

Treatment and Replenishment of G.I. Tract with Combined Regimen Therapy (CRT) of Allopathic (PPIs) and Ayurvedic (Aloe Vera) Medicine in Peptic Ulcer Disease to Counteract Relapse

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Abstract

Peptic ulcer remains a very common disease beside decrease in overall incidence rate. It includes gastric and duodenal ulcers. It comes under one of the leading causes of deaths, according to Center for Disease Control and Prevention, National Center for Health Statistics and National Vital Statistics System. According to the latest WHO data published in April 2011 Peptic Ulcer Disease Deaths in India reached 108,392 or 1.20% of total deaths.

The age adjusted Death Rate is 12.37 per 100,000 of population, and which leads India to 5th rank in the world. Usually, recurrent ulcer tended to recur at its original site of occurrence, gastric ulcer is more likely to relapse than duodenal ulcer. Acidic environment of stomach helps keeping stomach free from bacteria (except for *Helicobacter pylori*). Somehow, when stomach becomes less acidic, it loses its protective mechanism, and ingested pathogens can survive and proliferate. Undoubtedly, acid-suppressive agents are of great value for the treatment of peptic ulcer disease, gastro esophageal re-flux disease, or for prophylaxis against non-steroidal anti-inflammatory drug-related gastrointestinal complications.

But this therapy can be shortened up with the effective recovery from the ulcer condition by use of combined treatment, which will lead to control from the relapse of infections. Recurrence in peptic ulcer can also occurs when infection eradication or recovery of G.I layer or cytoprotective mechanism slows down and which results in recurrence in the partially recovered patients.

So for this problem, acid control could be done with the help of PPIs (Allopathic) and using Aloe Vera (Ayurvedic) for its cytoprotective mechanism and acceleration in the cicatrization of the ulcerous wounds which will lead to cure of the relapse condition.

Keywords: Peptic ulcer; Medicinal plants; Aloevera; Ayurvedic; Proton pump inhibitors; Herbal; Chronotherapy; Mechanism of Aloe vera

Introduction

Peptic ulcer

The word 'peptic' derives from the Greek term '*peptikos*,' meaning related to digestion and an ulcer is a crater like lesion in a membrane [1,2] as shown in Figure 1. Peptic ulcers are due to exposure of stomach and duodenum to pepsin and gastric acid [3,4].

Imbalance occurs between aggressive factors like acid, pepsin, *H. pylori* and defensive factors such as gastric mucus, bicarbonate ions, and prostaglandins along with innate resistance of mucosal cells as shown in Figure 2. Gastro duodenal mucosa utilizes several defense mechanisms against the aggressive factors such as hydrochloric acid and pepsin.

Most common symptom include burning pain and complications include bleeding, tumors and may lead to cancer if relapse not treated well [5,6].

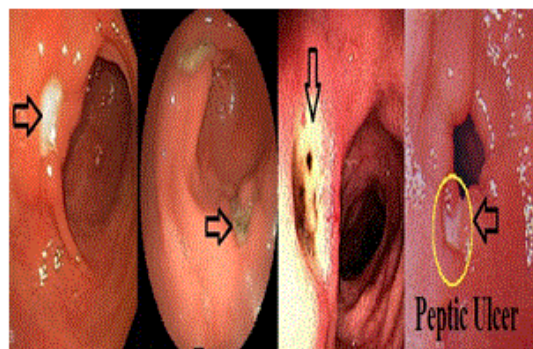


Figure 1: Different conditions of peptic ulcer.

Classification of Peptic Ulcers Depending on Severity

Acute peptic ulcers

These ulcers involve tissues to the depth of the submucosa and may arise in the form of single or multiple lesions. They are found in many sites of stomach and in the first few centimeters of duodenum [10,11].

Chronic peptic ulcers

These ulcers penetrate through the epithelial and muscle layers of stomach wall and may include the adjacent pancreas or liver. Recurrence ulcers are generally chronic in nature [10].

Components providing defense against ulceration

There are the factors distributed as pre-epithelial, epithelial and sub-epithelial like mucus formation, bicarbonate secretion, HCl formation to kill microorganisms etc, which protect gastroduodenal cells from ulceration [12].

Recurrence and treatment of refractory ulcers

Peptic ulcer is one of the leading causes of death in heavily populated country India [13,14]. Regardless, what mode of therapy is being used, healing of ulcers are time dependent till now; 90 to 95 percent of all ulcers heal if the therapy is continued for 12 weeks. After that, ulcers or symptoms (or both) can be considered refractory to therapy. Factors like poor patient compliance, use of NSAIDs, smoking and gastrinoma are common causes of refractory ulceration. Duodenal ulcers recur in 70 to 90% of patients within 1 year of the cessation of drug therapy. Adults are found more prone for relapse [15,16]. The evidence suggests that the rate of recurrence differs depending on the initial therapy used. The relapse rates are higher after healing with H₂-antagonists [17-21].

NSAIDs causing relapse and PPIs role

NSAIDs are one of the most widely used and responsible drug to cause recurrence. Besides causing ulcer formation, they can also delay in healing of pre-existing ulcers and promote their bleeding [22] as shown in Figure 4. This ability of NSAIDs to promote the bleeding of pre-existing ulcers is most probably related to their inhibitory effects on platelet aggregation. The inhibition of platelet aggregation by NSAIDs occurs as a consequence of the inhibition of thromboxane synthesis. They enhance mucosal injury by increasing the absorption of acidic NSAIDs. The NSAIDs have been shown to increase basal acid secretion as a result of COX-1 mediated prostaglandin depletion in rats with gastritis, but not in those with intact stomach. In humans, NSAID-induced acute gastric injury has been shown to be greater. Acid plays a key role in the development of acute gastric mucosal lesions in the rat stomach and that NSAID-induced reduction in gastric mucosal blood flow only occurs in the presence of acid. On the other hand, administration of NSAIDs leads to early release of interleukin-1b (IL-1b) [23], one of the most potent inhibitors of gastric acid secretion, which may be a protective mechanism against NSAID-induced mucosal injury [24]. Also, reported that a pathway mediated by lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4) plays an important role in the development of small ulcers and ulcer like injuries [25]. It was found that mucosa involves the disruption of intercellular junctions, which results in increased mucosal permeability. These disruptions are caused by NSAIDs as they inhibit

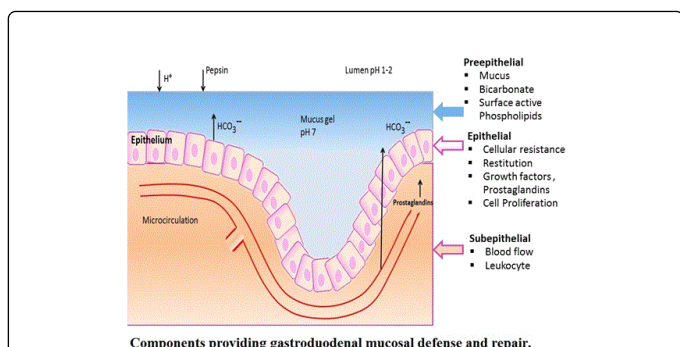


Figure 2: Various protective and repair processes involved to provide defense against toxins, increased HCl, bacteria, viruses etc separated on the basis of preepithelial, epithelial and subepithelial tissues.

Regulation of gastric acid secretion

The primary exocrine secretions are pepsinogens, from the chief or peptic cells, while hydrochloric acid and intrinsic factor from the parietal or oxyntic cells. Men secrete more acid than women; that's why they are more prone to ulceration. Gastric acid secretion is regulated by intricate central and peripheral mechanisms as shown in Figure 3 [7,8]. Parietal cells have receptors for several stimulants of acid secretion and these cells possess a specific Hydrogen Potassium-ATPase enzyme (proton pump), which is responsible for the exchange of H⁺ for K⁺ ions across the apical surface of the parietal cells. Calcium ions and cyclic AMP are the principal second messengers released from parietal cell receptors, which in turn activate the gastric proton pump situated near the luminal apex of the parietal cell. This process helps in the formation of HCl resulting in acidic environment [5,9,10].

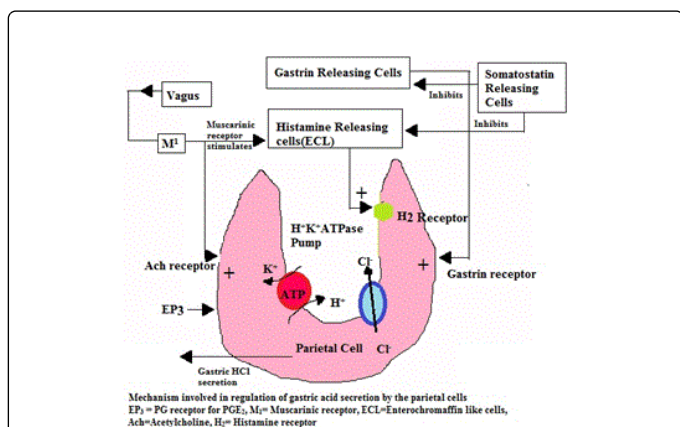


Figure 3: Mechanism involved in the secretion and regulation of H⁺ ions by H⁺K⁺ATPase pump. Vagus nerve provide signal with the help of muscarinic receptors which further stimulates Histamine releasing cells i.e enterochromaffin cells. Acetylcholine (Ach) works on acetylcholine receptors and lead to H⁺ ions release. Gastrin releasing cells release gastrin which work on gastrin receptors which further aid the process. Somatostatin releasing cells inhibits the histamine and gastrin releasing cells and thus regulates the secretion [11,12].

the production of mitochondrial ATP in intestinal epithelial cells and with this increased mucosal permeability, mucosal injuries can be caused by the penetration of bile acid, proteolytic enzymes, intestinal bacteria, or toxins [26]. Heme oxygenase (HO-1) protein in the intestinal mucosa significantly increase with the use of PPI like lansoprazole, HO-1 also called as heat shock protein 32 (HSP 32) and is the rate limiting enzyme in heme metabolism. It is responsible for degradation of free heme, which has high cytotoxicity. This degradation produces highly cytoprotective carbon monoxide and biliverdin resulting in cytoprotection and anti-inflammatory effect [27].

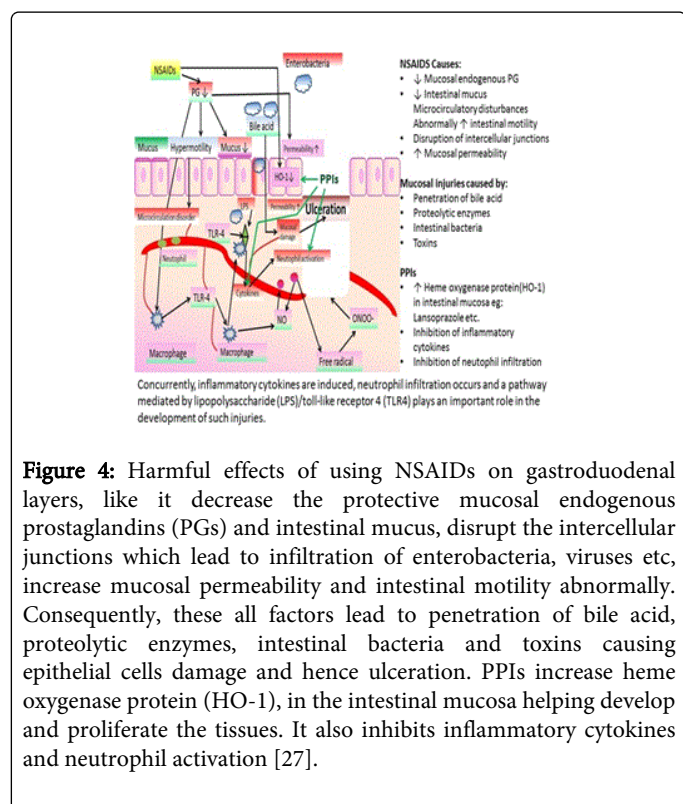


Figure 4: Harmful effects of using NSAIDs on gastroduodenal layers, like it decrease the protective mucosal endogenous prostaglandins (PGs) and intestinal mucus, disrupt the intercellular junctions which lead to infiltration of enterobacteria, viruses etc, increase mucosal permeability and intestinal motility abnormally. Consequently, these all factors lead to penetration of bile acid, proteolytic enzymes, intestinal bacteria and toxins causing epithelial cells damage and hence ulceration. PPIs increase heme oxygenase protein (HO-1), in the intestinal mucosa helping develop and proliferate the tissues. It also inhibits inflammatory cytokines and neutrophil activation [27].

Aloe Vera

Aloe barbadensis (Miller), *Aloe vera* (Family-Liliaceae), has a long history of use in topical and oral therapeutics. The plant is the source of two products, gel and latex, which are obtained from its fleshy leaves as shown in Figure 5 [28-30]. This herbal gel has been proved to be very effective in treatment of hyperacidity, gastric and duodenal ulcer. It can be applied as drug supplementing or enhancing the activity of synthetic medicines. Moreover, aloe vera gel has been successfully applied in prophylactic of hyperacidity, gastric and duodenal ulcer [31,32]. Aloe vera leaf juice or gel has number of chemical constituents like anthraquinone glycosides, carbohydrate fraction, alkaloids, phenolic compounds (Flavonoids), chromones, lectins, phytosterols, leaf gel consists of saponins, tannins, cardiotonic glycosides, terpenoids (limonene, myrcene), p coumaric acid, biological growth factors (auxins and gibberilins), amino acids and Vitamins etc. [33].



Figure 5: Different parts of Aloe Vera i.e upper covering layer called rind, internally latex and inside gel or leaf juice is present.

Traditional use in ulcers

Among herbal drugs, aloe gel has been used extensively and many of its health benefits associated have been attributed to the polysaccharides contained in the gel of the leaves, and its clinical efficacy is documented against ulcers. Products derived from the inner gel of the *Aloe vera* L. plant have demonstrated multiple clinical activities, and are used routinely to accelerate wound healing [34,35]. Topical application of an Aloe vera gel resulted in accelerated wound healing in the group treated with Aloe vera compared to control. Aloe vera presented an earlier onset of the proliferative phase compared to the control group. Same type of activity was found when given orally [36,37].

Aloe vera as an ulcer healing agent and cell proliferator

When activity of Aloe Vera is tested in rats for ulcer healing property and it shows considerable healing of the ulcer. In the ulcer groups treated with Aloe vera, leukocyte adherence in postcapillary venule and TNF-alpha level get reduced as shown in Figure 6. It also reduced gastric inflammation, increased epithelial cell proliferation and gastric glands became elongated. It elevated IL-10 level and promotes gastric ulcer healing and also acted as gastroprotective agent. Aloe vera has been claimed to have anti-inflammatory effects and, despite a lack of evidence of its therapeutic efficacy, is widely used by patients with inflammatory bowel disease. Oral aloe vera taken for 4 weeks produced a clinical response more often than placebo; it also reduced the histological disease activity and appeared to be safe [24,37-43]. Anti-ulcer effect of Aloe vera in non-steroidal anti-inflammatory drug induced peptic ulcers is seen and found to be effective [44]. Aloe vera can reduce vasoconstriction and improve perfusion of gastric mucosal capillaries, thus promotes ulcer healing [45]. Acid secretion inhibition is may be due to lectins [46]. Lectins inhibit aminopyrine uptake by parietal cells. Thus, the ability of the extract to inhibit gastric acid output maybe as a result of direct action on the acid producing cells [47].

Two way ulcer treatment

Aloe extracts showed significant antioxidant activity which could also help in ulcer healing and other biological activities which help in healing ulcers include promotion of wound healing, antiinflammatory, anticancer, immunomodulatory, mucus secreting, cytoprotective and gastroprotective properties [48-51]. Treatment of inflammation is still the key factor for the most types of healing. It also has immunomodulatory properties in the gel polysaccharides, especially the acetylated mannans from Aloe vera which help to control complication of gastric ulcer and has anticancer activities [52]. Gingival fibroblasts play an important role in oral wound healing and the anti-ulcer activity of the plant is reported in Indomethacin induced ulcer model [53]. Aloe gel had a prophylactic effect and was also found curative if given as a treatment for stress-induced gastric ulceration in rats [24,35,44]. This fraction contained substances with molecular weights between 5000 and 50000 Da, which were considered to both suppress peptic ulcers and to heal chronic gastric ulcers [54] (Table 1).

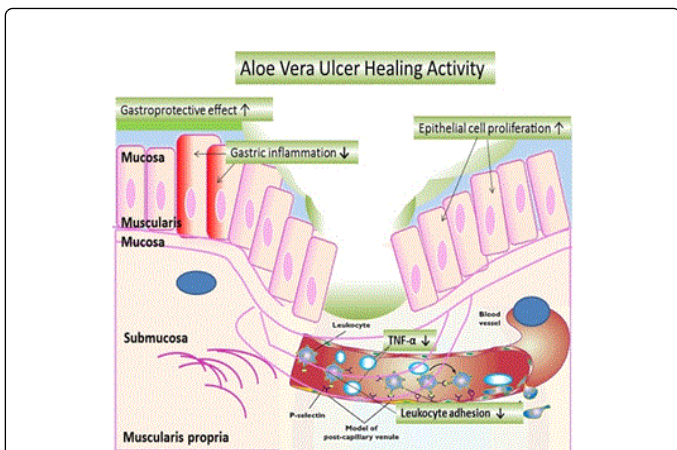


Figure 6: Action of Aloe Vera as gastroprotective, it decreases TNF- α and Leukocyte adhesion on P-selectin post capillary venule which lead to reduced inflammation, helps epithelial cells proliferation and its emollient action as forming layer on gastric epithelial cells.

Protective	Healing
Mucus Secreting, may be due to gel like structure [52,53,55].	Antiulcer and Acceleration of wound healing [55-57]
Cytoprotective, due to active ingredients like tannin, saponins and flavonoids [50,53,55,58].	Antiinflammatory [24,59-61]
Emollient Agent, due to gel like structure and water content [57,59,62]	Anticancer (Cancer complication of peptic ulcer) Acemannan is the name given to the major carbohydrate fraction obtained from the gel of the Aloe vera leaf [56,63]
Antibacterial [56,63]	Immunomodulatory, gel polysaccharides acetylated mannans, [55,63,64]
Antiseptic [56,63]	Decrease Acid secretion due to lectin [13] leukocyte adherence in postcapillary venule and TNF-alpha level [65].
Antioxidant, Aloe vera	Increased epithelial cell proliferation and gastric glands became elongated Level [36,39,66,67] Hematopoietic activity [34]
contains vitamin C, E, zinc and seven superoxide dismutases [53,66]	

Table 1: Two way ulcer treatment.

Toxicological evaluation

Plant materials derived from the Aloe plant that is *Aloe Barbadensis*, shows more promising results with respect to ulcer healing and had very minor side effects if any. *Aloe barbadensis* (also known as Aloe vera)-derived ingredients were not toxic in acute oral studies using mice and rat assay using *Aloe barbadensis*-derived material, Aloe Ferox-derived material, and various anthraquinones derived from Aloe. Other animal data also suggest that components of Aloe inhibit tumor growth and improve survival. Various *in vitro* assays also demonstrated anticarcinogenic activity of aloe-emodin. Several clinical studies of preparations derived from *Aloe barbadensis* plants demonstrated no phototoxicity or other major side effects, confirm that the concentration of anthraquinones in such preparations are too low to induce photo toxicity [68-70]. It was found that it does not have any major side effect, which makes it suitable medicine for our CRT to be used in ulcer healing therapy [71-75].

Proton pump inhibitors (PPIs)

The proton pump inhibitors (PPIs) includes drugs like omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole magnesium (S-isomer of omeprazole) etc. These are most potent suppressors of gastric acid secretion and inhibit gastric H⁺K⁺ATPase enzyme (proton pump). In typical doses, these drugs decrease the daily production of acid (basal and stimulated) by 80% to 95%. PPIs are prodrugs that require activation in an acidic environment. After absorption into the systemic circulation, the prodrug diffuses into parietal cells of the stomach and accumulates in the acid secretory canaliculi [76-82]. The activated form then binds covalently with sulfhydryl groups of cysteines in the H⁺K⁺ATPase irreversibly inactivating the pump molecule. Investigators have attempted to estimate the proportion of gastric cancer cases that could have been avoided if relapse of gastric ulcers could be controlled, caused by one or other reason. PPIs are effective in preventing chronic NSAIDs induced gastric and duodenal ulcers. In practice, proton pump inhibitors should not be used

indiscriminately, especially in hospital patients and in persons at increased risk of C. difficile infection as it may worsen or even help the disease to recur [83-89]. Proton pump inhibitors (PPIs) remove most of the acid from the gastro esophageal refluxate. Therapeutic measures are directed at reducing the noxiousness of the refluxate; reducing the gastro-oesophageal reflux; enhancing clearance; protecting the mucosa; reducing the mucosal sensitivity and improving healing [90-94].

Pantoprazole	Erosive esophagitis healing
	Erosive esophagitis maintenance
	GERD(Gastroesophageal reflux disease) symptomatic treatment
	Hyper secretory condition in Zollinger
Rabeprazole	Erosive esophagitis healing
	Erosive esophagitis maintenance
	GERD(Gastroesophageal reflux disease) symptomatic treatment
	H.Pylori eradication in combination with antibiotics
	Active Duodenal ulcer short term treatment
	Hyper secretory condition in Zollinger
Omeprazole	Erosive esophagitis healing
	Erosive esophagitis maintenance
	GERD(Gastroesophageal reflux disease) symptomatic treatment
	H.Pylori eradication in combination with antibiotics
	Active Gastric ulcer short term treatment
	Active Duodenal ulcer short term treatment
	Upper Gastrointestinal(G.I) bleeding risk reduction
	Hyper secretory condition in Zollinger
Lansoprazole	Erosive esophagitis healing
	Erosive esophagitis maintenance
	GERD(Gastroesophageal reflux disease) symptomatic treatment
	H.Pylori eradication in combination with antibiotics
	Active Gastric ulcer short term treatment
	Active Duodenal ulcer short term treatment
	Healed duodenal ulcer treatment
	NSAID associated gastric ulcer healing
	NSAID associated gastric ulcer risk reduction
	Hyper secretory condition in Zollinger

Table 2: Commonly used PPIs with their FDA approved indications [108].

Also, another important benefit of using PPIs in our combination therapy is, it's very economic price and uncompromised effectiveness in treating peptic ulcer [95,96]. Use of PPIs can also help to reduce the complications of peptic ulcer and control the development of ulcers in tumors and cancers [97-107] (Table 2).

Chronotherapeutic Administration of PPIs and Aloe Vera for Increased Efficacy

Chronotherapy is to synchronize drug delivery with circadian rhythm in order to optimize efficacy and/or minimize side effects, that is, to deliver the drug in higher concentration during the time of greatest need and in lower concentration when need is less [109]. Gastric acid secretion increases at night and gastric motility and emptying are decreased. Ulcer therapy with PPI's is aimed at increasing the pH of the gastric environment. PPI's such as lansoprazole and omeprazole have been proven to be more effective in increasing gastric pH when administered in the morning [110]. Aloe vera can be administered in the afternoon and evening in small doses, which could prevent any interaction chances and enhance ulcer healing.

Discussion

Acid suppression with PPI's remains the cornerstone of therapy in our combination and addition of ulcer protective and proliferative effect by Aloe vera as proven can improve the results of healing and controlling relapse. Reason behind choosing PPI's in our Combined Regimen Therapy (CRT) is their effectiveness in treating gastro-duodenal ulcers and treating recurrence in bleeding ulcers [111-114]. Proton pump inhibitors control acid secretion and provide time to the gastric epithelial cells for recovery and growth. But, this homeostasis of recovery is not that much efficient in large number of peoples, commonly including elderly, weak and immune-compromised patients. This CRT have benefits from its overall additive effect in treating ulcer condition, no synergism is expected.

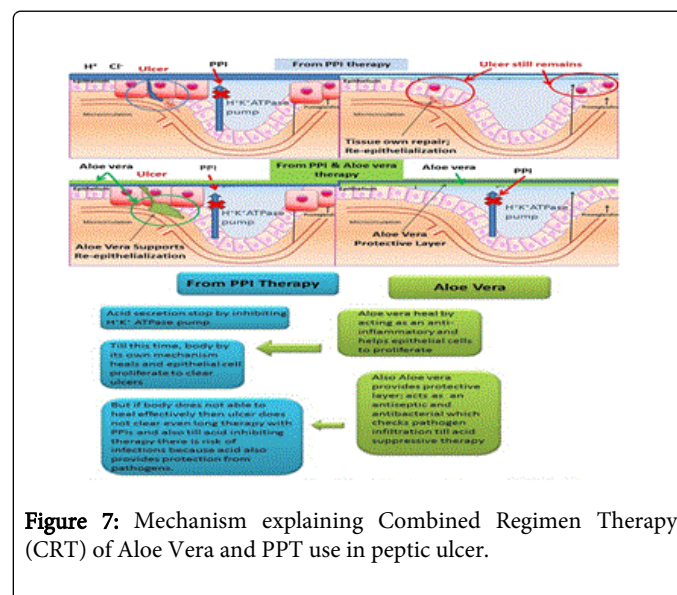


Figure 7: Mechanism explaining Combined Regimen Therapy (CRT) of Aloe Vera and PPT use in peptic ulcer.

As proven and studied Aloe vera ulcer protective effects and traditional use from centuries in humans overrule any possibility of its ineffectiveness as an antiulcer and cell proliferator agent. This CRT is

not actual combining two medicines; it's using two different medicines to treat different indications involved in one disease i.e. peptic ulcer as explained in Figure 7.

Conclusion

So, therefore if Aloe vera and PPIs are used in CRT for its epithelial cells proliferation, cytoprotective effect with PPIs providing acid suppression in appropriate time regimens, then recovery of tissues and ulcer healing process can be fastened controlling relapse to a much greater extent, as complete healing of ulcerous tissues can be expected. Further, both drugs are proven to be effective in humans and already in use for their antiulcer property. In this review, only their combined effectiveness is presented in peptic ulcer based on their proven studies available according to their expected mechanism.

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