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## A Systematic Review: Pathogenesis of Peptic Ulcer and Role of Chronotherapy in Its Treatment

Prashant K Dhakad\*, Mitali Srivastava, Birendra Srivastava

Department of Pharmacology, School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur, Rajasthan, India

\*Corresponding author: Dr. Prashant K Dhakad, Assistant Professor, School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur, Rajasthan, India, E-mail: [dhakadprashant654@gmail.com](mailto:dhakadprashant654@gmail.com)

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### ABSTRACT

The most well-known reasons for peptic ulcer sickness are *Helicobacter pylori* disease and utilization of Non-steroidal anti-inflammatory drugs. Urea breath tests and stool antigen tests are generally precise for recognizing *Helicobacter pylori* disease and can be utilized to affirm fix; serologic tests are a helpful however less exact other option and can't be utilized to affirm fix. Constant utilization of NSAIDs in patients with *Helicobacter pylori* contamination expands the danger of peptic ulcer malady. Suggested treatments for forestalling peptic ulcer sickness in these patients incorporate proton pump inhibitors and misoprostol. Medication conveyance frameworks that unequivocally control the discharge rates or target medications to a particular site enormously affect the medicinal services framework particularly peptic ulcer the management. Circadian rhythm can be characterized as endogenous sub-atomic time-keeping frameworks that are associated with activating day by day vacillations in different physiological and biochemical procedures. This article expects to give a reasonable review of the most recent advances in the pathogenesis of peptic ulcers, advancement of chronotherapy in treating peptic ulcer, impact of herbal therapies in treatment of peptic ulcer complications related with analgesics and anti-inflammatory drugs and the neglected needs as far as our insight and the management of this inexorably testing condition.

**Keywords:** Peptic ulcer, Anti-inflammatory drugs, *Helicobacter pylori*, Chronotherapy.

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### INTRODUCTION

The profound sores infiltrating through the thickness of the gastro-intestinal mucosa and solid mucosa are known as ulcers. Ulcers are of various types, for example, peptic ulcer in which there is sore in stomach lining and duodenal ulcer in which there is over the top acid discharge in stomach. Break in the covering of stomach, initial segment of the small digestive tract or in lower throat is alluded to as peptic ulcer sickness. Ulcers are the aftereffect of lopsidedness between forceful factors, for example, NSAIDs, gastric acid, *Helicobacter pylori* and defensive factors, for example, mucosal linings, bicarbonate, prostaglandins. Every day schedule, propensities, way of life, liquor, psychosocial factors, smoking, passionate pressure additionally plays a significant commitment [1]. In spite of the fact that patients with gastric ulcers have ordinary or reduced acid generation, yet ulcers may happen even in complete nonattendance of acid. Duodenal ulcers are found toward the start of small digestive system and are portrayed by extreme torment with copying sensation in upper midriff that stirs patients from rest. For the most part, torment happens when the stomach is vacant and assuages in the wake of eating. A duodenal ulcer is increasingly regular in more youthful people and transcendently influences guys. In the duodenum, ulcers may show up on both the front and back dividers. At times, peptic ulcer can be hazardous with indications like bleeding stool, extreme stomach agony, and spasms alongside heaving blood [2]. The gastric mucosa is persistently presented to possibly harmful operators, for example, acid, pepsin, bile acids, nourishment fixings, bacterial items (*Helicobacter pylori*) and medications. These specialists have been involved in the pathogenesis of gastric ulcer, including improved gastric acid and pepsin emission, restraint of prostaglandin combination and cell multiplication development, reduced gastric blood stream and gastric motility. An enormous number of flavors and herbs have been assessed by different scientists for their antiulcer impacts to accomplish a positive result. Huge quantities of therapeutic plants and dietary supplements have been appeared to have gastro-defensive exercises, for example, Aloe, Terminalia chebula, Vetiveria zizanioides, Ginseng, Capsicum [3].

### PATHOGENESIS OF PEPTIC ULCER

Pathogenesis of peptic ulcer significantly relies upon the lopsidedness among forceful and defensive variables. The pathology can be partitioned in 2 classifications peptic ulcer brought about by NSAIDs and peptic ulcer brought about by *H. pylori* microscopic organisms. The gastric barrier instrument against peptic ulcers, incorporate the nearness of prostaglandins (PGE2 and PGI2) in the gastric mucosa which hinders acid emission by restraining cAMP development in parietal cells. PGE2 additionally improves mucosal blood stream and invigorates discharge of

bodily fluid and bicarbonate [4]. NSAIDs intervene there helpful impact by restraining prostanoid blend. Prostanoid subordinates emerge from the transformation of arachidonic acid by cyclo-oxygenase (COX) isoenzymes following cell damage. NSAIDs apply their remedial calming and pain relieving impacts by hindering COX-2. The gastric and renal toxicities of the medications are identified with hindrance of the COX-1 isoform. There is a range of COX-1 and COX-2 restraint over the class of NSAIDs [4]. Corresponding utilization of NSAIDs or headache medicine with particular serotonin-reuptake inhibitors, corticosteroids, aldosterone opponents, or anticoagulants generously increment the danger of upper gastrointestinal dying. *H. pylori* have high urease movement which produces smelling salts to shield it from acidic condition in gut. It causes a fiery reaction in gastric mucosa, and furthermore advances deluge of neutrophils and macrophages with arrival of lysosomal proteins, leukotrienes which hampers the mucosal resistance of the mucosal coating. *H. pylori* produces urease to make a basic domain, which is basic for its endurance in the stomach under the mucosal boundary. It additionally communicates adhesins, for example, blood bunch antigen adhesin (BabA) or external provocative protein adhesin (OipA), which encourage connection of microorganisms to gastric epithelium. A genome pathogenic island encodes the destructive elements CagA and PicB, which—together with other bacterial elements—are thought to connect unequivocally with have tissue and be connected to gastric mucosal fiery cell invasion and gastric epithelial damage. It additionally causes increment in the degrees of COX2 in *H. pylori* positive gastritis. Colonization of the stomach by *H. pylori* can bring about the incessant gastritis, an aggravation of the stomach lining, at the site of the disease. Helicobacter cysteine-wealthy in proteins (Hcp), especially HcpA (hp0211), are known to trigger an insusceptible reaction, causing aggravation [5,6]. Figures 1 and 2 represent the pathogenesis of peptic ulcer and integrative therapy used for peptic ulcer disease treatment.

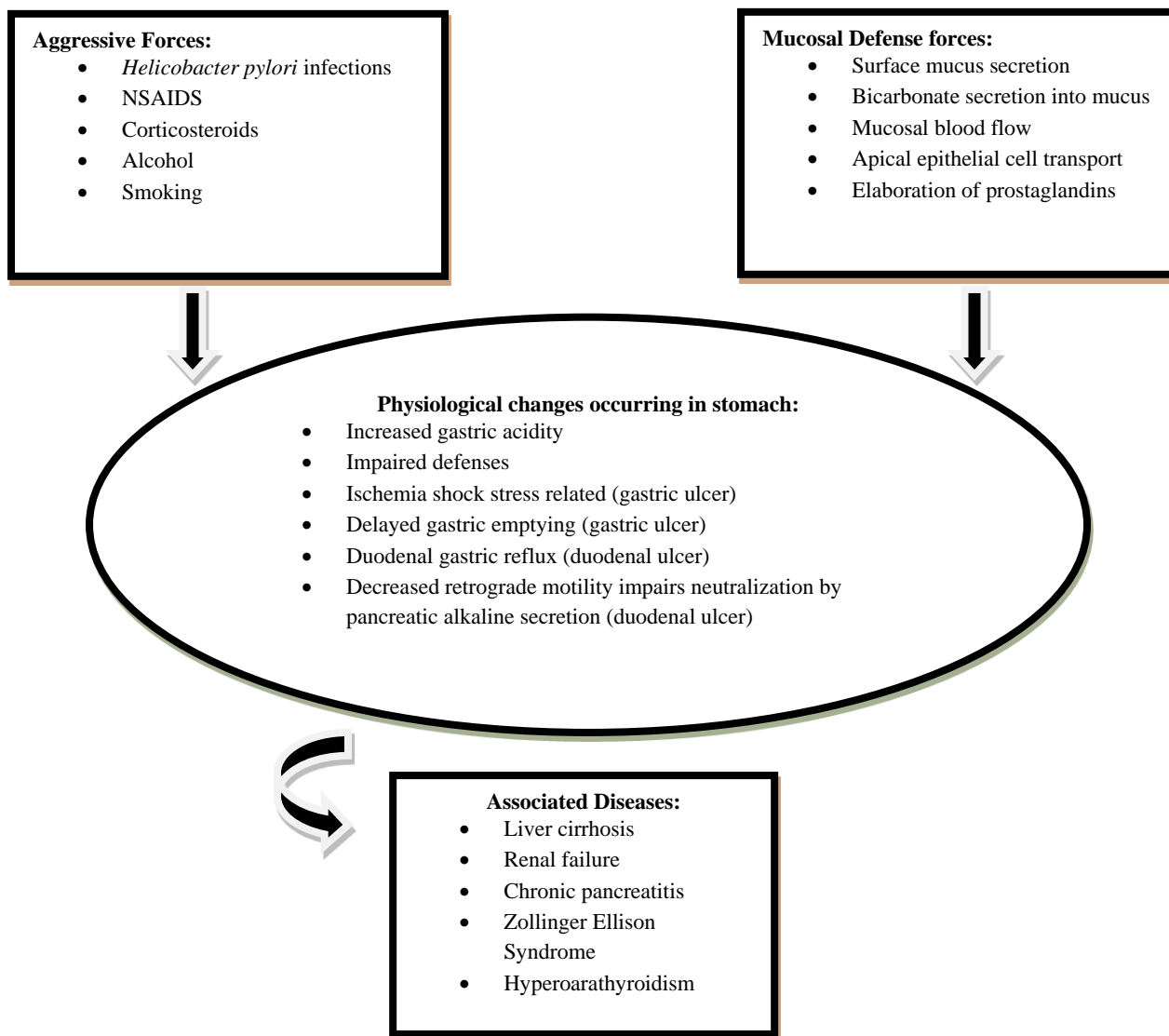


Figure 1: Pathogenesis of Peptic ulcer.

#### TREATMENT OF PEPTIC ULCER

H2 Receptor Antagonists-Cimetidine and ranitidine are the basic H2 receptor enemies which are utilized in the treatment of the peptic ulcer sickness. Its utilization for duodenal ulcer is demonstrated by different scientists and been distributed ordinarily in various papers. It is seen through endoscopy that after utilization of this class of medications ulcer recuperating is equipped for 70% in initial a month. Be that as it may, with high rate impact, high rate symptoms are likewise observed with these medications, for example, dazedness, retching, mental perplexity,

meddle with digestion of medications, antiandrogenic impact and so forth. These medications are just palliative. They don't fix the ailment totally. There are odds of reoccurrence of the malady after the end of the prescriptions. To keep away from this reoccurrence of the malady it is essential for the patients to take support portion of cimetidine of 400mg/day. By this it is seen that odds of reoccurrence of the malady decline 86%-91%. On the off chance that portion is expanded it could reach up to 100%. In this way, the disappointment of this treatment routine is because of two fundamental driver, initial one is the disappointment of ulcer to mend totally notwithstanding of complete 12 weeks treatment. Also, second, odds of reoccurrence of the ailment and to maintain a strategic distance from it need of support portion. Anticholinergic medications are strong gastric acid emission silencers. Anticholinergic are not all that utilized these days because of their different symptoms, for example, dazedness, dry mouth, obscured vision, urinal maintenance and so on. Over 20% patients experience the ill effects of the symptoms because of this class of medications. Prostaglandins have capacity to give protection from the gastric mucosa. This property is known as cytoprotection. System of activity of prostaglandins are that the restrain histamine - invigorated acids creation by blocking AMP. Its analogs increment bicarbonate emission in gastric mucosa and furthermore increment gastric mucous discharge. Proton Pump Inhibitors-Omeprazol, Lansoprazol, Pantoprazole, Rabeprazole have a place with this class of medications. This class of medications being feeble acid amasses in the gastric condition and stays dormant and gets dynamic in intestinal pH. There they are ingested travel to parietal cells and restrain hydrogen - potassium - adenosine - triphosphate. It is accounted for that 92% patients with duodenal ulcer mend totally after full course of about a month [7,8].

Endoscopy Therapy - By endoscopy treatment, the patients can be given legitimate treatment as indicated by the need and the seriousness of the case. In post - endoscopy treatment, PPIs are the most favored medication routine given to the patients explicitly to control their dying. In high hazard patients, after endoscopic treatment and 72 hours I.V Proton Pump Inhibitors portion, oral acid concealment is advantageous [9].

Herbal Therapy demonstrated that the researched restorative plants could avert ulcer in rodents in a portion subordinate way. Histological investigations uncovered that therapeutic plants didn't show any intense poisonous quality. Fundamental photochemical screening of this restorative plant distinguished the nearness of significant auxiliary metabolites like flavonoids and tannins. An assortment of natural products have been accounted for to have antiulcer action however the archived writing has focused basically on pharmacological activity in test creatures. With the exception of a couple phytogetic mixes (for example aloe, liquorice and cold), restricted clinical information are accessible to help the utilization of herbs as gastro-defensive operators and consequently, the information on viability and wellbeing are constrained. Regardless of this, there are a few herbal plants with potential remedial applications in view of their high adequacy and low harmfulness. At last, it ought to be noticed that substances, for example, flavonoids, aloe gel and numerous others, that have antiulcer action are of specific helpful significance. Dynamic standards of antiulcer activities are Flavonoids, terpenoids and tannins (Table 1).

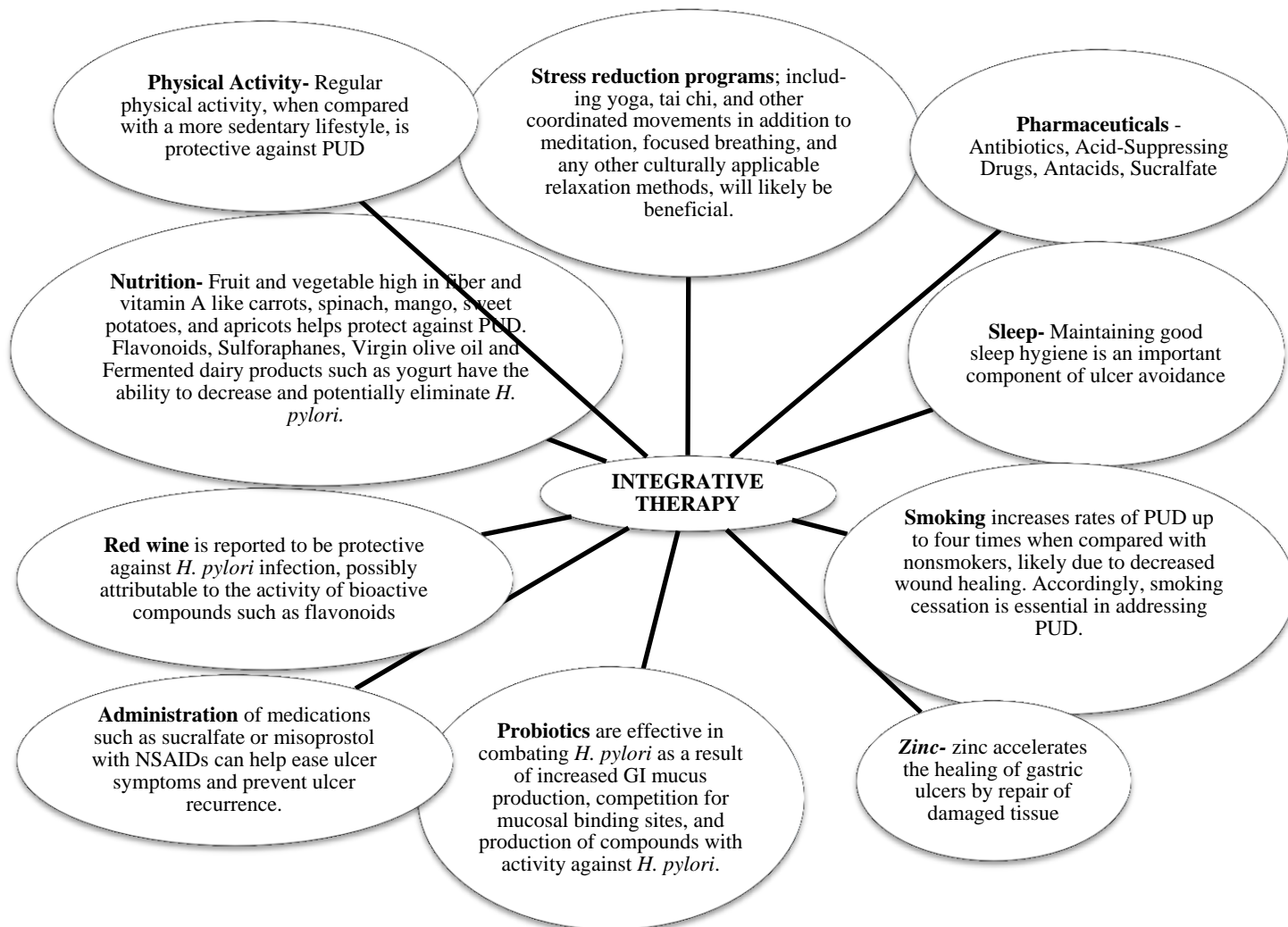


Figure 2: Representation of Integrative Therapy for PUD (Peptic Ulcer Disease).

Table 1: Medicinal plants with anti-ulcer activity

PLANT NAME	PHYTOCONSTITUENTS	PLANT PARTS USED	REFERENCES
<i>Curcuma longa</i> (Haldi) Fam: Zingiberaceae	Phenolic, tannins, flavonoids	Rhizome	[10]
<i>Azadirachta indica</i> (Neem) Fam: Meliaceae	Phenolic compounds, saponin, flavonoids	Leaves	[10]
Aloe Vera (Gritkumari) Fam: Liliaceae	Barbaloin, isobarbaloin, saponins.	Leaves	[10]
<i>Basella rubra</i> (Indian spinach) Fam: Apocynaceae	Saponin, protein, flavonoids	Leaf	[11]
Capsicum (Paprika) Fam: Solanaceae	Triterpenoids saponin	Fruit	[11]
<i>Glycyrrhiza glabra</i> (Liquorice) Fam: Leguminosae	Glycyrrhizic acid, a triterpenoids saponin	Root and rhizome	[11]
<i>Allium sativum</i> (Garlic) Family: Liliaceae	Volatile oil, allin, and allicin	Bulb	[12]
Ginseng (Gurmar) Fam: Araliaceae	Polysaccharides, triterpenoids, flavonoids, volatile oils, peptides, amino acids, fatty acids.	Root, leaf stem	[11]
<i>Beta vulgaris</i> (Beet root) Fam: Chenopodiaceae	Betin	Root	[11]
<i>Jatropha curcas</i> Linn. (Ratanjot) Fam: Euphorbiaceae	Phenolic compounds, saponin, flavonoids	Leaves	[10]
<i>Carica papaya</i> (Papaya) Fam : Caricaceae	Chymopapain and papain	Fruit	[10]
<i>Zingiber officinalis</i> (Ginger) Fam: Zingiberaceae	Phenolic compounds, flavonoids	Root	[12]
<i>Tamarindus indica</i> (Tamarind) Fam: Caesalpiniaceae	Tartaric acid, citric acid, malic acid, oxalic acid	Leaves	[13]
<i>Moringa oleifera</i> (Drumstick tree) Fam: Moringaceae	Quercetin, beta sitosterol, and beta carotene	Leaves	[11]
<i>Mangifera indica</i> (Mango) Fam: Anacardiaceae	Mangiferin	Leaves	[11]
<i>Psidium guajava</i> (Guava) Fam: Myrtaceae	Quercetin, guaijaverin, flavonoids, and galactose-specific lecithins	Leaves	[13]
<i>Momordica charantia</i> (Bitter gourd) Fam: Cucurbitaceae	Flavonoids, saponins, and sterols	Fruit	[13]
<i>Lawsonia alba</i> (Henna) Fam: Lythraceae	Hanno, tannic acid	Leaves	[12]
<i>Ophiopogon japonica</i> (Mondo grass) Fam: Asparagus	Ruscogenin	Rhizome	[14]
<i>Vernonia condensata</i> Baker Fam: Asteraceae	Luteolin	Leaves	[15]
<i>Brassica oleracea</i> (Cabbage) Fam: Brassicaceae	Glutamine and sulfuraphanes	Whole plant	[16]
<i>Tetracarpidium conophorum</i> nuts (Nigerian walnut) Fam: Euphorbiaceae	Flavonoids and terpenoids	Fruit	[17]
<i>Terminalia chebula</i> (Chebulic myrobalan) Fam: Combretaceae	Chebulinic acid	Fruit	[18]
<i>Pogostemon cablin</i> (Blanco) Fam: Labiatae	$\beta$ -patchoulene	Whole plant	[19]

### APPLICATIONS OF CHRONOTHERAPY

Chronotherapy is the comprehension and use of various organic cycles, for example, circadian, ultradian, infradian and occasional or other musical cycles. There are different body capacities which relies upon circadian example, for example, digestion, conduct, hormone generation and so on and investigation of these examples helps in modifying the organization of medications as indicated by the circadian beat of the infection. It is the investigation of how the impacts of medications shift with organic timings and endogenous periodicities [20]. The objective of the examination is to improve the comprehension of circadian check and be unsurprising in changes of both resistance of meds and wanted impacts. The medication treatment can be upgraded by fitting the dosing plan dependent on chronobiological design. The security and adequacy of the medication is accomplished by planning the pinnacle plasma convergence of the medication with circadian musicality of the body [21].

The upsides of having chronotherapy in treatment of any illness are various, for example, it improves people organic cycle and other physiological and digestion forms which legitimately benefits in the patient wellbeing and treatment, so it is medicate free treatment. Chronotherapy is helpful in different infections, for example, asthma, sleep deprivation, peptic ulcer, cardiovascular illnesses, malignancy, diabetes, state of mind issue. Our human body pursues distinctive sort of rhythms, for example, circadian cadence, ultradian beat, infradian mood, occasional musicality [22]. Points of interest Chronotherapy has no reactions, and is a medication free treatment. The more patient comprehends his natural cycle the more he gets advantage from this treatment. This treatment improves that patient wellbeing in a characteristic manner with no mischief. This treatment has no beginning and closure point. Whenever pursued appropriately, it gives mental harmony also. Legitimate direction and supervision is required in this treatment. There is requirement for ordinary subsequent meet-ups to the specialist to maintain a strategic distance from symptoms. It's somewhat awkward for the patient now and then to stay conscious until the following rest plan. Because of the unsettling influence in rest design during the treatment, patient may be denied of rest. Bizarre sensations, hotness and chilliness

are felt by certain patients [22].

Circadian rhythm in gut regulation- A large number of the elements of the gastrointestinal tract are dependent upon circadian rhythms. As a result of circadian beat, GI tract works distinctively in day time during nourishment admission and at evening during rest. The organic clock of the body deals with every one of the elements of GI tract, for example, motility, discharge, assimilation, retention, digestion of the supplements and so forth [23]. Any modification or aggravation in the circadian clock, for example, absence of rest, dietary problems and other outside natural changes prompts circadian misalignment. It is seen that circadian misalignment and poor rest quality can prompt GI issues, for example, causticity, swelling, stoppage, heartburn. The significant gatherings of individuals are influenced with circadian misalignment because of their way of life, for example, night move work, fly slack, and light presentation around evening time, (for example, utilization of TV, telephone around evening time, light contamination) [23].

### CHRONOTHERAPY IN TREATMENT OF PEPTIC ULCER DISEASE

From numerous decades, it is realized that patients with duodenal ulcer have exorbitant acid discharge during night, than ordinary people. In an examination on duodenal ulcer patients it is seen that, there is extreme acid discharge during night and day in correlation with the control gathering (typical people) [24]. It is likewise seen that gut motility and gastric exhausting is slower around evening time. In this way, for dynamic mending of peptic ulcer it is imperative to smother the nighttime acid. In an examination done on DU patients, it is seen that, when 400 mg of cimetidine ingested with breakfast there mean acid discharge was diminished till the following portion which was to be given at night, at with that the acid emission was restrained for 8h in night until the following morning. In this way, it was seen that acid discharge was fundamentally lower in DU patients during day and night. In this manner, by utilizing chronotherapy in, we can choose the best time to give a medication to the patients to treat their significant or continued decrease of 24h intragastric acidity including the risk of enteric disease, and invasion, potential bacterial excess with conceivable nitrosamine development [22]. It is seen that numerous manifestations and issues are seen on a particular time in 24-hour cycle. In this way, it is particularly important to comprehend the circadian musicality of the body and to rehearse chronotherapy [22]. Gastric Instability in the Stomach-Due to every day rehearse and occupied calendar of the life there is regular issue of gastric aggravation and gastric shakiness. Absence of rest, inappropriate dietary patterns, alcohol, smoking every one of these variables adds to this. Chronotherapy is the best alternative to bring back life on the track [24]. Contrasts in medicate retention in various locales of GIT fragments The example of gastric emission in the stomach assumes a significant job in the ingestion of the medication. A few medications are not absorbed in the gastric media. Or on the other hand, some expansion the gastric discharge in the body. Along these lines, it is particularly imperative to comprehend the example of the gastric emission and as needs be the prescription is recommended [25].

### CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM

The pharmacokinetic of the medication which is generally viewed as perfect for the customary meds, is influenced by different physiological and circadian mood of the body. Gastric acid discharge, gastrointestinal motility, gastrointestinal blood stream all are influenced by the circadian musicality and hence may influence the time - subordinate variety of medication plasma fixation [26]. Proton pump inhibitors are one of the plans to shield the acid labile medication from corruption. The enteric covering of the tablet, when taken orally enters in stomach, begins debasing in order to discharge the medication in the particular piece of the digestive system, where the medication is assimilated and plays out its instrument of activity [27]. Remotely controlled pulsatile medicate conveyance frameworks This sort of framework utilizes outside upgrades as trigger, for example, electrical flow, attractive field, and so forth. At the point when these triggers are applied to the frameworks, the conductors present in them get enacted and discharge the medication from the framework.

Other than these frameworks there are different late chronopharmaceutical advances; OROS innovation OROS represents osmotic - controlled discharge oral conveyance framework. This innovation is completely founded on assimilation. This framework is utilized to convey the medication in site explicit and time explicit way. In this framework, the API is secured by a semi penetrable containing a little conveyance hole from where the medication is discharged. It is planned in tablet structure. There are two layers in this tablet, one layer is of medication and the other layer is of osmotically dynamic specialist. At the point when, the tablet comes in contact of liquid, the osmotic specialist pushes away the dynamic fixing. [28]. Pulsincapo innovation - This framework comprises of hydrophilic top, hydrophobic body and a medication which is fixed with hydrogel plug. After the ingestion of the case, the hydrogel swollen and launched out from the case, and the medication is discharged from the framework after a foreordained time. Along these lines, this kind of frameworks is helpful for the conveyance of the medication in various districts of the gut at unmistakable time [26].

### CONCLUSION

The worldwide decrease of peptic ulcer infection during the previous century has happened most quickly in the previous two decades. The parallel decrease in the pervasiveness of *H. pylori* contamination coming about because of upgrades in financial status has had a significant job. Far reaching utilization of Proton Pump Inhibitors has presumably additionally added to the fast decay of peptic ulcer ailment. In any case, an abuse of Proton Pump Inhibitors, which are assessed to be utilized improperly in practically half of cases, may have prompted sudden new symptoms that are currently being bit by bit unwound. Innovative advances in genome-wide affiliation studies may give some knowledge by distinguishing hereditary polymorphisms related with peptic ulcer infection in explicit populaces. Anti-microbial opposition keeps on being a significant test for fruitful treatment of *H. pylori* contamination. Sub-atomic focuses against fundamental bacterial proteins could be critical to settling anti-infection obstruction. By picking the ideal time to accomplish the ideal impact, treatment openings may emerge, and unwanted reactions limited. Subsequently the long haul enthusiasm of both the general population and the business is to grow new and increasingly powerful strategies on the present investigation center - chronopharmaceuticals. It likewise stays to be resolved job of circadian rhythms and the utilization of chronotherapeutics may likewise assume a job in deciding an ideal treatment calculation in other sort of peptic ulcer ailments.

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