Review Article ISSN:2456-1622

Asia Pacific Journal of Pharmaceutical and Applied Sciences

PATHOPHYSIOLOGY AND CONVENTIONAL THERAPEUTIC APPROACHES FOR PEPTIC ULCER: AN OVERVIEW

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ABSTRACT

Peptic ulcers, characterized by the erosion of the gastrointestinal mucosa, remain a significant clinical challenge worldwide. This overview delves into the intricate pathophysiological mechanisms underlying peptic ulcer development, with a focus on the roles played by *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and gastric acid secretion imbalance. Understanding the multifactorial etiology of peptic ulcers is crucial for devising effective therapeutic strategies. The review further explores conventional therapeutic approaches employed in the management of peptic ulcers. Proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), and mucosal protective agents constitute the cornerstone of pharmacological interventions. The rationale behind their use lies in modulating gastric acid secretion and promoting mucosal healing. Additionally, eradicating H. pylori infection through antibiotic regimens is pivotal in cases where bacterial involvement is identified. This overview synthesizes current knowledge regarding the pathophysiology of peptic ulcers and outlines the conventional therapeutic approaches used in their management. By shedding light on the complexities of this prevalent gastrointestinal disorder, it aims to guide clinicians, researchers, and healthcare practitioners toward more informed decision-making and foster the development of innovative and personalized treatment strategies for peptic ulcer

Keywords: Peptic ulcer, *Helicobacter pylori*, gastric ulcer, Oesophagus, NSAID's, etc.

Submitted: 15-Oct-2023; Revised: 15-Nov-2023; Accepted: 25-Nov-2023

INTRODUCTION

Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract (g.i.t) mucosa. It is believed that the Gastric ulcer develop due to an imbalance between aggressive factors (Helicobacter pylori, NSAIDS, Gastric acid) and protective factors (mucin, bicarbonate, prostaglandins) leading to the interruption in the mucosal integrity [1]. It has been suggested that peptic ulcer disease, became remarkably more prevalent in Western countries in the 19th century possibly because of a change in the epidemiology of *H. pylori* infections [2]. Another common cause of Gastric ulcer is consumption of NSAIDs. NSAIDs causes inhibition of enzyme cyclooxygenase which further leads to the inhibition of prostaglandins (E2 and I2) and causes decrease in mucosal secretion and leads to gastric ulcers. NSAIDs like Indomethacin act on mitochondria and inhibit the oxidative phosphorylation and leads to the formation of free radicals like super oxides and hydrogen peroxide which ultimately leads to lipid peroxidation and apoptosis. There are also various behavioural factors which lead to the development of stomach ulcers. The various factors include:-Smoking, Frequent use of steroid , Hypercalcemia, Excessive consumption of alcohol. adenosine is an important endogenous regulator of many physiological processes including blood flow, seizure activity, air way resistance and neuronal activity. There is now increasing direct and indirect evidence that adenosine and its receptors are involved in the control of gastric acidity and modulation of gastric responses to the histamine and acetylcholine [3]. Adenosine promotes tissue protection and repair through four general modes of action: increased oxygen supply/demand ratio, preconditioning, anti-inflammatory effects and stimulation of angiogenesis. Thus, adenosine down regulation of inflammatory and immune responses in injured tissues plays a crucial role in the beneficial effects induced by this nucleoside (Linden et al., 2005) Adenosine, adenosine 5′-triphosphate (ATP), ADP, AMP, uridine 5′-triphosphate (UTP), UDP, and UDP-glucose are endogenous purines that activate P1, P2X, or P2Y purinoceptor families that are widely and differentially distributed in the ENS and non-neuronal cells in the git The tissue distribution and/or biological experiments suggest that up to 14 of 18 purinoceptor may be involved in secretomotor reflexes in the GI tract [4]. P1 purinoceptor or adenosine (ADO) receptors, mediate the biological effects of the endogenous nucleoside adenosine and its analogs. Adenosine acts on cell surface receptors that are coupled to intracellular signalling cascades [5]. Purinergic signalling is rapid in synaptic neurotransmission, in neuromuscular transmission leading to contraction or relaxation of smooth muscle, and in exocrine or endocrine secretion. However, there are now many examples of Purinergic signaling regulating long-term events such as cell proliferation, differentiation, migration, and death in development, regeneration, and wound healing. Both P2X and P2Y receptors play prominent roles both directly and by modulation of other signalling systems in embryonic development, including the nervous system, cartilage in limb buds, the mesonephros, retina, myotubes, and neuromuscular junctions [6]. Adenosine inhibits gastric acid secretion, either directly by acting on acid-secreting parietal cells or indirectly by stimulating the release of the acid inhibitor, somatostatin [7].

METHODOLOGY

A thorough survey of literature was conducted on *Betula utilis* using various online and offline resources. The primary source of data collection was various research and review articles published by various publishers like Elsevier, PSCI, Springer, JDDT etc. Various online databases were also referred for collecting data on ulcers. The databases are NEJM, Science Direct, PubMed, Sci-Hub and Library Genesis. Some various other sources were gone through for the collection of literature on ulcers like various journals, book chapters and web pages to gather the maximum possible information.

Anatomy of the normal stomach:-

The stomach is a muscular organ located on the left side of the upper abdomen. The stomach receives food from the oesophagus. As food reaches the end of the oesophagus, it enters the stomach through a muscular valve called the lower oesophageal sphincter. The stomach secretes acid and enzymes that digest food. Ridges of muscle tissue called rugae line the stomach. The stomach muscles contract periodically, churning food to enhance digestion. The pyloric sphincter is a muscular valve that opens to allow food to pass from the stomach to the small intestine [8].

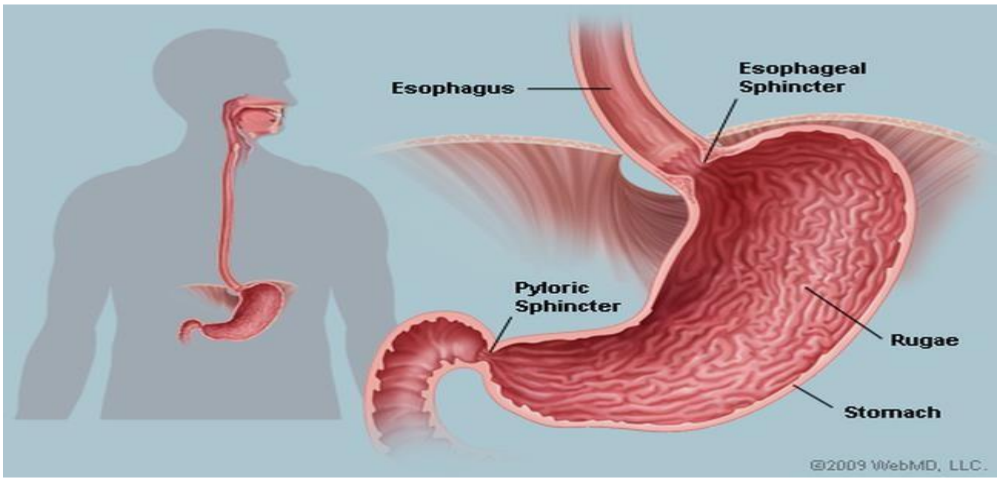

Figure 1. Anatomy of normal stomach.

Pathophysiology of Ulcers

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and Indomethacin are the most commonly prescribed drugs for arthritis, inflammation, and cardiovascular protection. However, they cause gastrointestinal complication such as ulcers and erosion. The pathophysiology of these complications has mostly been ascribed to NSAID’s action on the cyclooxygenase (COX) inhibition and the subsequent prostaglandin (PG) deficiency [9]. The pathogenesis of gastric mucosal damage includes reactive oxygen species (ROS), because of their high chemical reactivity, due to the presence of uncoupled electron within their molecules. Therefore, there cause tissue damage, mainly due to enhanced lipid peroxidation. Lipid peroxides are metabolizing to Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). The local increase of MDA and 4-HNE concentration indicates ROS-dependent tissue damage. Superoxide dismutase (SOD) is the main enzyme, which neutralizes ROS into less noxious hydrogen peroxide. A decrease of SOD activity is an indicator of impairment of the protective mechanism and significantly contributes to cell damage. Hydrogen peroxide is further metabolized to water in the presence of reduced glutathione (GSH). GSH can also work synergetically with SOD to neutralize ROS. The reactions between GSH and ROS yield glutathione free radical ($GS^{\bullet}$), which further reacts with GSH leading to free radical of glutathione disulphide ($GSSG^{\bullet}$). This free radical of GSSG can then donate an electron to the oxygen molecule, producing $O_2^{\bullet -}$. Subsequently, $O_2^{\bullet -}$ is eliminated by SOD. A decrease of the GSH level has detrimental consequences for antioxidative defence cellular properties. Gastric mucosa, exposed to stress condition, exhibits an enhancement of lipid peroxidation (increase of MDA and 4-HNE), as well as a decrease of SOD activity and GSH concentration. This chain reaction of ROS formation triggered by NSAID’S and stress, appears to be an essential mechanism for understanding the pathogenesis of NSAID’S-induces functional disturbances in the gastric mucosa leading to ulcerogenesis.

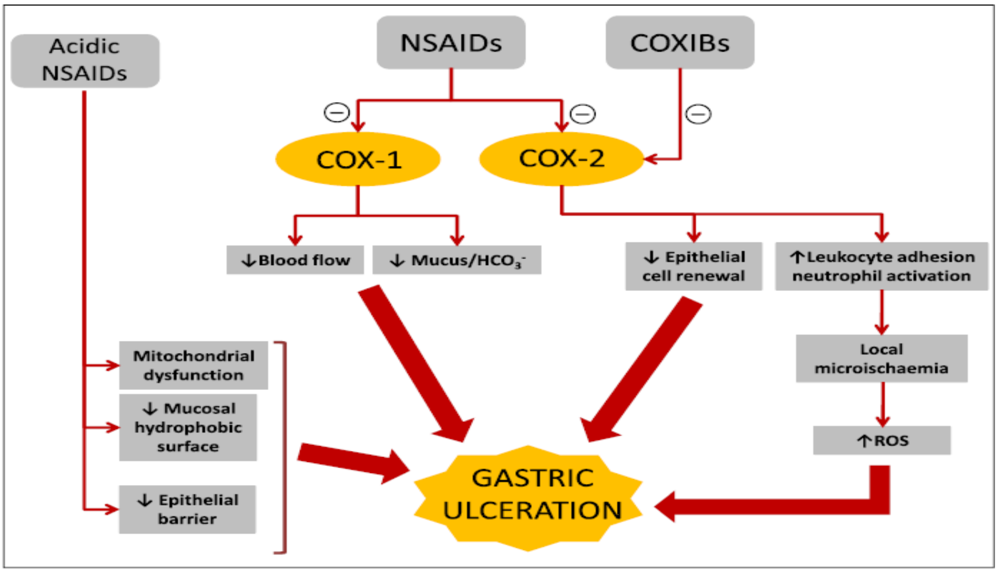

Figure 3. Pathophysiology of Gastric ulcer induced by non-selective NSAIDs.

Different types of ulcers

Gastric ulcer

Gastric ulcer is a common disease that affects millions of people worldwide, considering its global prevalence finding, a new approach for treating it is important. According to WHO, peptic ulcer disease death in India reached 85487 or 0.96% of total death. The age adjusted death rate is 9.12%, i.e. one lac of population is suffering from peptic ulcer due to which India is ranked 26th in the world [10]. Ulcers are open sores in the upper part of the digestive tract that can cause stomach pain and stomach upset which can lead to internal bleeding. There are two types of peptic ulcer (1) Gastric ulcer (2) Duodenal ulcer. Peptic ulcer disease is a multicausal and complex disease that occurs when biological balance between defensive and aggressive factors in gastrointestinal tract is disturbed [11]. The aggressive factors are endogenous factors like gastric acid, endothelin's and pepsin secretion [12], active free radicals and oxidants, leukotrienes [13] as well as exogenous factors like ethanol [14] or nonsteroidal anti-inflammatory drugs (NSAIDS). On the other side gastric mucus, bicarbonate, normal blood flow, prostaglandins (PGs), nitric oxide (NO), and antioxidant enzymes like catalase (CAT), or antioxidant peptides like glutathione (GSH) work as defensive barrier [15], Mucosal cell death results from increase in H^+ concentration in its immediate environment due to this pH decreases [16]. There are many drugs that are used in the treatment of peptic ulcer. Until now, there is no drug without a side effect, that gives 100% curative rate or complete cure of the disease.

Duodenal ulcer: - When a peptic ulcer is in duodenum, it is called a duodenal ulcer. This type of peptic ulcer develops in the first part of the small intestine. Some of the symptoms of a duodenal ulcer are interestingly quite opposite to those of gastric ulcers. Duodenal ulcers are the most common ulcers found in the Western world.

Oesophageal Ulcers:- Oesophageal ulcers are lesions that occur in the oesophagus (food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Oesophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs and smoking [17].

Bleeding Ulcer:- Internal bleeding is caused by a peptic ulcer which has been left untreated. When this happens, it is referred to as a bleeding ulcer, this is the most dangerous type of ulcer and it requires an immediate treatment.

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

Stress Ulcer: Stress ulcers are a group of lesion (or lacerations) found in the esophagus, stomach or duodenum. These are normally only found in critically ill or severely stressed patients [18].

Purinoceptors

Purinoceptor, the other name for Purinergic receptors are a family of plasma membrane molecules which play an important role in several cellular functions such as vascular reactivity, apoptosis, and cytokines secretion. The term *Purinergic receptors* was first introduced to describe classes of membrane receptors that, when activated by either neurally released ATP (P_2 purinoceptor) or its breakdown product adenosine (P_1 purinoceptor), mediated relaxation of gut smooth muscle [19]. Purinergic receptors are widely distributed in the body and its activation causes plasma membrane permeabilization, Ca^{2+} influx and cell death. Many evidences indicate that extracellular nucleotides play an important role in the regulation of neuronal and glial functions in the nervous system via Purinergic receptors. These nucleotides are either released from or leaked through nonexcitable cells and neurons during normal physiological and pathophysiological conditions [20]. On the basis of cloning, signal transduction and pharmacology, purinergic receptors are divided into P_1 adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3 subtypes) and P_2 receptors which are further divided to P_2Y metabotropic receptors ($P_2Y_{1,2,4,6,11,12,13,14}$ subtypes) and P_2X ionotropic receptors (P_2X_{1-7} subtypes). The P_1 and P_2Y receptors are classical 7-transmembrane domain receptors, the action of which is mediated through G-proteins and numerous intracellular second messengers, including the cAMP and IP_3 cascades. In addition, some of these receptors are linked to membrane ion channels, thus mediating plasmalemmal ion fluxes and electrophysiological effects. P_2X receptors are ligand-operated cationic channels, many of which have an appreciable Ca^{2+} permeability (Pankratov *et al*., 2009). The P_2X channels are assembled (in a homo or heteromeric manner) from seven subunits, designated as P_2X_1- P_2X_7, which determines the variability of their biophysical and pharmacological properties [21].

Receptor subtypes:

P1 (ADO) Receptors

P_1 purinoceptor or adenosine (ADO) receptors, mediate the biological effects of the endogenous nucleoside adenosine and its analogs. Adenosine acts on cell surface receptors that are coupled to intracellular signalling cascades and are mainly divided into 4 subtypes: A_1, A_{2A}, A_{2B}, and A_3 (Mustafa *et al*, 2009) and all of these ADO receptor subtypes are G-protein coupled receptors (GPCRs) [22].

P_2 (ATP) Receptors

Extracellular ATP released from the cells is sensed by P_2 plasma membrane receptors which are further divided in P_{2X} and P_{2Y} subtypes. P2X receptors are ligand gated ion channels (LGIC), which are specific for ATP, whereas P2Y receptors belong to GPCR superfamily and show responses to various nucleotides including ATP, adenosine diphosphate (ADP), uridine triphosphate (UTP) and uridine diphosphate (UDP). On the basis of specific tissue expression and pharmacology , seven P2X receptors (P2X1-7) and eight P2Y receptors (P2Y1,2,4,6,11,12,13,14) have been identified [23].

9. Role of Theophylline:

Theophylline, also known as 1,3-dimethylxanthine, is a methylxanthine drug used in therapy for purine synthesis. Theophylline (3-methyxanthine) has been used to treat airway diseases for over 70 years. It was originally used as a bronchodilator but the relatively high doses required are associated with frequent side effects, so its use declined as inhaled β_2-agonists became more widely used. More recently it has been shown to have anti-inflammatory effects in asthma and COPD at lower concentrations. The molecular mechanism of bronchodilatation is inhibition of phosphodiesterase (PDE)3 and PDE4, but the anti-inflammatory effect may be due to histone deacetylase (HDAC) activation, resulting in switching off of activated inflammatory genes. Theophylline remains one of the most widely prescribed drugs for the treatment of asthma and COPD world-wide, since it is inexpensive and widely available. In many industrialized countries, however, theophylline has become a third-line treatment that is only used in poorly controlled patients as an add-on therapy. This has been reinforced by various national and international guidelines on asthma and COPD therapy. Some have even questioned whether theophylline is indicated in any patients with asthma, although others have emphasized the special beneficial effects of theophylline which still give it an important place in management of asthma. The frequency of side-effects at the previously recommended doses and the relatively low efficacy of theophylline have recently led to reduced usage, since inhaled β_2-agonists are far more effective as bronchodilators and inhaled corticosteroids have a greater anti-inflammatory effect. Despite the fact that theophylline has been used in asthma therapy for over 70 years, there is still considerable uncertainty about its molecular mode of action in asthma and its logical place in therapy. Recently novel mechanisms of action that may account for the effectiveness of theophylline in severe asthma have been elucidated. Because of problems with side effects, there have been attempts to improve on theophylline and recently there has been increasing interest in selective phosphodiesterase (PDE) inhibitors, which have the possibility of improving the beneficial and reducing the adverse effects of theophylline [24].

Antagonistic effect of Theophylline on Adenosine Receptors

Theophylline is a potent inhibitor of adenosine receptors at therapeutic concentrations. Both A_1- and A_2-receptors are inhibited, but theophylline is less effective against A_3-receptors, suggesting that this could be the basis for its bronchodilator effects (Pauwels, 1995). Although adenosine has little effect on normal human airway smooth muscle *in vitro*, it constricts airways of asthmatic patients *via* the release of histamine and leukotrines, suggesting that adenosine releases mediators from mast cells The receptor involved appears to be an A_3- receptor in rat mast cells but in humans A_{2B}-receptors are involved. Adenosine causes bronchoconstriction in asthmatic subjects when given by inhalation. The mechanism of bronchoconstriction is indirect and involves release of histamine from airway mast cells. The bronchoconstrictor effect of adenosine is prevented by therapeutic concentrations of theophylline however, this only confirms that theophylline is capable of antagonizing the effects of adenosine at therapeutic concentrations, and does not necessarily indicate that this is important for its anti-asthma effect. Adenosine antagonism is likely to account for some of the side effects of theophylline, such as central nervous system stimulation, cardiac arrhythmias (both *via* blockade of A_1-receptors), gastric hypersecretion, Gastroesophageal reflux and diuresis. A novel AMP receptor, $P2Y_{15}$, has been identified which is more potently inhibited by theophylline [25]

Role of Theophylline in Gastric Ulcer:

Helicobacter pylori infection and gastric hyperacidity results in the development of gastric ulceration. ATP was shown to be involved in the development of gastric hypersecretion and ulceration in pylorus-ligated rats. It was shown that in pylorus-ligated rats, gastric acid secretion was an ATP-dependent process and that adenosine acting via P1 receptors inhibited the development of ulceration. Methylxanthines, which blocked the action of adenosine, stimulated the acid content of gastric secretions and promoted gastric ulceration. Dipyridamole, which leads to an increase in extracellular adenosine, significantly reduced the extent of gastric bleeding and ulcer formation [26].

CONCLUSION

In conclusion this review summarizes the various types of ulcers and the role of purinoreceptors in these types of ulcers. The review has given emphasis on the role of adenosine on purinergic receptors in the treatment of gastric ulcer.

REFERENCES

1. Borrelli F, Izzo AA. The plant kingdom as a source of anti-ulcer remedies. Phytother Res. 2000;14:581-591.
2. Burnstock G. Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev. 2007;87:659-797.
3. David YG. History of Helicobacter pylori, duodenal ulcer, gastric ulcer, and gastric cancer. World J Gastroenterol. 2014.

4. Fievos LC. Purinergic receptors and gastrointestinal secretomotor function. J Purinergic Signal. 2008.
5. Gartland A, Orriss IR, Rumney RM, Bond AP, Arnett T, Gallagher JA. Purinergic signalling in osteoblasts. Front Biosci. 2012;17:16-29.
6. Matsui H, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in the stomach and small intestine. J Clin Biochem Nutr. 2011;48(2):107-111.
7. McCormack JG, Marx R, Boyett B, Brain R, Jewell C. Department of Biochemistry and Physiology. J Mol Cell. 1988.
8. Kaur A, Singh R, Sharma R, Kumar S. A review on etiology and pathogenesis of peptic ulcer. Int Res J Pharm. 2012.
9. Kudo F, Nishiguchi N, Nakano M, Ito K. Expression and function of the P2Y14 receptor in murine peritoneal macrophages. Hirosaki Med J. 2012;63:96-104.
10. Landells LJ, Jensen MW, Orr LM, Spina D, O'Connor BJO, Page CP. The role of adenosine receptors in the action of theophylline on human peripheral blood mononuclear cells from healthy and asthmatic subjects. Br J Pharmacol. 2000.
11. Linden J. Adenosine in tissue protection and tissue regeneration. Mol Pharmacol. 2005;67(5):1385-7.
12. Laine L, Takeuchi K, Tamawski A. Gastric mucosal defense and cytoprotection. 2008.
13. Lalo U, Roberts JA, Evans RJ. Identification of human P2X1 receptor-interacting proteins reveals a role of the cytoskeleton in receptor regulation. J Biol Chem. 2011;286:30591-30599.
14. Ludovico B, Eric S, Annemarthe G, Van DV, Rino R, Antonello C, et al. Helicobacter pylori cytotoxin-associated gene A subverts the apoptosis-stimulating protein of P53 AAPP2 tumor suppressor pathway of the host. 2011;1-6.
15. Majundar D, Bebb J, Atherton J. Helicobacter pylori infection and peptic ulcers. Med. 2011;39:154-161.
16. Migalovich-Sheikhet H, Friedman S, Mankuta D, Levi-Schaffer F. Novel identified receptors on mast cells. Front Immunol. 2012;3:238-257.
17. Al-Mofarreh MA, Ibrahim A, Al Mofleh. Esophageal ulceration complicating doxycycline therapy. World J Gastroenterol. 2003;9:609-611.
18. Mundell S, Kelly E. Adenosine receptor desensitization and trafficking. Biochim Biophys Acta. 2011;1808(5):1319-1328.

19. Mustafa SJ, Ansari HR, Abebe W. P1 (adenosine) purinoceptor assays. Curr Protoc Pharmacol. 2009;45:4.7.1-4.7.13.
20. Muller N, Payan E, Lapicque F, Bannwarth B, Netter P. Pharmacological aspects of chiral nonsteroidal anti-inflammatory drugs. Fundam Clin Pharmacol. 1990;4(6):617–634.
21. Rayah A, Kanellopoulos JM, Di Virgilio F. P2 receptors and immunity. Microbes Infect. 2012;14:1254-1262.
22. Sibel K, Burak S, Ahmet S, Mehmet A, Polat K, Ali A, Hasan D. Effect of subclinical Helicobacter pylori infection. Radiology. 2008;14:138-142.
23. Soll A, Graham D. Peptic ulcer disease. In: Yamada T, editor. Textbook of Gastroenterology. 5th ed. USA: Blackwell Publication Ltd; (5):936-941.
24. Tripathi KD. Essentials of Medical Pharmacology. 6th ed. Jaypee Brothers Medical Publisher (P) Ltd; New Delhi: 627-683.
25. Wallace JL, Mcknight GW, Keeran CM, Byles NI, MacNaughton WK. Effects of leukotrienes on susceptibility of the rat stomach to damage and investigation of the mechanism of action. Gastroenterology. 1990;98:1178-1186.
26. Yang GK, Yip L, Fredholm BB, Kieffer TJ, Kwok YN. Involvement of adenosine signaling in controlling the release of ghrelin from the mouse stomach. J Pharmacol Exp Ther. 2011;336:77–86.

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