



PATHOPHYSIOLOGY OF ULCERS AND HERBAL DRUGS USED IN MANAGEMENT OF ULCERS

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ABSTRACT:

Peptic ulcer is the most common gastro-intestinal tract disorder (GIT). A number of drugs including proton pump inhibitors and H₂ receptor antagonists are available for the treatment of peptic ulcer, but these drugs have shown various incidences of relapses, adverse effects and drug interactions. Thus the development of a new antiulcer drugs and the search for a new molecule has been extended to herbal drugs, as herbal drugs offer better protection and decreased relapse rate. Herbal medicinal plants provide an effective and safer way for the management of various disorders. Thus the present review explores various herbal interventions employed in the management of ulceration.

KEYWORDS: Peptic ulcer, Proton pump inhibitors, H₂ receptor antagonists.

INTRODUCTION:

Ulcer is an open and painful sore in the lining of the upper gastrointestinal tract caused due to mucosal erosions. Pathophysiology of ulcer is due to an imbalance between the two factors i.e. aggressive (acid, pepsin, *H. pylori* and NSAIDs) and local mucosal defensive factors (mucin, bicarbonate, blood flow, prostaglandin, nitric oxide and growth factors).^{1,2} The gastric mucosa is continuously exposed to potentially injurious agents such as acid, pepsin, bile acids, food-ingredients and bacterial products (*Helicobacter pylori*). These agents have been implicated in the pathogenesis of gastric ulcer, including enhanced gastric acid and pepsin secretion, inhibition of prostaglandin synthesis (PG'S) and cell proliferation growth, diminished gastric blood flow and gastric motility.³ The predominant causes of peptic ulcer are infection with the bacterium called *Helicobacter pylori* (*H. pylori*) and the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin and ibuprofen.⁴ The stomach defends itself from hydrochloric acid and pepsin by creating a mucus coating and producing bicarbonates. *H. pylori* infection and NSAIDs has been reported to impair these protective functions as the G.I. tract become susceptible to hydrochloric acid and pepsin and leads to the formation of ulcer. *H. pylori* infection alone is the major causative factor (95% of the duodenal ulcer and 80% of gastric ulcers). Factors related with lifestyle such as smoking, alcohol, spicy foods and stress are also associated with peptic ulcer formation.⁵ So, with this view emphasis is laid down to explore such herbal drugs which would be effective in the management of ulcers.

PATHOPHYSIOLOGY OF ULCER'S**NSAIDS (Non-steroidal anti-inflammatory drugs)**

NSAIDs are mainly used all around the world. Thus the drug related problems due to NSAIDs are most common. NSAIDs inhibit the activity of COX, the key enzyme in PG production.^[5] Various studies indicates that NSAIDs helps in the progression of ulceration by overcoming the expression of enzyme cyclo-oxygenase (COX) which has been documented to inhibit the conversion of AA to PG's, that impairs the mucosal barrier and results in corrosive action with pepsin and results in the progression of peptic ulcers.^{6,7} Further, COX-1 inhibition by the NSAIDs leads to the significant release of the endothelin-1 (ET-1) which is a

potent vasoconstriction which has been shown to induce mucosal injury. NSAIDs by inhibiting the prostaglandins causes the activation of neutrophils and the local release of reactive oxygen species (ROS) and thus initiates the gastric injury.⁸ Further NSAIDs also causes marked reduction in the mucosal blood flow, mucus-bicarbonate secretions, impaired platelet aggregation, reduced epithelial cell renewal and increased leukocyte adherence that are responsible for pathogenesis of ulceration.⁹

H. Pylori

H. pylori is the main cause of stomach ulcers. *H. pylori* is gram negative bacillus, motile, microaerophilic, flagellated and spiral shaped bacteria.¹⁰ *H. pylori* causes increases expression of cytokines such as TNF- α in gastritis. IL-1 β is too overexpressed in the *H. pylori*-induced gastritis.¹¹ *H. pylori*-infected gastric mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration.¹²

Ethanol

The mechanism of ethanol induced gastric lesions is varied, including the depletion of gastric mucus content, damaged mucosal blood flow and mucosal cell injury. It has been documented that ethanol causes severe damage to the gastrointestinal mucosa starts with microvascular injury results in increase vascular permeability, edema formation and epithelial lifting. Szabo et al suggested that after intragastric administration of ethanol a rapid and time dependent release of endothelin-1 into the systemic circulation preceded the development of the hemorrhagic mucosal erosion by vasoconstriction.¹³ Ethanol has also initiate apoptosis which lead to cell death.¹⁴

NO (Nitric oxide)

Nitric oxide has been involved in gastric ulceration and show to diminish neutrophil adhesion raise gastric blood flow and mucus secretion¹⁵ and promotion of angiogenesis.¹⁶ Nitric oxide inhibits gastric secretion by inhibition of histamine release from enterochromaffin-like cells.¹⁷ NO has been studied to play an important role in GI mucosal defense and the pathogenesis of mucosal injury.¹⁸

TNF- α

Tumour necrosis factor (TNF- α) too plays a vital role in ulcer progression. TNF- α is capable of inhibiting gastric

secretion and parietal cell apoptosis induction by a nuclear factor- κ B (NF- κ B).¹⁹ Synthetic anti-ulcer drugs like H₂ blocker, Proton pump inhibitor (PPI) and Cytoprotectants are available in the market for the management of ulcers, but they possess major Adverse drug reaction (ADR) that restrict their use, herbal medicine deals with plants and plant extracts in treating diseases. These medicines are considered safer because of the natural ingredients with no side effects.²⁰

Table 1: Indicates The Major Adverse Drug Reaction Associated With Synthetic Anti-Ulcer Drugs.

Drug Name (Synthetic)	Adverse Drug Reaction
H₂ Receptor Blocker Cimetidine	Bowel upset, Convulsions, Restlessness, Bradycardia, Arrhythmias, Cardiac arrest, Gynaecomastia, impotence and temporary decrease in sperm count
Famotidine Roxatidine	Dizziness and Bowel upset. Diarrhoea
Proton Pump Inhibitor Omeprazole	Abdominal pain, Muscle and joint pain, Dizziness, Rashes, Leucopenia, Hepatic dysfunction and Atrophic gastritis (on prolonged treatment).
Lansoprazole Pantoprazole	Hepatic dysfunction and Diarrhoea Diarrhoea, Subacute myopathy.

HERBAL PLANTS SHOWS ANTIULCER ACTIVITY

Centella asiatica, *Mentha piperita*, *Azadirachta indica*, *Curcuma longa*, *Ocimum sanctum*, *Zingiber officinale*, *Kalmegh*, *Terminalia chebula*, *Momordica charantia*, *Glycyrrhiza glabra*, *Emblica officinalis*, *Withania somnifera*.

Centella asiatica :-

Brahmi, scientifically known as *Centella asiatica* consists of the fresh leaves and the stems of the plant known as *Centella asiatica* Linn, belonging to family *Scrophulariaceae*.²¹

Abdulla *et al.*, Evaluated methanolic extract of leaves of Brahmi at the dose of 100mg/kg b.w, 200mg/kg b.w. (body weight) and 400mg/kg b.w. separately against ethanol induced ulcer in rats.²³

Mentha piperita :-

Peppermint, scientifically known as *Mentha piperita* consists of the fresh plant of the *Mentha piperita*, belonging to family *labiatae*.²¹

Mofleh *et al.*, Evaluated aqueous extract of leaves at the dose of 250mg/kg b.w. and 500mg/kg b.w. separately against ethanol, pylorus ligation and by necrotising agent induced ulcer in rats.²⁴

Azadirachta indica :-

Neem, scientifically known as *Azadirachta indica*. Neem consists of all aerial parts of plant known as *Azadirachta indica*, belonging to family *meliceae*.²¹

Bandyopadhyay *et al.*, Evaluated aqueous extract of Neem bark at the dose of 30mg/kg b.w. 60mg/kg b.w. separately against ulcer in rats.²⁵

Curcuma longa :-

Indian saffron and Turmeric, scientifically known as *Curcuma longa*. Turmeric consists of dried as well as fresh rhizomes of the plant known as *Curcuma longa*, belonging to family *Zingiberaceae*.²²

Rafatullah *et al.*, Evaluated ethanolic extract of Turmeric dried rhizomes at the dose of 125mg/kg b.w, 250mg/kg b.w. and 500mg/kg b.w. separately against ethanol and indomethacin induced gastric ulcer in rats.²⁶

Ocimum sanctum :-

Tulsi, scientifically known as *Ocimum sanctum*. Tulsi consist of dried and fresh leaves of *ocimum sanctum*, belonging to family *Labiatae*.²¹

Ghangale *et al.*, Evaluated aqueous extract of Tulsi leaves at the dose of 100mg/kg b.w. and 200mg/kg b.w. separately against ethanol induced gastric ulcer in rats.²⁷

Zingiber officinale :-

Ginger, scientifically known as *Zingiber officinale*. Ginger consists of rhizomes of *Zingiber officinale*, belonging to family *Zingiberaceae*.²¹

Anosike *et al.*, Evaluated ethanolic extract of ginger rhizomes at the dose of 100mg/kg b.w, 200mg/kg b.w, and 400mg/kg b.w. separately against indomethacin induced ulcer in rats.²⁸

Andrographis paniculata :-

Kirayat, scientifically known as *Kalmegh*. It consists of dried leaves and tender shoots of the plant known as *Andrographis paniculata*, belonging to family *Acanthaceae*.²¹

Saranya *et al.*, Evaluated ethanolic extract of Kalmegh dried whole aerial part at the dose of 200mg/kg b.w. against Cysteamine induced duodenal ulcer in rats.²⁹

Terminalia chebula :-

Myrobalans, scientifically known as *Terminalia chebula*. Myrobalans are the dried fruits of *Terminalia chebula*, belonging to family *Combretaceae*.²¹

Raju *et al.*, Evaluated Methanolic extract of Myrobalan dried fruits at the dose of 250mg/kg b.w. and 500mg/kg b.w. separately against ethanol and pylorus ligation induced ulcer in rats.³⁰

Momordica charantia :-

Karela, scientifically known as *Momordica charantia*. Karela consists of fresh green fruits of the plant known as *Momordica charantia*, belonging to family *cucurbitaceae*.²¹

Venkatrao *et al.*, Evaluated alcoholic and aqueous extract of karela fruits at the dose of 200mg/kg b.w. and 400mg/kg b.w. separately against aspirin, stress and pylorus ligation induced ulcer model in rats.³¹

Glycyrrhiza glabra :-

Liquorice, scientifically known as *Glycyrrhiza glabra*. Liquorice consists of the dried unpeeled roots and stolons of *Glycyrrhiza glabra*, belonging to family *Leguminosae*.²¹

Mostafa *et al.*, Evaluated methanolic extract of liquorice roots at the dose of 200mg/kg b.w, 400mg/kg b.w, and 800mg/kg b.w. separately against ethanol induced ulcer in rats.³²

Emblica officinalis :-

Amla, scientifically known as *Emblica officinalis*. Amla consists of the dried, as well as fresh fruits of the plant *Emblica officinalis* Gaerth (phyllanthus emblica Linn.), belonging to family *Euphorbiaceae*.²¹

Al-rehaily *et al.*, Evaluated methanolic extract of amla fruit at the dose of 250mg/kg b.w. and 500mg/kg b.w. separately against indomethacin and pylorus ligation induced ulcer in rats.³³

Withania Somnifera :-

Ashwagandha, scientifically known as *Withania somnifera*. Ashwagandha consists of dried roots and stem bases of *Withania somnifera*, belonging to family *Solanaceae*.²¹

Bhatnagar *et al.*, Evaluated methanolic extract of ashwagandha root at the dose of 100mg/kg b.w. against stress and pylorus ligation induced ulcer in rats.³⁴

Table 2:- Indicates The Chemical Constituent And Uses Of The Herbal Plants Shows Anti-Ulcer Activity

PLANT NAME	CHEMICAL CONSTITUENTS	USES
<i>Centella asiatica</i>	Saponins :- - Asiaticoside - Madecassoside Volatile oils	Braintonic, Asthma Epilepsy Antianxiety Antistress Anticancer
<i>Mentha piperita</i>	Menthol Pulegone Menthone Menthofuran	Carminative Stimulant Mild Antiseptic Spasmolytic Smooth Muscle Relaxant Antitussive
<i>Azadirachta indica</i>	Diterpenes :- - Sugiol - Numbiol Triterpenes :- - β -sitosterol Limonoids :- - Nimbidine, Azadirachtin	Antimicrobial Antifeedant Insecticide
<i>Curcuma longa</i>	Volatile oil Resin Starch Turmerone Curcumin	Antiinflammatory Antiarthritic Cervical cancer
<i>Ocimum sanctum</i>	Volatile oil :- - Eugenol - carvanol Fixed oil Alkaloids Glycosides Tannins Vitamin- C	Stomachic Aromatic Carminative Stimulant Flavouring agent Motion-sickness
<i>Zingiber officinale</i>	Volatile oil Starch Fat Fibre Inorganic material Residual moisture Acrid resinous matter	Stomachic Aromatic Carminative Stimulant Flavouring agent Motion-sickness
<i>Andrographis paniculata</i>	Andrographolide Bicyclic triterpenoid- -lactone Kalmeghin	Stomachic Dysentery Dyspepsia Hepatoprotective
<i>Terminalia chebula</i>	Tannin Chebulic acid d-galloyl glucose Glucose Sorbitol	Astringent Laxative Stomachic Anthelmintic Piles External ulcers
<i>Momordica charantia</i>	Charantin Steroidal saponin Momordicin Carbohydrates Ascorbic acids	Stomachic Carminative Rheumatism Gout Dissorders of spleen Dissorders of liver Diabetes mellitus
<i>Glycyrrhiza glabra</i>	Triterpenoids Flavonoids Glycyrrhetic acid	Expectorant Demulcent Cough mixtures Antigastric effects Antispasmodic Rheumatoid arthritis Anti-inflammatory Addison's disease
<i>Emblica officinalis</i>	Vitamin- C Phyllembin Tannin Pectin	Diuretic Laxative Diarrhoea Dysentery Jaundice Dyspepsia Anaemia Promote hair growth Asthma Bronchitis
<i>Withania somnifera</i>	Alkaloids :- - Somniferine - Somnine	Sex stimulant Sedative Hypnotic effects

	- Somniferinine - Withananine Withanolides Withanine	Bradycardia Immunomodulatory Antistress Rheumatism Gout Hypertension Nerve Skin disease
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CONCLUSION

Peptic ulcer disease is a very common global health problem today. There are lots of synthetic drugs used for the antiulcer but they possess major adverse drug reaction. Herbal medicines are being used by about 80 % of the world population particularly in the developing countries for the primary health care. The herbal plants are consider in primary health care because they possess no adverse effect and health curative properties.

REFERENCES

- Bethesda MD. National Digestive Diseases Information. Clearinghouse 2010;10:4225.
- Hoogerwerf WA, Pasricha PJ. Agents used for control of gastric acidity and treatment of peptic ulcers and Gastro Esophageal Reflux Disease. In: Goodman and Gilman's the Pharmacological Basis of Therapeutics, Hardman JG and Limbird LE (Eds). McGraw Hill, New York 2001;1005-1020.
- Goroll AH, Mulley AG. Primary Care Medicine. Philadelphia 2009;6:537-548.
- Akthar MS, Akthar AH, Khan MA. Int. J Pharmacog 1992;30:97-104.
- Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. Nature 1971;231:232-235.
- Scarpignato C, Hunt RH. Nonsteroidal anti-inflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis and prevention. Gastroenterol Clin North Am 2010;39:433-464.
- Vane JR, Botting RM. Mechanism of action of non steroidal anti-inflammatory drugs. Am J Med 1998;104:2s-8s.
- Whittle BJ. Gastrointestinal effects of non steroidal anti-inflammatory drugs. Fundam Clin Pharmacol 2002;17:301-313.
- Allen A, Flemstrom G, Garner A, Kivilaakso E. Gastro duodenal mucosal protection. Physio Rev 1993;73:823-857.
- Mazumdar D, Bebb J, Atherton J. Helicobacter pylori infection and peptic ulcers. Med 2011;39:154-161.
- Martin JB. Not all Helicobacter pylori strains are created equal; should all be eliminated. Lancet 1997;349:1020-1022.
- Fan XG, Kelleher D, Fan XJ, Xia HX, Keeling PW. Helicobacter pylori increases proliferation of gastric epithelial cells. Gut 1996;38:19-22.
- Szabo S, Vincze A, Sanor Z, Jadas M, Gombos Z, Pedram A. Vascular approach to gastroduodenal ulceration. New studies with endothelins and VEGF. Dig Dis Sci 2010;2:370-375.
- Vidya S, Ramesh A, Alekhya N, Lohitha I. Antiulcer activity of *Eugenia Jambolana* leaves against ethanol-induced gastric ulcers in albino rats. IJPRD 2001;3:106-112.
- Li M, Wallace JL. Endothelial nitric oxide synthase modulates gastric ulcer healing in rats. Am J Physiol Gastrointest Liver Physiol 2000;279:G341-G346.
- Takeuchi K, Ohuchi T, Okabe S. Effects of nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester on duodenal alkaline secretory and ulcerogenic responses induced by mepirazole in rats. Dig Dis Sci 1995;40:670-677.
- Kato S, Kitamura M, Korolkiewicz RP, Takeuchi K. Role of nitric oxide in the regulation of acid secretion in rats: Effect of NO donors and NO synthase inhibitor. Br J Pharmacol 1998;123:839-846.
- Wallace JL, Miller MJ. Nitric oxide in mucosal defence: a little goes a long way. Gastroenterology 2000;119:512-520.
- Boraschi D, Cifone MG, Falk W, Flad HD, Tagliabue A, Martin MU. Cytokines in inflammation. Eur Cytokine Netw 1998;9:205-212.
- Arul V, Miyazaki SD, Hananjayana R. Studies on the antiinflammatory, antipyretic and analgesic properties of the leaves of *Aegle marmelos* Corr. J Ethnopharmacol 2005;96:159-63.
- Kokate CK, Purohit AP and Gokhale SB. "Book of Pharmacognosy." Nirali prakashan 36th edition.
- Evans WC. "Book of pharmacognosy." 15th edition.
- Abdulla MA, Al-bayty FH, Younis LT, Abu-Hassan MI. Antiulcer activity of *Centella asiatica* leaf extract against ethanol-induced gastric mucosal injury in rats. Journal of medicinal plant research 2010;4(13):1253-1259.
- Al-Mofleh I, Alhaider A, Mossa J, Al-Sohaibani M, Qureshi S, Rafatullah S. Antisecretagogue, antiulcer and cytoprotective effects of 'peppermint' *Mentha piperita* in Laboratory Animals". J Med Sci 2006;6:930-936.
- Bandyopadhyay U, Biswas K, Sengupta A, Moitra P, Dutta P, Sarkar D, Debnath P, Ganguly CK, Banerjee RK. Clinical studies on the effect of Neem '*Azadirachta indica*' bark extract on gastric secretion and gastroduodenal ulcer. Elsevier 2004.
- Rafatullah S, Tari q M, Al-Yahya MA, Mossa JS, Ageel AM. Evaluation of turmeric for gastric and duodenal antiulcer activity in rats. Journal of ethnopharmacology 1990;29:25-34.
- Ghangale GR, Mahale T, Jadhav ND. Evaluation of antiulcer activity of *Ocimum sanctum* in rats. Veterinary world 2009;2(12):465-466.
- Anosike CA, Obidoo O, Ezeanyika LU, Nwuba MM. Anti-inflammatory and anti-ulcerogenic activity of the ethanol extract of ginger '*Zingiber officinale*'. Af J Biochem Res 2009;3:379-384.
- Saranya P, Geetha A. "Antiulcer activity of *Andrographis paniculata* against cysteamine-induced duodenal ulcer in rats." Indian Journal of Experimental Biology 2011;49:525-533.
- Raju D, Ilango K, Chitra V, Ashish K. Evaluation of Antiulcer activity of methanolic extract of *Terminalia chebula* fruits in experimental rats. J Pharm Sci & Res 2009;1(3):101-107.
- Venkatrao N, Venu K, Sowmya U, Gangadi JR, Anirudh K. Evaluation of anti-ulcer activity of *momordica charantia* in rats. Int J Pharm Bio Sci 2011;1:1-16.
- Mostafa AS, Hoda SI, Elham MM, Amal FM. Some effects of glycyrrhiza glabra liquorice roots extract on male rats. Egyptian Journal of Natural Toxins 2004;1:83-94.
- Al-Rehaily AJ, Al-Howiriny TA, Al-sohaibani MO, Rafatullah S. Gastroprotective effects of amla '*Emblca officinalis*' on invivo test models in rats. Phytomedicine 2002;9:515-522.
- Bhatnagar M, Jain CP, Sisodia SS. Anti-ulcer activity of *withania somnifera* in stress plus pyloric ligation induced gastric ulcer in rats. Journal of cell and tissue research 2005;5(1):287-292.

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