT PROFILE

DESCRIPTION OF THE PLANT

Figure:4 - *Solanum pubescens willd* leaves

- **Botanical information : Solanum pubescens willd**
- **Family : Solanaceae**
- **Synonyms :** *Cyphomandra luteoalba* (Pers.) A.Child

  Cyphomandra luteoalbum (Pers.)

  Solanum luteoalbum var. tunya J.F.Macbr.

  Solanum pubescens Ruiz & Pav.

Vernacular Names

English	:	Wild brinjal
Telugu	:	Mulla vankaya

Taxonomical classification

Kingdom	:	Plantae – Plants
Super division	:	Spermatophyta – seed plants
Division	:	Magnoliophyta – Flowering plants
Class	:	Magnoliopsida - Dicotyledons
Subclass	:	Rosidae
Order	:	Solanales
Family	:	Solanaceae
Genus	:	Solanum
Species	:	*Solanum pubescens willd*

Description:

Solanum pubescens willd. Commonly known as wild brinjal is a sherb, with ovate 12 cm long leaves, Flowers are violet, arranged in leaf axils. Fruits are berry, on mature orange colour, seeds are copious-drying brown, *Solanum pubescens willd.*. Growing to about 2.5 metre.Its inflorescence is raceme and size up to 2.5-3 cm long. *Solanum pubescens willd.*. Native range extends from Africa to Asia including India, Philippines, China, Indonesia, Malaysia, and Thailand

Habitat:

Solanum pubescens willd.. is widely distributed throughout the tropics and can be found both in wild ,among thron plants&road edges, states on the plains of India. **(Muthu karthick et al 2010)**

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Propagation : By seeds

Parts used : Leaves and flowers

Chemical constituents:

The leaves of *solanum pubescens willd.* Contain steroids, tannins and flavonoids. Other constituents such alkaloids, carbohydrates, resins have also been reported. **(HEMAMALINI. K et al 2011)**

Uses:

The juice of the roots and leaves of the plant are considered to be useful in treatment of asthma. The juice of the stem is used as hepato protective. The leaves are used as poultice in the treatment of skin eruptions. The plant is used as a laxative and analgesic. Its roots contain resins, alkaloids, starch, glucose, gums, fatty acids, carbonic acid. Besides these, it contains minerals like Ca, Fe, and Ph. (**HEMAMALINI. K et al 2011**)

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3. LITERATURE RIVIEW

☞ ***P.*** **Thirunavukkarasu et al., 2009** has studied the Anti-ulcer Activity of *Excoecaria agallocha* bark on NSAID-induced Gastric Ulcer in Albino Rats. The plant extract of *Excoecaria agallocha* bark herbal preparation has been used in the treatment of varies diseases such as in anti tumor, anti microbial, anti wound killing agents and anti oxidant. The study report showed that the gastro protective effect of E. agallocha in a model of NSAID induced ulcer rat. The lyophilized extract was given by oral gavages (125 and 62.5mg/kg) three times at 12 h intervals before administering dicolofenac 100mg/kg. Pretreatment with the extract resulted in a significant decreased of the ulcerated area. The volume and acidity of the gastric juice decreased in the pretreated rats. The plant extract was elevated in the gastric juice of untreated rats, showed hear normal levels in the pretreated rats. The E. agallocha was able to decrease the acidity and increase the mucosal defense in the gastric areas, there by justifying its use as an antiulcerogenic agent.

☞ **HEMAMALINI. K et al., 2011** has reported that the methanolic extract of *solanam pubescens* and *gymnosporia emerginata* leaves for its anthelmintic activity using earthworm's phertima posthuma. Various concentrations (10 – 35 mg /ml) of plant extract were tested in bioassay. Piperazine citrate (10mg/ml) was used as reference standard drug whereas distilled water as control. Determination of paralysis time and death time of the worms were recorded. Extract exhibited significant anthelmintic activity at highest concentration of 50 mg/ml.The result showed that methanolic extract possess vermicidal activity and found to be effective as an anthelmintic.

☞ **Mayank Kulshreshtha et al., 2011** has studied the effect of aqueous extract of *Ficus bengalensis (FBE)* in different acute and chronic gastric ulcer models in rats. Gastric ulcers induced in Swiss albino rats (200g, N=6) by oral administration of aspirin suspension and pylorus ligation. The anti ulcer activity was studied by determining and comparing the ulcer index in the test drug groups with that of the vehicle control and standard ranitidine & sucralfate. FBE, 250–500 mg/kg administered orally, twice daily for 5 days

showed dose-dependent ulcer protective effect in pylorus ligation (51.28, 63.24% protection, P < 0.01 to P < 0.001), aspirin (28.94, 64.91 protection, P < 0.001). The parameters taken to assess antiulcer activity were pH of gastric juice.

Total acidity and ulcer index. The results indicated that aqueous extract significantly (p<0.05) Ph, total acidity and ulcer index. On the basis of histopathology analysis, the results indicate that FBE possesses antiulcer activity in a dose dependent manner.

☞ **Hemant Kumar et al., 2011** has reported that *Ficus religiosa* is being used in Ayurvedic and Malay traditional medicine for the treatment of various diseases including gastric ulcer. They validated the anti-ulcer potential of the ethanol extract of leaves of *Ficus religiosa* against in vivo aspirin induced ulcer and pylorus ligation assays. Gastric ulcers induced in Swiss albino rats by oral administration of aspirin suspension and ligate the pylorus part of stomach. The antiulcer activity was examined by determining and comparing the ulcer index in the test drug groups with that of the vehicle control and standards. Therefore all models showed significant anti-ulcer property in a dose dependent manner. The parameters taken to assess antiulcer activity were volume of gastric juice, free deity, total acidity and ulcer index. The results indicated that ethanolic extract significantly p<0.001) decreased the volume of gastric acid secretions, free acidity and total acidity and ulcer index.

☞ **M.A. Al-Yahya et al., 1988** has studied the Gastroprotective Activity of *Ginger Zingiber Officinale Rose,* in Albino Rats**.** They studied the cytoprotective and gastric anti-ulcer properties of ginger was carried out in albino rats. Cytodestruction was produced by 80% ethanol, 0 .6M HCl, 0. 2M NaOH and 2 5% NaCl. Whereas gastric ulcers were produced by ulcerogenic agents including indomethacin, aspirin and reserpine, beside hypothermic restraint stress and by pylorus ligated Shay rat technique. The results of this reported that the extract in the dose of 5 0 mg/kg orally exert highly significant cytoprotection against 8 0% ethanol, 0. 6M HC1, 0. 2M NaOH and 25% NaCl induced gastric lesions. The extract also prevented the occurrence of gastric

ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) and hypothermic restraint stress. These observations suggest cytoprotective and anti-ulcerogenic effect of the ginger.

☞ **MOHAMED S. KARAWYA et al., 2010** has reported that the anti-inflammatory activity of different extracts of five plants abundantly growing in Egypt, namely *Ipomoea palmata Forsk. (Convolvulaceae), Alstonia scholaris R.Br. (Apocynaceae), Salix subserrata Willd. Salix tetrasperma Roxb. and Populus nigra Linn. (Salicaceae)* has been studied. They studied on Photochemical properties of selected bioactive extracts was carried out as well as their possible mechanism of action. They reported that the anti-inflammatory activity of the extracts under investigation to different degrees. A chromatographic study of the bioactive lipoidal extracts of A. scholaris and I. palmata was carried out and the results revealed the presence of unsaturated fatty acids (linoleic and linolenic). Beta-sitosterol and campesterol were present in A. scholaris and I. palmata, respectively. Chromatographic and spectral investigation of the flavonoids in the bioactive aqueous extract of I. palmata revealed the presence of luteolin, quercetin 7-glycoside and apigenin. The anti-inflammatory activity may be due to the presence of these phytochemical constituents.

☞ **Ramachandran.S et al., 2011** has studied t the Evaluation of anti-inflammatory and analgesic potential of methanol extract of *Tectona grandis* flowers. They evaluated anti-inflammatory and analgesic activity of methanol extract of *Tectona grandis (T. grandis)* flowers (METGF) in animal models to support its traditional use. Acute toxicity study was performed to determine the toxicity level of METGF in mice and rats. Carrageenan (1% w/w) was administered and inflammation was induced in of rat paw. Analgesia was induced by intraperitoneal injection of 0.6% v/v acetic acidin mice to assesperi pheral analgesic of METGF also,hot-plate was used to induce pain in mice to evaluate central analgesic action of METGF

☞ **Biswa Nath Das et al., 2009** has screened the Anti-inflammatory activity of bark of *Xeromphis spinosa*. The bark of Xeromphis spinosa extracted by a mixture of equal proportions of petroleum ether, ethyl acetate and methanol at an oral dose of 200 and 400 mg/ kg body weight exhibited significant anti-inflammatory activity when compared with control.

☞ **Hossein Hosseinzadeh et al., 2002** has reported that the Anti-nociceptive and anti-inflammatory effects of *Crocus sativus L.* stigma and petal extracts in mice. *Crocus sativus L. (saffron)* is used in folk medicine, for example as an antiedematogenic agent. They evaluated the anti-nociceptive and anti-inflammatory activity of saffron extracts in mice. They used aqueous and ethanolic maceration extracts of *Crocus sativus L.* stigma and petals. Anti-nociceptive activity was examined using the hot plate and writhing tests. The effect of extracts against acute inflammation was studied using xylene induced ear edema in mice. The activity of the extracts against chronic inflammation by formalin-induced edema in the rat paw. In the hot plate tests, intraperitoneal injection of both extracts showed no significant anti-nociceptive activity in mice. The extracts showed anti-nociceptive activity against acetic acid induced writhing. Naloxone partially blocked only the antinociceptive activity of the stigma aqueous extract. Only the stigma extracts showed weak to moderate effect against acute inflammation. In chronic inflammation, both aqueous and ethanolic stigma extracts, as well as ethanolic petal extract, exerted anti-inflammatory effects. Conclusions: They conclude that aqueous and ethanolic extracts of saffron stigma and petal have an antinociceptive effect, as well as acute and/or chronic anti-inflammatory activity.

☞ **Sharma U.S** et **al.,** has screened the Anti-inflammatory activity of *Cordia dichotoma forst f.* seeds extracts. The effects of *Cordia dichotoma forst f.* seeds extract on different phases of acute inflammation were examined. Investigations were performed using different phlogistic agents-induced paw edema viz., Carrageenan-induced paw oedema and Dextran- induced paw oedema in rats. Various extracts (ethanol and aqueous) of Cordia dichotoma forst seeds at a dose of 250 mg/kg and 500 mg/kg orally were tested.

Diclofenac sodium at the dose of 10mg/kg was used as standard. Both the extracts showed significant activity (*p<0.05 & **p<0.01) compared with the control in both of these models. The dry powdered seeds were found to contain alkaloids, glycosides, saponins, tannins and carbohydrates. Thus it is revealed from the screening model used that the ethanol extract and aqueous fraction of this plant possesses acute anti-inflammatory activity.

☞ **Yazmín K. Márquez et al., 2009** has studied the Anti-inflammatory activity of aqueous and methanolic extracts of *Oenothera rosea L´ Hér. ex Ait* in the rat. *Oenothera rosea L´ Hér. ex Ait. (Onagraceae)* is commonly known as hierba del golpe. It is used in Mexican Folk Medicine to treat inflammatory, renal and bacterial diseases. They evaluated the anti-inflammatory activity of aqueous and methanolic extracts of this plant. Aqueous extract at a dose of 500 mg/kg body weight (b.wt.) and methanolic extract (100 mg/kg b.wt.) of *Oenothera rosea* were evaluated for anti-inflammatory activity using the cotton pellet-induced granuloma formation model in rat and histological techniques. Both extracts produced a significant decrease of the inflammatory rocess in relation with the control groups (p<0.05). The anti-inflammatory effect of methanolic extract was similar to the effect of indomethacin. This data was supported by the histological results. No extracts produced gastrointestinal damage. The LD50 of aqueous and methanol extracts, was higher than 40 and 8 g/kg, respectively. They evaluated that both extracts of *Oenothera rosea* induced anti-inflammatory activity and it was considered not toxic**.**

☞ **FAYYAZ AHMAD et al., 1992** has reported that the anti inflammatory activity from Plant extracts of *lactuca scariola and artemisia absinthium* Seeds and samples of stems from the two medicinal plants, *Lactuca scariola and Artemisia absinthium* respectively were extracted in absolute methanol to determine their analgesic and anti-inflammatory activity. They studied analgesic activity on intact mice by tail flick latency in tail immersion method. The anti-inflammatory activity was estimated volumetrically by measuring the mean increase in hind paw volume of rat with the help of plethysmometer.

Acetylsalicylic acid in the dose of 300 mg/kg is used as standard drug. Both plant extracts were given in the doses of 300, 500 and 1000 mg/kg. Control group received 0.9% NaCI (saline) solution. All the doses administered orally. Results showed that Lactuca had potent analgesic activity and Artemisia had significant analgesic and anti-inflammatory activity.

☞ **M.J. Abada et al., 2006** has studied Anti-inflammatory activity of four *Bolivian Baccharis species (Compositae).* Hexanic, dichloromethanic, ethanolic and aqueous extracts from *Baccharis obtusifolia HBK, Baccharis latifolia (R. et P.) Pers., Baccharis pentlandii D.C. and Baccharis subulata Wedd*., plants used in the traditional medicine of South America have been studied for their in vitro anti-inflammatory activity in cellular systems. Calcium ionophore A23187-stimulated mouse peritoneal macrophages were validated as a source of cyclooxygenase-1 (COX-1) (prostaglandin E2, PGE2) and 5-lipoxygenase (5-LOX) (leukotriene C4, LTC4), and mouse peritoneal macrophages stimulated with Escherichia coli lipopolysaccharide (LPS) were used for testing cyclooxygenase-2 (COX-2) (PGE2), nitric oxide (NO) and tumour necrosis factor-_ (TNF-_) activity.

☞ **RICARDO GONZA´LEZU et al., 1999** has screened the anti-inflammatory activity of *phycocyanin* extract in Acetic acid-induced colitis in rats. The anti-inflammatory effect of *c-phycocyanin* extract was studied in acetic acid-induced colitis in rats. *Phycocyanin* -150, 200 and 300 mg kgy1 p.o.. Was administered 30 min before induction of colitis with enema of 1 ml of 4% acetic acid per rat. Twenty-four hours later myeloperoxidase _MPO activity was determined as well as histopathological and ultrastructural studies were carried out in colonic tissue. *Phycocyanin* substantially reduced MPO activity which was increased in the control colitis group. Also, histopathological and ultrastructural studies showed inhibition in inflammatory cell infiltration and reduction to some extent in colonic damage in rats treated with *phycocyanin*. The probable role of antioxidative and the scavenging properties of *phycocyanin* against reactive oxygen species in the anti-colitic effect is

discussed in this paper. To our knowledge this is the first report on the anti-inflammatory effect of *phycocyanin* in an experimental model of colitis

☞ **Priyanka Vijay and Rekha Vijayvergia et al., 2010** has studied the Analgesic, anti-inflammatory and antipyretic activity of *Cissus quadrangularis*. They evaluated the analgesic anti-inflammatory and antipyretic activity of ethanolic extract of *Cissus quadrangularis* in experimental standard modals i.e. albino rats following oral administration. The reported that the ethanolic extract significantly reduce the edema induced by carrageenan within 1 to 5 hrs. Post dosing at all the dose levels used. On the analgesic property acetic acid induce writhing was significantly reduce in the formalin test, the extract also significantly decreases the painful stimulus in both phases of test which confirms central and peripheral effects of the drugs. Its effects on antipyretic activity were also appreciable it significantly reduces fever at higher doses within 2 hrs. On yeast induce hyperthermia in rats.

☞ **C. O. Okoli et al., 2005** has reported that the anti-inflammatory activity of extracts of root bark of *securidaca longipedunculata fres (polygalaceae)*. The effect of extract and fractions of the root bark of *Securidaca longipedunculata Fres (Polygalaceae)* on acute inflammation was evaluated. Solvent extraction yielded the crude methanol extract (ME) while solvent–guided extraction yielded a petroleum ether fraction (PF) and methanol fraction (MF). The extract and fractions inhibited topical edema induced by xylene in the mouse ear. In the systemic edema of the rat paw, the methanol extract (ME) and methanol fraction (MF) significantly ($P<0.05$) suppressed the development of paw edema induced by egg albumin in rats while the petroleum ether fraction (PF) was devoid of such activity. Ulcerogenic assay in rats indicated that the extract and fractions exhibited varying degrees of gastric irritation in rats in the order of magnitude: MF > PF > ME. Phytochemical tests showed that ME and MF tested positive for carbohydrates, reducing sugars, glycosides, flavonoids, terpenoids, sterols and saponins while PF gave positive reaction for resins only.

☞ **P. Muthusamy et al.,** has screened the Ethanolic extract of *Azima tetracantha* leaves. The extract was studied for its ulcer protective activity on aspirin and pylorus ligation and cold restraint stress induced ulcer models. Various biochemical parameters such as gastric volume, pH of gastric content, free acidity and total acidity, were examined on the test and control group animals. The extract at a concentration of 200 and 400 mg/kg exhibited a protective effect on ulcer-induced models in a dose dependent manner and was comparable with the standard drugs ranitidine and Omeprazole.

☞ **R. S. Deoda et al.,** has studied the Gastro-protective effect of *Rubia cordifolia Linn.* On Aspirin plus Pylorus-Ligated Ulcer. They studied that the effect of *Rubia cordifolia (Rubiaceae)* against experimentally induced gastric ulcer and compare activity with its fractions by employing aspirin plus pylorus-ligated ulcer screening model in Wistar rats. Total acidity, volume of gastric acid secretion, total acid output, and pepsin activity show significant reduction, when compared with the control group. The study confirmed that chloroform fraction showed the significant activity at lower doses compared to parent extract. The mechanism can be attributed to decrease in gastric acid secretary activity along with strengthening of mucosal defensive mechanism by prostaglandin synthesis and antioxidant potential.

☞ **Raju.D et al.,** has screened the anti-ulcer activity of *Terminalia chebula* fruits in experimental rats. He investigated the anti ulcer activity of methanolic extract of *T.chebula* fruits in pylorus ligated and Ethanol-induced ulcer models in wistar rats. In both the models the common parameter determined was Ulcer Index. The study showed that the Methanolic extract produced significant inhibition of the gastric lesions induced by Pylorus ligation induced ulcer & Ethanol induced gastric ulcer .The extract (250 mg/kg & 500 mg/kg) also showed significant ($P<0.01$) reduction in gastric volume, free acidity and ulcer index as compared to control.

☞ **Vivek Sharma and Rajini. G. P et al.,** have evaluated the anti-inflammatory and anti-ulcer activities of Ethanolic and aqueous extract of aerial parts of *Caesalpinia pulcherrima (linn)*. Pylorus-ligation and aspirin induced models were employed for evaluating the anti-ulcer activity of the extracts. For evaluating the anti-inflammatory action, cotton-pellet granuloma model was used. Ethanolic and Aqueous extracts significantly decreased the granuloma tissue developed. Also Ethanolic and Aqueous extracts showed significant reduction in anti-ulcer activity by decreasing ulcer score in both models of ulcer.

4. SCOPE OF WORK

Inflammation or phlogosis is a pathophysiological response of living tissue to injury that leads to the local accumulation of plasmatic fluid and blood cells. Whereas an ulcer is an erosion in the GIT which results when the lining of the GIT gets corroded by the acidic juices secreted in the stomach. Inflammation is a symptom and is expressed in many disease conditions like rheumatoid arthritis, gout and some allergic reactions to name a few.

Many synthetic anti-inflammatory and anti-ulcer drugs are available in the market but most of them are associated with many adverse and unwanted effects like Gastro-intestinal irritation, ulceration and fluid retention. In addition to aggravating the ulcers, NSAIDS also produce hepato-toxicity and nephro-toxicity. Since ancient times people have been relying on plants either as prophylactic of therapeutic agents to restore and maintain the health. Medicinal plants have been used in the development of new drugs which may have an invaluable role in the progress of drug discovery. Therefore a need for the development of newer anti-Inflammatory and anti-ulcer agents from natural source with more powerful activity and lesser side effects which act as effective substitute for chemical therapeutics.

According to ethnobotanical information the plant *Solanum pubescens willd* has been used for the treatment of various conditions including ulcer and inflammation and for the same clear scientific evidence was not proved by any means. So, it is considered as worthful in selecting the above plant for the research work.

5. PLAN OF STUDY

The present study is undertaken to standardize the leaves of the plant *solanum pubescens willd* and to evaluate its anti-inflammatory and anti-ulcer activity potential with emphasize on its mechanism of action.

The study is divided into two parts

I. PHYTOCHEMICAL EVALUATION ETHANOLIC EXTRACT OF *SOLANUM PUBESCENS WILLD*

1. Collection of plant (Solanum *pubescens willd*) leaves and shade dried.
2. Extraction of *Solanum pubescens willd* leaf powder using Ethanol in soxhlet apparatus for 72 hrs.
3. Phytochemical investigation of ethanolic extract of *Solanum pubescens willd* leaf.

II. PHARMACOLOGICAL EVALUATION OF ETHANOLIC EXTRACT OF *SOLANUM PUBESCENS WILLD*

1. Anti-ulcer activity

- Pylorus ligation induced ulcer.
- Aspirin induced ulcer.

2. Anti-inflammatory activity

- Carrageenin induced paw oedema.

6. MATERIALS AND METHODS

6.1 PLANT COLLECTION:

The leaves of *Solanum pubescens willd were* collected from Tirupati, chittoor district, Andhra Pradesh. It was identified and authenticated by Prof k.madhava chetty,Msc,Med,M.phill ,Ph.D., department of botany, sri venkateswara university, tirupati.

6.1.1 Preparation of extract:

The leaves of *Solanum pubescens willd were* shade dried and then ground till they became coarse powder in a motar-pestle. The powdered material thus obtained was subjected to extraction using Petroleum Ether and Ethanol. The extracts obtained were distilled to remove excess of the solvent and then evaporated at 40^{o}C to get a semi-solid mass. These extracts were subjected to phytochemical tests which have been described below.

6.1.2 Animals:

Wistar rats of either sex (150-200gms) were housed in separate cages at controlled room temperature (24 ±2^{o}C; relative humidity 60-70%) in a 12hr light-dark cycle. They were fed with standard pellet diet and water *ad libitum*.

6.2 QUALITATIVE PHYTOCHEMICAL ANALYSIS:

6.2.1 Chemical Tests:

General method followed for screening of the constituents present in the extract is as follows.

Detection of Carbohydrates:

Extracts were dissolved individually in 5ml of distilled water & filtered. The filtrates were used to test the presence of carbohydrates.

1).Molisch's Test:	Filtrates were treated with 2 drops of alcoholic α-naphthol solution in a test tube & 2ml concentrated sulphuric acid was added carefully along the sides of the test tubes. Formation of violet ring at the junction indicates the presence of carbohydrates
2).Benedict's Test:	Filtrates were treated with Benedict's reagent & heated on water bath. Formation of an orange red precipitate indicated the presence of reducing sugars
3).Fehling's Test:	Filtrates were hydrolysed with dilute hydrochloric acid, neutralized with alkali & heated with Fehlings A & B solutions. Formation of red precipitate indicates the presence of reducing sugars.

(B). <u>Detection of Alkaloids:</u>

Extracts were dissolved individually in dilute hydrochloride acid & filtered. The filtrates were tested carefully with alkaloid reagents.

1).Mayer's Test:	Filtrates were treated with Mayer's reagent (potassium mercuric iodide), formation of a yellow cream precipitate indicate the presence of alkaloids.

2).Wagner's Test:	Filtrates were treated with Wagner's reagent (iodine in potassium iodide) & observed. Formation of brown/reddish brown precipitate indicates the presence of alkaloids.
3).Dragendroff's Test:	Filtrates were treated with dragendroff's reagent (solution of potassium bismuth iodide). Formation of red precipitate indicates the presence of alkaloids

(C). Detection of Phytosterols:

1).Salkowski's Test:	The extracts were treated with chloroform & filtered separately. The filtrates were treated with few drops of concentrated sulphuric acid, shaken & allowed to stand. If the lower layer turns red, sterols are present. If lower layer turns golden yellow tri-terpenes are present.
2).Libermann Burcchard Test:	The extracts were treated with chloroform solution & few drops of concentrated acetic anhydride solution followed by sulphuric acid. A blue color shows the presence of phytosterols.

(D). <u>Detection of Glycosides</u>:

Extracts were hydrolysed with dilutes hydrochloric acid & the hydrolysate was subjected to glycosides tests.

(i). Test for Cardiac Glycosides: **1).Legal's Test:**	To the hydrolysate 1ml of pyridine & few drops of sodium nitro prusside solution are added & then it is made alkaline with sodium hydroxide solution. Color change shows the presence of glycosides
2).Liebermann's Test:	3ml of extract with 3ml acetic anhydride was heated, cooled then added few drops of concentrated.sulphuric acid. Blue color appears in presence of bufadenolids.
(ii).Test for Anthraquinone Glycosides: **1).Borntrager's Test:**	Hydrolysate is treated with chloroform & the chloroform layer is separated. To this, equal quantity of dilute ammonia solution is added. Color changes in the ammonical layer shows the presence of 'O' glycoside (zero glycosides).

(E). Test for Deoxy Sugars (Keller Killiani Test):

To 2ml of extract, glacial acetic acid, one drop of 5% $FeCl_3$ & conc.H_2SO_4 was added. Reddish brown color appears bluish green.

(F). Test for Saponins:

1).Froth's Test:	The extracts were diluted with distilled water to 20ml shaken in a graduated cylinder for 15min. the formation of 1cm layer of foam indicates the presence of saponins.

(G).Test for Phenolic & Tannins:

1).Ferric Chloride Test: **6** **.**	The extract was treated with few drops of neutral ferric chloride solution. The formation bluish black color indicates the presence of phenolic nucleus.
2).Gelatin Test: **.** **D** **E**	To the extract, 1% gelatin solution containing sodium chloride was added. The formation of white precipitate indicates the presence of tannins.

(H). Test for Flavonoids:

1).Lead Acetate Test:	The extracts were treated with few drops of lead acetate solution; formation of yellow precipitate indicates the presence of flavonoids.
2).Alkaline Reagent Test:	The extracts were treated with few drops of sodium hydroxide separately. Formation of intense yellow color, which becomes colorless on addition of few drops of dilute acid, indicates the presence of flavonoids
3).Shinoda Test:	The extracts were treated with few fragments of magnesium metal separately, followed by drop wise addition of concentrated Hcl. The formation of magenta color indicates the presence of flavonoids.

(I). Detection of Proteins & Amino Acids:

1).Millon's Test:	The extracts were treated with 2ml of Millon's reagent. The formation of white precipitate, which turns to red upon heating, indicates the presence of proteins.
2).Ninhydrin Test:	To the extracts, 0.25% ninhydrin reagent was added & boiled for few minutes. Formation of blue color indicates presence of amino acid.

3).Xanthoprotein test:	The extract, was added with 20% of sodium hydroxide any orange color produced indicates presence of aromatic amino acid. **(Khandelwal, 2004)**

6.3.DETERMINATION OF ACUTE ORAL TOXICITY (LD_{50}) OF *Solanum pubescens willd*

Test substance details:

Name of the test substance: Ethanolic extract of *Solanum pubescens willd leaves*.

Color **:** Greenish black

Nature of the test **:** gummy

Substance

Experiment protocol:

Name of the study	Acute toxicity
Guideline followed	OECD 425 method-acute toxic class method
Animals	Healthy young adult non-pregnant Swiss albino mice.
Body weight	25-30 g
Sex	Male
Administration of dose and volume	2000 mg/kg body weight, single dose in 0.2ml
Number of groups and animals	2groups and 6animals
Route of administration	Oral by using mice oral feeding needle
Vehicle	Carboxy methyl cellulose(CMC)

Housing and feeding conditions:

Room temperature	22°C ± 3°C
Humidity	40-60%
Light	12 h : 12h (light : dark cycle)
Feed	Standard laboratory animal food pellets with water *ad libitum*

Study period and observation parameters:

Initial observation	First 30 minutes
Special attention	First 1-4 hrs after drug administration
Long term observation	Up to 14 days
Direct observation parameters	Diarrhea, sitting in the corners, sniffing excessively, standing on hind limbs,
Additional observation parameters	Skin and fur, eyes and mucous membrane, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern etc.

6.3.1. Study procedure:

Acute oral toxicity was performed as per Organization for Economic Co-operation for Development (OECD) guideline 425 methods. The extract was administered in a single dose by gavages using specially designed mice oral needle. Animals are fasted 24h prior to dosing (food was withheld, but not water). **(OECD Guideline for testing of chemicals 425**). Ethical clearance (for handling of animals and the procedures used in study) was obtained from the institutional Animal Ethics

Committee before performing the study on animals. The proposal number being 22MP01DEC10.

6.4. PHARMACOLOGICAL EVALUATION:

6.4.1 Animal selection:

Healthy adult male Wistar albino rats weighing between 150 and 200gms were selected for the anti-ulcer studies.

6.4.2 Housing and feeding condition:

The temperature in the experimental animal room was kept 22±30C. Artificial lighting was provided. The animals were acclimatized to standard laboratory conditions of temperature (22 ± 30^{o}C) and maintained on 12:12 h light: dark cycle. The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They were provided with regular rat chow diet and distilled water *ad libitum.*

6.4.3. Preparation of animals:

The animals were randomly selected and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions.

6.4.4. Extracts & Standards used:

Extract used: Dried leaves of *Solanum pubescens willd Ethanolic* extract.

Standard used:

- Omeprazole: 20 mg/kg b.w..
- Indomethacin: 10 mg/kg b.w

Drugs, viz, Omeprazole and Indomethacin and the test extract of *Solanum pubescens willd* were suspended in 0.5% CMC and used for anti-ulcer and anti inflammatory studies. Each drug suspension was freshly prepared just before administration.

6.4.5. Preparation and administration of doses:

The extract was solubilised in 0.5% Carboxy Methyl Cellulose prior to experimental use to obtain the desired concentrations (200 and 400 mg/kg body weight) in 1 ml. The test substances were administered in a single dose using a gastric intubation tube after fasting for 3 to 4 hrs.

6.4.6. ANTI-ULCER ACTIVITY:

6.4.6.1 Aspirin induced Gastric ulcers:

Albino rats were divided into four groups of six animals each. The weight of the animals chosen was between 150 and 180gms. The animals were fasted 36hrs prior to the commencement of the experiment but were allowed free access to water.

- Group I(control): 0.5% CMC
- Group II: 20mg/kg omeprazole.
- Group III: ethanolic extract at dose 400mg/kg.
- Group IV: ethanolic extract at dose 200mg/kg.

All the animals received 200mg/kg of aspirin orally to the rats. In the treatment group, drugs were administered orally 1hr before the administration of aspirin. After 2hrs of treatment with aspirin, animals were sacrificed by an excess dose of ether. The stomachs were removed, opened along the greater curvature and examined for lesions. Lesions severity was determined by ulcer index. The ulcers were scored according to the following scale **(*P. Thirunavukkarasu et al 2009*)**:

- Normal coloration – 0
- Red coloration – 0.5
- Spot ulcer – 1
- Haemorragic streaks – 1.5
- Ulcer - 2
- Perforation - 3

Mean ulcer score for each animal will be expressed as ulcer index. The percentage of ulcer protection was determined as follows:-

$$\%\ Protection = \frac{(control\ mean\ ulcer\ index) - (test\ mean\ ulcer\ index)}{control\ mean\ ulcer\ index} \times 1$$

Statistical Analysis:

Statistical analysis was carried out using Graph Pad Prism5 software version 5.04 (Graph Pad prism software Inc.) The values were expressed as mean ± SEM. The statistical analysis was carried out by one way analysis of variance (ANOVA) followed by Dunnet's t-test. P values< 0.05 were considered significant.

6.4.6.2. Pylorus ligation induced Gastric ulcers:

Rats were divided into four groups of six animals each. All the animals selected for the study were of weight between 200-250gms.

- Group I (control), received, 0.5% CMC.
- Group II (reference standard) was treated with 20mg/kg omeprazole.
- Group III treated with 400 mg/kg ethanol extract of *Solanum pubescens willd*.
- Group IV was treated with 200mg/kg ethanolic extract of *Solanum pubescens willd*.

Animals in all the groups were fasted for 36 h after the respective assigned treatment and were anaesthetized with anaesthetic ether. The abdomen was opened by a small midline incision below the xiphoid process and pylorus portion of stomach was lifted out and ligated. Precaution was taken to avoid traction to the blood supply. The stomach was sutured with interrupted sutures. Animals were allowed to recover and stabilize in individual cages and were deprived of water during post-operative period. Four hours after the pyloric ligation, the animals were sacrificed by an excess dose of ether. The stomach was carefully removed and the gastric contents were collected. The gastric juice was centrifuged at 1000rpm and gastric volume was measured. Free and total acidites of the supernatant were determined by titration with 0.1 N NaOH and expressed as mEq/ L /100 gms. The stomach was cut open along the greater curvature and pinned onto a

soft board for evaluating the gastric ulcers and to calculate ulcer index. Ulcer scoring is done according to the scale mentioned below.

Ulcer Index:

After the incision of the stomach at the greater curvature the ulcers were observed. And the number of ulcers was counted using a magnifying glass and the diameter of the ulcers were measured using vernier calipers. The following arbitrary scoring system was used to grade the incidence and severity of lesions.

- ☞ Normal coloration – 0
- ☞ Red coloration – 0.5
- ☞ Spot ulcer – 1
- ☞ Hemorrhagic streaks – 1.5
- ☞ Ulcer - 2
- ☞ Perforation - 3

Determination of Free Acidity and Total Acidity:

The gastric contents were centrifuged at 1000rpm for 10mins. 1ml of supernatant was diluted with 9ml distilled water. A volume of 2ml diluted gastric juice was treated with 0.1 N sodium hydroxide run from a micro burette using 3-4 drops of Topfer's reagent as indicator until a canary yellow colour was observed. The volume of NaOH run down was noted. This corresponds to free acidity.

Further, 2-3 drops of phenolphthalein was added and titrated with NaOH until pink colour was restored. This gives total acidity.

Free acidity and Total acidity are expressed in terms of ml of 0.1N HCl per 100 gms of gastric contents. This is the same as mEq/lit. Acidity may be calculated by using

The following formula:

following formula:

$$Acidity = \frac{volume\ of\ NaOH \times Normality\ of\ NaOH \times 100}{0.1}\ mEq/L$$

6.4.6.3. Histopathological Evaluation:

The gastric tissue samples were fixed in neutral buffered formalin solution for duration of 24 hrs. Sections of tissue from stomachs were examined histopathologically to study the ulcerogenic and/ or anti-ulcerogenic activity of ethanolic extract of *Solanum pubescens*. The tissues were fixed in 10% buffered formalin and were processed using a tissue processor. These sections were stained with hematoxylin and eosin using routine procedures. The slides were examined microscopically for Pathomorphological changes such as congestion, haemorrhage, oedema and erosions using an arbitrary scale for the assessment of severity of these changes **(*P. Thirunavukkarasu et al*., 2009).**

6.4.3. ANTI-INFLAMMATORY ACTIVITY:

6.4.3.1. Carrageenin Induced Paw Oedema in Rats:

Male wistar rats weighing between 150-180gms were used for the study. The animals were divided into 3groups (n=5). The first group received 0.5% Carboxy Methyl Cellulose (1ml/kg p.o) served as control, while the second group received reference drug Indomethacin (20mg/kg p.o). The third and fourth group of animals were administered with 400mg/kg and 200mg/kg of ethanolic extract of *Solanum pubescens willd* respectively by oral route. Acute inflammation was produced by the sub-plantar administration of 0.1% Carrageenin (in 0.9% normal saline) in the right hind paw of the rats. The paw thickness was measured at 0min, 30min, 60min, 120min and 240min after carrageenin injection by using vernier calipers. The animals were pretreated with the test drugs 1hour before the administration of Carrageenin **(perez *et al*., 1995).**

Statistical Analysis:

Statistical analysis was carried out using Graph Pad Prism5 software version 5.04 (Graph Pad prism software Inc.) The values were expressed as mean ± SEM. The statistical analysis was carried out by one way analysis of variance (ANOVA) followed by Dunnet's t-test. P values< 0.05 were considered significant.

7. RESULTS

The ethonolic extract of *Solanum pubescens* willd was subjected to Phytochemical and pharmacological screening. Pharmacological screening involved the evaluation of anti-ulcer and anti-inflammatory activities. The results of the ethonolic extract of solanum pubescens has been documented below.

7.1 RESULTS OF PRELIMINARY PHYTOCHEMICAL EVALUATION:

The colour of the Alcoholic test extract (Ethonolic extract of *Solanum pubescens willd*) was found to be dark green in colour and the consistency was found to be sticky. The extracts were subjected to phytochemical screening for the presence of type of phyto-constituents. The phytochemical screening revealed that ethonolic extract contains resins, alkaloids, Phytosterols, Phenols and Flavonoids. Of the phytosterols, the ones identified were triterpenes. The results has been tabulated in the table no.3 showing various phytoconstituents in the extract.

Table No. 3

Phytoconstituents	**Extracts**	
	Petroleum ether	**Ehonol**
Carbohydrates	-	+
Glycosides	-	-
Alkaloids	-	+
Phytosteroids	-	_
Flavonoids	-	+
Protein and amino acids	-	-
Saponin	-	_
Phenols & tannins	-	+
Anthaquinone Glycosides	-	-
Triterpenoids	-	+

(-) represents Absence; (+) represents Presence.

7.2. ACUTE TOXICITY STUDY:

Ethonolic Extract of *Solanum pubescens* willd did not produce any toxic symptoms or mortality up to the dose level of 2000 mg/kg body weight. There was neither change in behavioral pattern nor any sign of toxicity during the observations up to 24hrs for mortality. Thus the extract was considered to be safe for pharmacological evaluation. Biological evaluation was carried out at doses of 200 and 400mg/kg.

Toxicological evaluations of ethonolic extract of *Solanum pubescens willd:*

Effect of ethonolic extract of *Solanum pubescens willd* on mice.

TABLE NO: 4 acute oral Toxicity study (425) observations.

S.NO	Response	
1	Alertness	N
2	Grooming	A
3	Anxiety	A
4	Roaming	N
5	Sniffing	N
6	Tremors	A
7	Convulsion	A
8	Depression	N
9	Gripping strength	N
10	Scratching	A
11	Defecation	A
12	Writhing	N
13	Pupils	N
14	Urination	N
15	Salivation	N
16	Skin colour	N
17	Lacrimation	N

N-Normal,A-Abscent

Result: From acute toxicity study it was observed that the administration of Ethonolic extract of *Solanum pubescens willd* to mice did not induce any toxicity of extract and mortality in the animals up to 2000mg/kg orally.

7.3. PHARMACOLOGICAL EVALUATION:

Evaluation of two activities, Anti-ulcer activity and anti-inflammatory activity, was carried out for the ethonolic extract of the plant.

Anti-ulcer was performed by two models,

i. Aspirin-induced gastric ulcers.
ii. Pylorus ligation induced ulcer.

The evaluation of Anti-inflammatory activity was carried out by means of Standard model:

i) Carrageenin induced hind paw oedema.

7.3.1. Anti-Ulcer Evaluation:

7.3.1.1Aspirin Induced gastric ulcers:

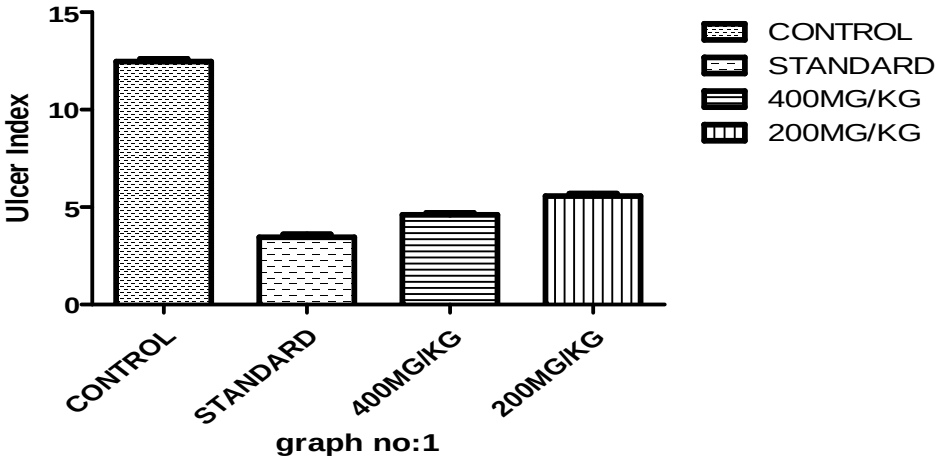
Table no: 5 shows the apparent effect of Omeprazole and Extract on the Ulcer Index and extent of mucosal damage in the stomach. In Group I i.e. control animals, oral administration of aspirin produced characteristic lesions in the glandular portion of rat stomach which appeared as elongated bands of thick, black & dark red lesions. Group II animals, pretreated with the standard drug, Omeprazole, showed considerable protection from ulcer in gastric mucosa. And in case of Group III and IV, EESP significantly reduced the ulcer Index at 400mg/kg and 200mg/kg doses to and respectively. Omeprazole as reference had the ulcer protection of. The intensity of heamorrhage and lesions was significantly reduced upon pretreatment, revealing the protective effect of EESP.

Table No. 5

Groups	**Ulcer Index**	**% Protection**
Group I- Control	12.24±0.06	--
GroupII- Standard(omeprazole)	3.49±0.08***	71.48 %
Group III – *s.pubescens willd* Extract 400mg	4.5±0.10***	63.23%
Group IV – *s.pubescens willd* Extract 200mg	5.72±0.05*	53.26 %

All values represent Mean ± SEM, n=6 in each group. P < 0.05. Control group (Group I) is compared with standard and extract doses, * represents significance.

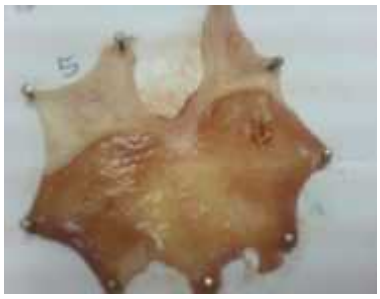
GRAPHICAL REPRESENATION:



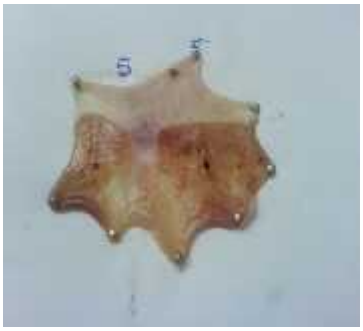
graph no:1

ULCER IMAGES (Aspirin Induced Ulcers):

(A)



(B)

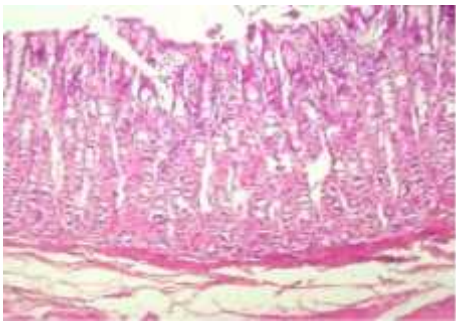


(C)

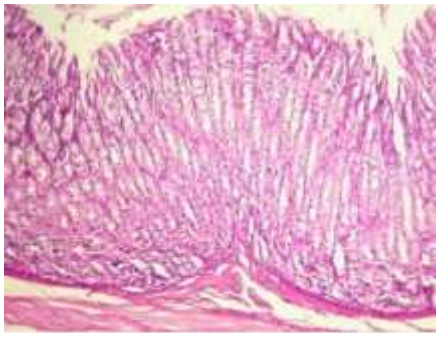
(D)

(A)– Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg

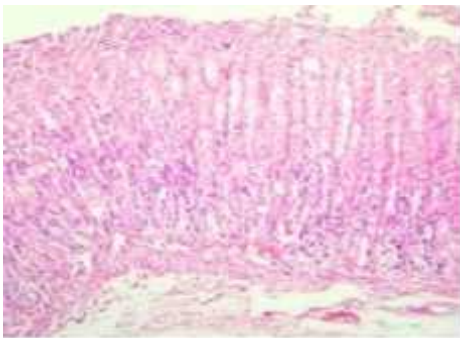
HISTOPATHOLGY IMAGES –ASPIRIN INDUCED ULCERS



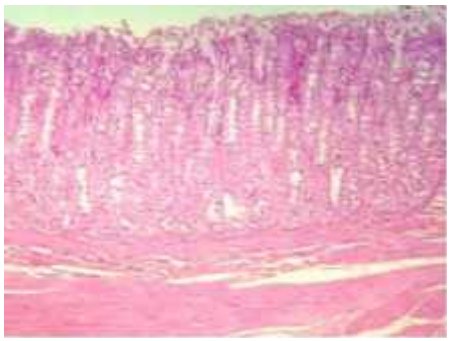
(A)



(B)



(C)



(D)

(A)- Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg.

Histopathology examination:

The images and the reports demonstrate a submucosal edema with mixed inflammatory infiltration consisting of lymphocytes and some neutrophils. The muscularis propria appears normal intervening and the lining of epithelial cells are seen aggregates of macrophages and neutrophils. In Group-II, the standard group showed no damage to the gastric mucosa. The histopathological sections of group-III, treated with EESP 400 mg/kg, shows mucosal mild edema with scattered chronic inflammatory infiltration and congested vascular spaces. The muscular is

propria appears normal. The section of IV- group rats shows mucosal edema with inflammatory infiltration . The muscularis propria appears normal.

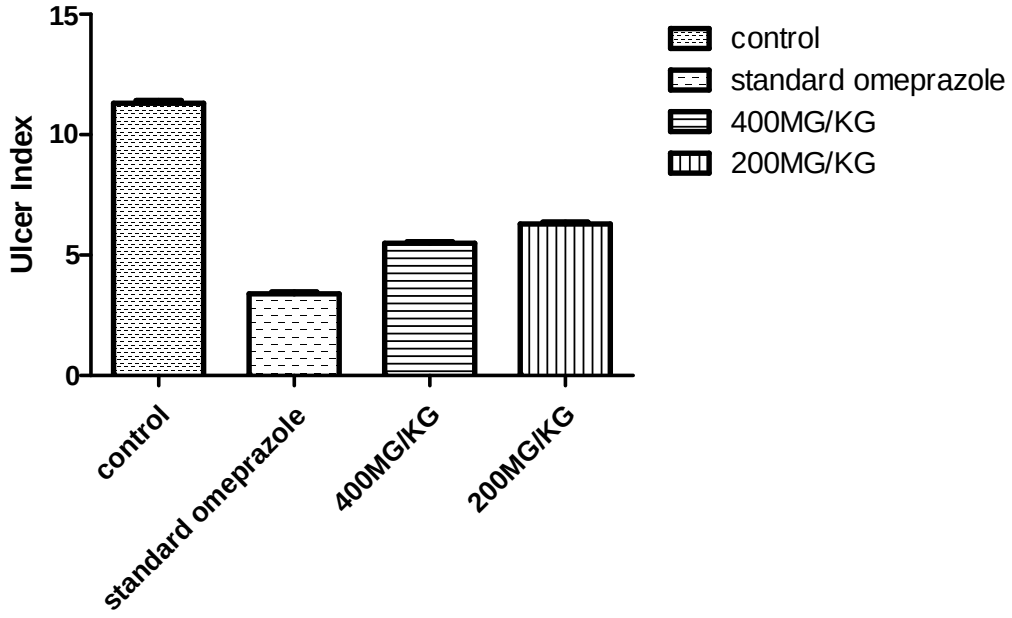
7.3.1.2. pylorus Ligation method:

In pyloric ligation induced ulcer model, Oral administration of EESP in two different doses (200mg/kg and 400mg/kg) showed significant reduction in ulcer index, gastric volume, free acidity, total acidity as compared to the control group. EESP was showing protection index of 52.3% and 36.28% at the dose of 400mg/kg and 200 mg/kg respectively in comparison to control whereas Omeprazole as reference standard drug a protection percentage of 70% has been observed. Since the ulcer protective percentage of EESP at 200mg/kg is 36.28% it can be considered to be less significant in the context of the study.

Table No. 6

Groups	**Ulcer Index**	**% Protection**
Group I- Control	11.3 ± 0.11	--
GroupIIStandard(omeprazole)	3.39 ± 0.07***	70%
GroupIII-*S.pubescens willd* Extract 400mg	5.48 ± 0.07***	52.3%
GroupIV*S.pubescens* willd Extract 200mg	7.2 ± 0.06*	36.28%

All values represent Mean ± SEM, n=6 in each group. P < 0.001. Control group is compared with standard and extract doses.



Graph No. 2

Gastric volume, Free Acidity and Total Acidity:

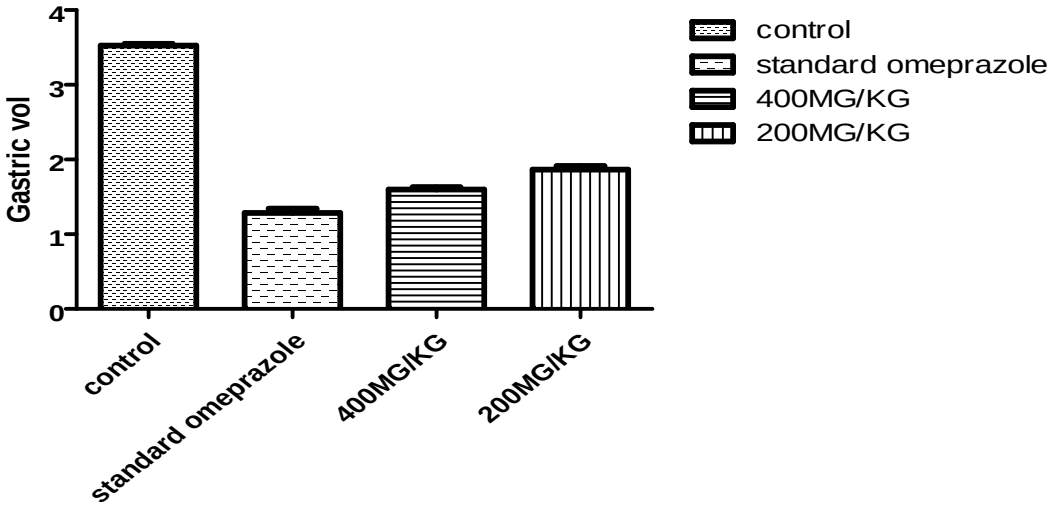
The results of various acid secretory parameters such as Gastric volume, pH, Free acidity and Total acidity of ethonolic extract of *solanum pubescens willd* on pylorus ligation induced gastric ulcer in rats are summarized in Table No 7. Estimation of acid secretory parameters was increased significantly in the control group. Administration of EESP exhibited a significant ($p < 0.001$) reduction in all the parameters and the results were comparable with the standard drug Omeprazole 20mg/kg. In control group the mean gastric juice was 3.52ml. Omeprazole, the standard drug decreased the mean gastric volume (1.28ml), which is statistically significant. Apart from the standard, ethnologic extract also showed decrease in the mean gastric juice at both the doses of 400 and 200mg/kg. The extracts reduced the mean gastric juice volume to 1.59ml and 1.86ml respectively. The test extracts showed the decreased in gastric juice volume on comparison to control group and thus indicate their anti-secretary mechanism. This demonstrates the dose dependent effect of EESP.

Table No. 7

Group	Gastric Volume	pH	Free Acidity	Total Acidity
Control	3.52 ± 0.02	1.41 ± 0.12	55.01 ± 2.28	67.79 ± 1.31
Std(omeprazole)	1.28±0.05***	5.21±0.13***	20.90±0.76***	32.06±3.316***
Extract 400mg	1.598±0.03**	3.5±0.08***	29.86 ± 0.77**	41.96±0.715***
Extract 200mg	1.86 ± 0.04**	4.63±0.14***	39.66 ± 1.14*	55.56 ± 0.99***

All values represent Mean ± SEM, n=6 in each group. P < 0.001. Control group is compared with standard and extract doses.

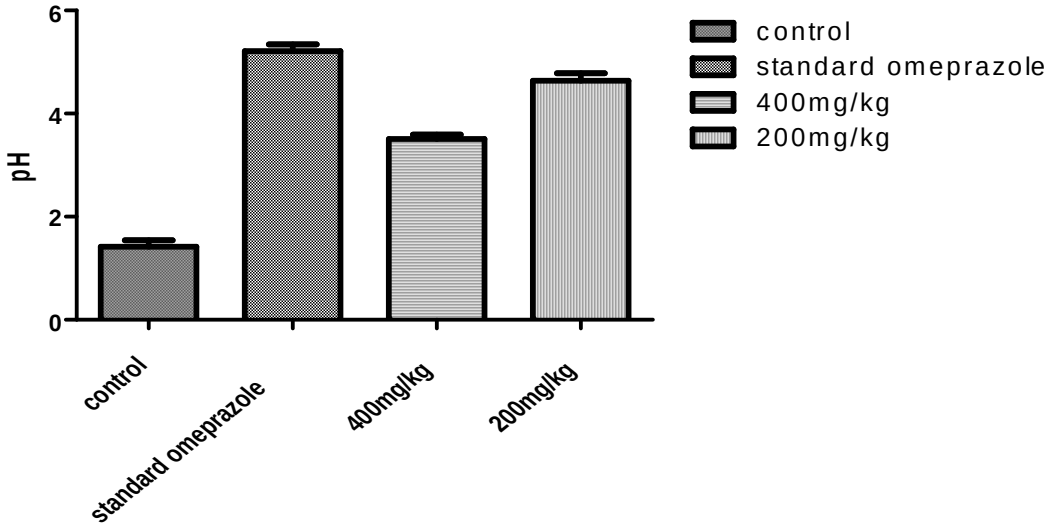
Graph Comparing the amount of Gastric volume collected from each of the Control, Standard and the Extract (400 and 200mg/kg) groups.



Graph No. 3

Graph Comparing the pH of Gastric contents collected from each

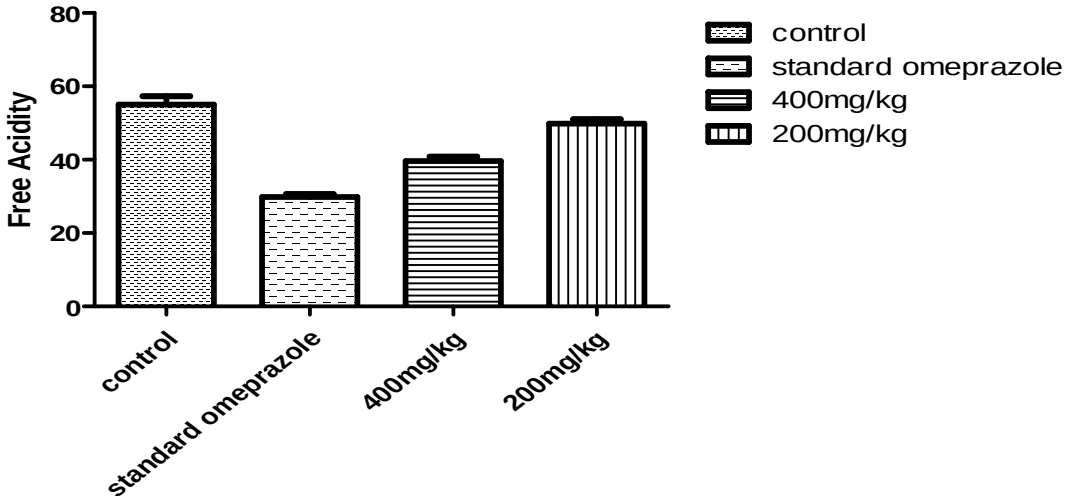
Of the Control, Standard and the Extract (400 and 200mg/kg) groups



Graph No.4

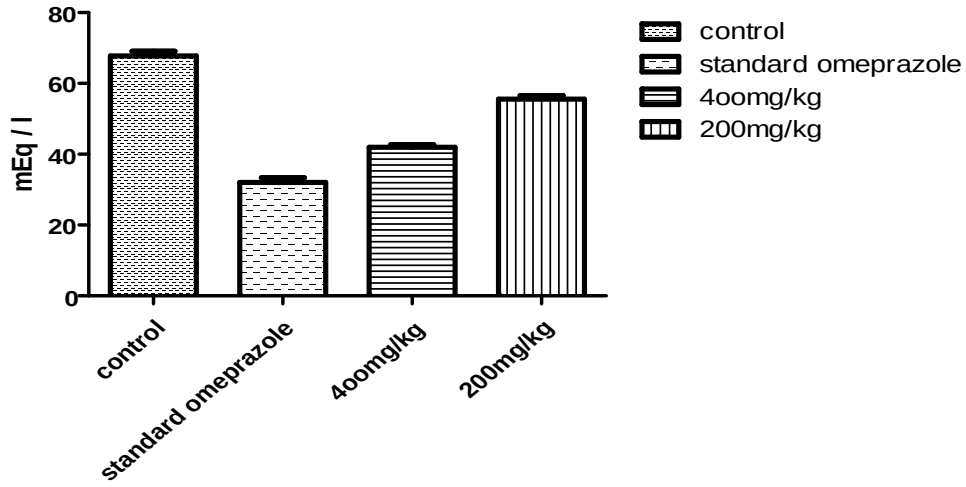
Comparison of Free Acidity of the Control, Standard and the

Extract (400 and 200mg/kg) groups.



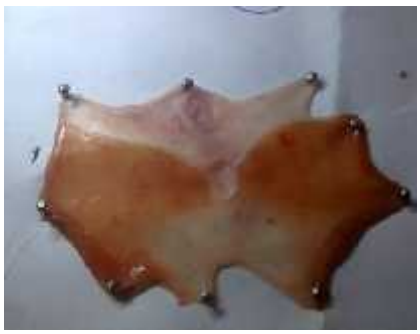
Graph no:5

Comparison of Total Acidity of the Control, Standard and the Extract (400 and 200mg/kg) groups.



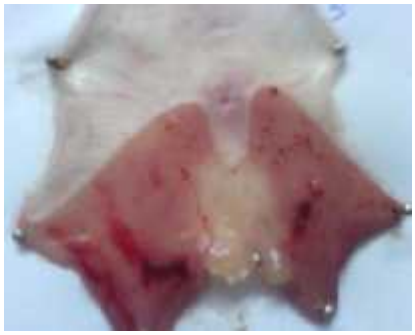
graph no:6

ULCER IMAGES (Pylorus Ligation):



(A)

(B)

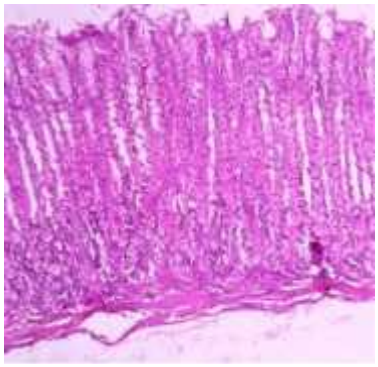


(C)

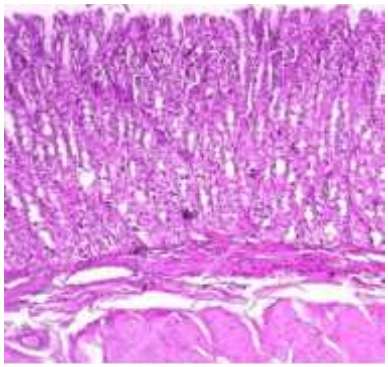
(D)

(A)– Control ; (B) – Standard ; (C) – Extract 400mg/kg ; (D) – Extract 200mg/kg

HISTOPATHOLOGY IMAGES –PYLORUS LIGATED ULCERS



(A)



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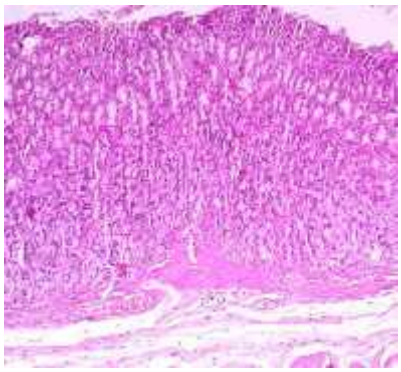
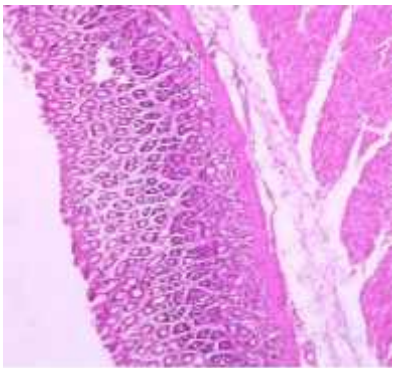


(C)



(D)

(A) – Control; (B) – Standard; (C) – Extract 400mg; (D) – Extract 200mg

Histopathology examination: The histopathological examination of stomachs of the rats showed a better picture of the gastric lesions and the damage occured to the stomach mucosa. Acute ulceration of stomach was observed in group-I, Group (A) (control group rats) shows mucosal ulceration consisting of necrosis, cellular debris, neutrophils and degenerated epithelial cells. Group-II(B) shows gastric mucosa with intact epithelium, lamina propria and muscularis mucosa. Group (C) shows intact mucosa with plenty of regenerative epithelial cells Group (D) shows focal mucosal ulceration consisting of degenerated cells and also contains few regenerated epithelial cells

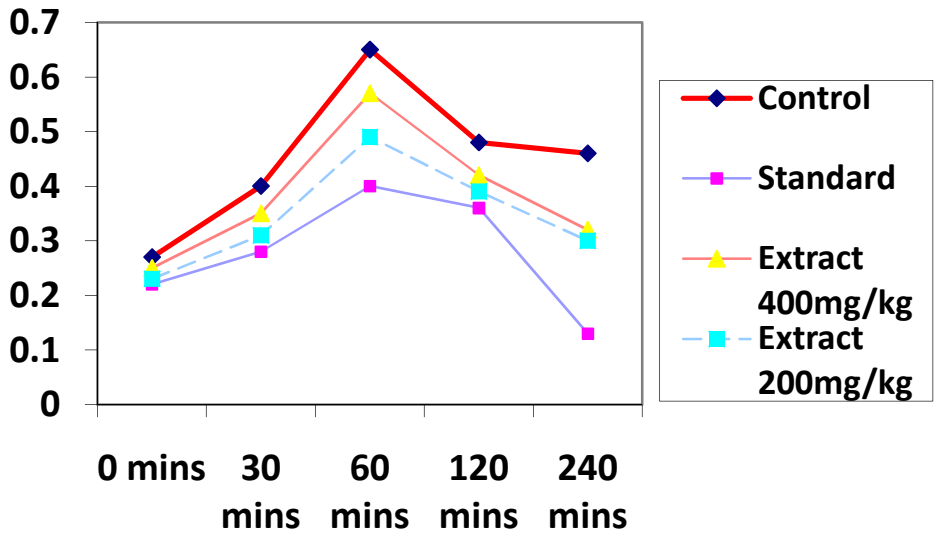
7.3.2. Anti-Inflammatory Evaluation:

Carrageenin-induced paw oedema:

The anti-inflammatory effect of ethonolic extract of *Solanum pubescens* willd at the dose levels of 400mg/kg and 200mg/kg was studied in Carrageenin induced hind paw oedema in Rats. The standard drug Indomethacin produced significant (P<0.01) anti-inflammatory activity. The test drug ethonolic extract of *Solanum pubescens willd* showed significant (P<0.01) anti-inflammatory activity against carrageenin induced paw oedema. The activity was observed to be dose dependant, with 400mg/kg dose showing more activity than the 200mg/kg dose but not as much extent to that of the standard.

The maximum activity of the standard drug Indomethacin was observed at 240min. but the reduction of thickness of the paw was evident from 60mins onward. The extracts 400mg/kg and 200mg/kg have followed a similar pattern but the amount of diminution of the inflammation was less when compared to the standard group.

Graph Comparing the of Paw Thickness at different time periods.



Graph no: 7

Table No. 8

Drug Treatment	***Dose***	***Paw Thickness (mm)***				
		0 min	***30 min***	***60 min***	***120 min***	***240 min***
Control	*0.5% CMC*	*0.27 ± 0.02*	*0.40 ± 0.01*	*0.65 ± 0.01*	*0.48 ± 0.22*	*0.46 ± 0.04*
Standard	*10 mg/kg*	*0.22 ± 0.03*	*0.28 ± 0.02***	*0.32 ± 0.03***	*0.36 ± 0.01***	*0.13 ± 0.03***
Alc 400	*400 mg/kg*	*0.23 ± 0.01*	*0.35 ± 0.01^{ns}*	*0.57± 0.01**	*0.42 ± 0.02**	*0.32 ± 0.02***
Alc 200	*200 mg/kg*	*0.23 ±0.01*	*0.31 ±0.01**	*0.41 ± 0.01***	*0.39 ± 0.02***	*0.30 ± 0.02***

Standard: Indomethacin (10mg/kg); Alc 400: Ethanolic Extract at dose 400mg/kg; Alc 200: Ethanolic Extract at dose 400mg/kg. Data represents the mean ± SEM (n=5). *p< 0.05, **p<0.01.

8. DISCUSSION

In this study, the anti-ulcer and anti-inflammatory activities of ethonolic extract of *Solanum pubescens willd* has been studied. The anti-ulcer activity was evaluated against Aspirin induced and Pylorus ligated ulcers. The anti-inflammatory study was studied using Carrageenin induced paw oedema.

Gastric ulcer disease is an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide, and other peptides and growth factors) and injurious factors (acid and pepsin). Ulcer caused by pylorus ligation is due to increased accumulation of gastric acid and pepsin leading to auto digestion of gastric mucosa and break down of the gastric mucosal barrier. The activation of the vagus-vagal reflux by stimulation of pressure receptors in the antral gastric mucosa in the hyper secretion model of pylorus ligature is believed to increase gastric acid secretion. NSAIDs are also frequently associated with peptic ulcers Topical injury by the luminal presence of the drug appears to play a minor role in the pathogenesis of these ulcers, as evidenced by the fact that ulcers can occur with very low doses of aspirin (10 mg) or with parenteral administration of NSAIDs. The effects of these drugs are instead mediated systemically; the critical element is suppression of the constitutive form of cyclooxygenase-1 (COX-1) in the mucosa and decreased production of the cytoprotective prostaglandin (PGE_2andPGI_2).

Antiulcer effect is supported by the decrease in the aggressive factors like gastric volume, decrease in free and total acidity and an increase in the resistance factors like pH showing the anti-secretary mechanism. It is significant to note when the pH was nearing 5.2 (Std) and 3.5 (Ext 400mg/kg), the ulcer score appeared less. The antiulcer agent may protect the mucosa from acid effects by selectively increasing prostaglandins. Prostaglandins have a vital protective role. The mucosal defense mechanism may be due to the epithelial cells of the gastric mucosa, which are impermeable to H+ ions thereby forming a physical barrier **(S.Narayan et.al.,)**.

The ethonolic extract of solanum pubescens willd was evaluated by using aspirin induced ulcer model, Oral administration of ethanol extract of *solanum pubescens willd* at doses of 200 and 400mg/kg exhibited dose dependent inhibition percentage of 53.26% and 63.23% ($p<0.001$) respectively compared to the ulcer control, proving the anti ulcer activity. The standard drug omeprazole (20mg/kg) exhibited percentage inhibition of 71.48% when compared with ulcer control. Extract treated and ulcer control group was compared with normal control group.

The ethonolic extract of solanum pubescens willd was evaluated by using pylorus ligation method , Oral administration of ethanol extract of *solanum pubescens willd* at doses of 200 and 400mg/kg exhibited dose dependent inhibition percentage of 36.28% and 52.3% ($p<0.001$) respectively compared to the ulcer control, proving the anti ulcer activity. The standard drug omeprazole (20mg/kg) exhibited percentage inhibition of 70% when compared with ulcer control. Extract treated and ulcer control group was compared with normal control group.

Inflammation is the protective response of the living individual to get rid of the cause and effect of injury (microbes, toxins, necrotic tissues). Inflammation of prolonged duration (weeks and months), in which active inflammation, tissue destruction and healing occur simultaneously The enzyme, phospholipase A2, is known to be responsible for the formation of mediators of inflammation such as prostaglandins and leukotrienes which by attracting polymer-pronuclear leucocytes to the site of inflammation would lead to tissue damage probably by the release of free radicals. Phospholipase A2 converts phospholipids in the cell membrane into arachidonic acid, which is highly reactive and is rapidly metabolized by cyclooxygenase (prostaglandin synthesis) to prostaglandins, which are major components that induce pain and inflammation **(Higgs *et al*., 1984; Vane, 1971).**

Carrageenan induced rat paw edema is a suitable experimental animal model for evaluating the anti-edematous effect of natural products. Induction of the oedema by this model is believed to be triphasic, namely

I. The first phase (1hr after carrageenan challenge) involves the release of serotonin and histamine from mast cells,
II. The second phase (2hr) is provided by kinins and
III. The third phase (3hr) is mediated by prostaglandins, the cycloxygenase products and lipoxygenase products **(Sertie et *al*., 1990)**.

The metabolites of arachidonic acid formed via the cycloxygenase and lipoxygenase pathways represent two important classes of inflammatory mediators, prostaglandins (products of the cycloxygenase pathway) especially prostaglandin E2 is known to cause or enhance the cardinal signs of inflammation, similarly, leukotriene B4 (product of lipoxygenase pathway) is a mediator of leukocyte activation in the inflammatory cascade.

The present study showed that ethonolic extract of solanum pubescens willd was evaluated by using Carrageenin-induced paw oedema.The anti-inflammatory activity evaluated by using a parameter - reduction in paw thickness. The ethonolic extracts and standard drug given at dose of 200,400and 10mg/kg. The ethonolic extract 200mg/kg showed reduced paw thickness (mm) was 0.23±0.01, 0.31±0.01*, 0.41± 0.01**, 0.39 ± 0.02**, 0.30 ± 0.02** at 0, 30, 60,120 and 240 mins. The ethonolic extract 400 mg/kg showed reduction of paw thickness(mm) was 0.23 ± 0.01, 0.35 ± 0.01^{ns,} 0.57± 0.01*,0.42 ± 0.02*,0.32 ± 0.02** at 0,30,60,120,240 mins.

The standard drug showed reduced paw thickness (mm) was 0.22 ± 0.03, 0.28 ± 0.02**, 0.32 ± 0.03**, 0.36 ± 0.01**, 0.13 ± 0.03** at 0, 30, 60,120, 240 mins. The maximum activity of the standard drug Indomethacin was observed at 240min. but the reduction of thickness of the paw was evident from 60mins onward. The extracts 400mg/kg and 200mg/kg have showed reduced paw thickness was evident from 60 min onwards, but the amount of diminution of the inflammation was less when compared to the standard group.

9. CONCLUSION

The present study showed that the ethonolic extract of *Solanum pubescens willd* leaves possess Anti-ulcer and Anti-inflammatory activity in animal models. *Solanum pubescens willd* showed a significant decrease in the ulcer development in both the animal models (pylorus ligated model and Aspirin-induced ulcer model) used in the study.

In pylorus ligation, both the doses showed significant anti-ulcer activity by reduction in ulcer index, gastric volume, free acidity, total acidity as compared to the control group. A similar result was observed in the aspirin induced ulcer model too. The intensity of heamorrhage and lesions was significantly reduced upon pretreatment with the extract, revealing the protective effect of EESP.

In the Anti-inflammatory study, *Solanum pubescens willd* leaves extract showed worthy anti-inflammatory action in the Carrageenin induced Paw oedema model in rats. Flavonoids and tannins are the major constituents that are present in the leaves of *Solanum pubescens willd* which may be responsible for its Ulcer-protective and Anti-inflammatory activity.

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