Gastro protective Mechanisms and its Augmentation by External Agents- A Review

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Abstract

Owing to its advantages such as non-invasiveness, patient compliance, and simplicity of administration, the oral route is the most often used method of medicine delivery. Non-steroidal anti-inflammatory drugs are among the pharmacological classes that are most frequently suggested for the treatment of inflammatory diseases and pain. PUD (peptic ulcer disease) is a side effect of non-steroidal anti-inflammatory drug therapy. Gastric ulcers are the result of an imbalance between the actions of aggressive and gastroprotective substances. The mucus layer, mucosal repair ability, gastric epithelium, and stomach blood flow are examples of gastroprotective systems. This review aims to give a current overview of gastroprotective mechanisms. As was covered in, the gastric epithelial defenses consist of a sensor on the mucosal surface, stem cells, and the cell barrier. Mucin serves as a filter.

Keywords: *Gastrointestinal-protective, Mucosa, Oral route, PUD and Ulcer*

1. Introduction

As a component of the digestive system, the stomach performs a number of tasks, including creating chyme. It is essential for the production of the peristaltic reflex, vitamin absorption, and microbiological defense (Durkin, N., 1979). The entire gastrointestinal tract is covered in mucus. Mucus in the stomach and colon is bilayered, with a 50–200 m thick interior layer affixed to the epithelium. It is simple to ignore the outer mucus layer, which has a thinly defined outer border (Shahsavari, D., & Parkman, H. P., 2022). The small intestine has a single layer of mucus, in contrast to the colon. Since mucus comprises more than 98% water, it is entirely transparent and undetectable to microscopists (Hyder et. al., 2023). Gut health depends on mucus, and neurological conditions can modify the qualities of mucus. Glycosylated mucin proteins are part of the hydrated polymer chain that makes up mucus (He et. al., 2023).

The most widely used medications for treating fever, inflammation, and aches are non-steroidal anti-inflammatory medicines (NSAIDs) (Day and Garry 2013). NSAIDs are frequently used to treat ischemic cerebrovascular disorders, rheumatoid arthritis, osteoarthritis, dysmenorrhea, and inflammatory conditions (Bindu and Bandyopadhyay 2020). For these medications to have a therapeutic impact, prostaglandin production must be disrupted (Alm et. al., 2008). On the other hand, prolonged use of NSAIDs might result in negative gastrointestinal (GI) side effects, such as bleeding, peptic ulcers, mucosal lesions, and intestinal inflammation (Collins et. al., 1993).

II. The body has the following built-in defense systems to offer gastro-protection: mucosal protection

The phrase "mucosal defense" describes the various components and characteristics that enable the mucosa to stay unaltered despite frequent exposure to substances with a wide range of temperature, pH, and osmolarity, as well as detergent and bacterial results that have the potential to induce inflammatory responses both locally and systemically (Newberry et. al., 2005).

It is crucial to realize that the stomach mucosa is not very resilient to harm from these substances. It's common to misunderstand the term "gastric mucosal barrier" to mean that this tissue is tight (Laine et. al., 2008). In actuality, mucosal injury is a common occurrence but does not disrupt the process in a way that is clinically meaningful.

This is because mucosal defense consists of multiple "coatings," with secondary elements developing more rapidly when the superficial elements are compromised and because the restoration process starts as soon as the epithelium is damaged (Newberry et. al., 2005).

Moreover, a range of endogenous compounds, such as prostaglandins, have the ability to regulate different aspects of mucosal defense. Thus, microbial products, bacteria, and other poisons are prevented from entering the bloodstream. However, there are some situations where the mucosa's defenses are compromised, such as with the use of NSAIDs (non-steroidal anti-inflammatory medicines), which increases the mucosa's sensitivity to harm (Stange and Schroeder, 2019).

The Following Are A Few Mucosal Defense Factors:

A. Illuminating Elements

Even while the epithelium is frequently thought of as the physical embodiment of "the barrier," the luminal side of the epithelium also contains a number of mucosal defense components.

Among the elements in gastric juice that can lessen bacterial colonization of the stomach are acid, immune globulins, and lactoferrin. Few bacteria are resistant to stomach acid.

Observations showing hypochlorhydria and achlorhydria promote local activity and make bacterial and parasite conditions more harsh demonstrate the role of acid as an achlorhydria defense component (Akiba and Kaunitz, 2009). The quantity of gastric acid secreted is inversely correlated with the number of bacteria in the duodenum and stomach (Pardo et. al., 2018). In addition to acting as a bacterial trapping and lubricant, the mucus produced onto the stomach surface also reduces significant harm to the epithelium caused by absorbed materials (Taherali et al., 2018). Mucus can thereby reduce bacteria's ability to penetrate the epithelium. Ironically, H. pylori colonization happens in the stomach's mucous layer mostly in the antrum (Neto el. Al., 2017). In addition to serving as a barrier against luminal pepsin, mucus is necessary for the creation of an undisturbed layer on the mucosal surface, which aids in maintaining a close-neutral pH there (McShane et. al., 2021). However, other studies have demonstrated that mucosal protection is more dependent on precisely regulated alkali secretion and the entrapment of those alkali within the unstirred layer on the surface of the epithelium than on mucus's ability to prevent proton penetration (Lentle et. al., 2011). Three main areas of disagreement are raised when discussing the significance of the mucus-bicarbonate "barrier" in mucosal protection:

1) If surface mucus consistency is necessary to shield the epithelium from acid injury (Allen and Flemstrom, 2005).

2) The consistency or irregularity of the mucus layer that shields the mucosal shell (Pearson et. al., 2016).

3) In the event that the mucus coating is continuous, how can the acid secreted by the stomach glands penetrate it and enter the lumen? Because of a surface-active phospholipid coating that resembles a surfactant, the stomach's exterior is hydrophobic, which prevents acid from diffusing backward. This coating is present on the surface of the epithelium or on the mucus covering the epithelium's most luminal surface (Atuma C., 2000).

It's interesting to note that phosphor lipid enzymes and ammonium ions eliminated by H. pylori have the ability to lessen the effectiveness of the stomach's hydrophobic lining, which causes the gastric surface to become less hydrophobic in H. pylori patients (Goggin et. al., 1992).

B) The Layer of Epithelium

The gastric epithelial cells' innate capacity to sustain their integrity and functionality in the face of prolonged exposure to high acid concentrations may be related to the epithelium. (Ballmann et. al., 2015 ; Ramchandran et. al., 2000) The apical shells of these cells remained intact after being subjected to a pH 2 solution for over 4 hours. In contrast, the baso lateral membrane of these cells was highly susceptible to acid, breaking down in the presence of a solution with a pH of only 5.5. The "youth" of the gastric epithelium—that is, the fact that it regenerates every two to four days in humans—is another element that contributes to its resistance to harm (Von’t Hof et. al., 1997). The process of cell ejection during apoptosis is responsible for the older cells' regular and fast return without causing a major disruption to epithelial continuity and barrier function. Until the apoptotic cell is detached from the basement membrane, the surrounding cells gradually enclose it at its base (Andrade and Rosenblatt et. al., 2011).

C) Vascular Circulation

When there is sufficient vascular circulation, epithelial damage typically does not result in the necrosis of deeper mucosal layers (Miller and Zachary et. al., 2017). Microscopically, there is evidence of epithelial damage, although minutes to hours after injury, epithelial integrity is restored. "Restitution," the term for this quick repair, is the migration of nutrient-rich epithelial cells from the stomach pits over the exposed basement membrane (Galberg H. 2018). This is an additional mucosal guard component whose modulation by prostaglandins has been demonstrated.

This approach may be seen as in vitro, but it is abundantly clear that vascular perfusion in vivo is essential for supplying a "back-up" layer of mucosal protection during the crucial stage that follows injury and basement membrane exposure to luminal contents. The "mucoid cap," an outer layer covering the exposed area, is formed when mucus released from ruptured epithelial cells interacts with plasma leaking from the mucosal vasculature (Holzer P. Et. al., 2011). The mucoid cap's pH can be maintained close to neutral (pH-1) in the stomach's exceptionally high hydrochloric acid content. It need regulated mucosal blood flow to keep the pH microenvironment high. Hemorrhagic lesions occur from a considerable fall in pH within the mucoid cap, the outer layer covering the bared area, when blood supply to the abdomen is disturbed. This holds true regardless of whether a vasoconstrictor is used or the gastric artery supply is automatically blocked (Donath et. al., 2023).

When the acid is let to permeate the mucosa more deeply, there is widespread necrosis and bleeding.

Prostaglandins appear to be important in maintaining mucosal blood flow during epithelial repair since luminal substances can stop these activities. It is possible to apply high acid concentrations to the gastric mucosa without seriously harming the epithelium. When acid is present in the superficial mucosa, the mucosal vasculature responds very fast, buffering, diluting, and eliminating the acid (Taranwaski A.S., 2005). A reflex mediated by a sensory afferent nerve enables this. The surface mucosa's sensory afferent nerve terminals sense the presence of acid, and in response, they release the vasodilator CGRP in the vicinity of submucosal arterioles (Holzer P., 2011). This results in a surge in blood flow in the mucosa by relaxing the smooth muscle around the arterioles.

There is evidence that prostaglandins play a role in this vasodilatory response (Tarnawski A.S. 2005), although nitric oxide (via soluble guanylate cyclase) mediates the relaxing effects of CGRP (calcitonin gene-related peptide) on vascular smooth muscle (Holzer P. 2011). Mucosa injury results from CGRP (calcitonin gene-related peptide) antagonists, NSAIDs, NOS inhibitors, or sensory afferent neuronablation during a severe hyperemic reaction (Laine et. al., 2008). Moreover, a number of medical disorders affect the reactive hyperemic response, raising the possibility of bleeding and stomach ulcers. Portal hypertension is one instance of this. A major disturbance of the prostaglandin and nitric oxide-mediated aggressive hyperemic reaction is the reason behind the failure of mucosal protection in portal hypertension (Laine et. al., 2008).

D) Swelling

An acute inflammatory response is also triggered when the stomach mucosa is damaged externally, as seen by increased blood flow, plasma exudation, and leukocyte recruitment into the mucosa. Reducing tissue damage, promoting tissue healing, and preventing extraneous substances (such as microorganisms and microbial byproducts) from entering the systemic circulation are the objectives of such a return. Mucosal mast cells, which act as "sentinels" inside the mucosa, are among the cells that release a range of soluble intermediates in conjunction with this inflammatory response (Laine et. al., 2008; Edmonds et. al., 2000).

Diseases of the digestive system necessitating gastro protection

A) Stomach illness

a) Gastritis

Any clinical condition characterized by upper stomach issues, such as dyspepsia or digesting, without any distinguishable clinical symptoms is frequently referred to as arthritis (Edmonds et. al., 2000). Based on its duration, course, histological features, anatomical location, and suggested pathogenic mechanism, arthritis has been categorized (Kayacetin and Guresci, 2014). With a pH that is nearly a million times lower than that of blood, the stomach lumen is exceedingly acidic. Although it facilitates digestion, this hostile environment may cause damage to the mucosa (Engevik et. al., 2014).

Numerous protective mechanisms have been developed for the gastric mucosa, including mucin-containing mucus, which encourages the formation of a continuous liquid coating over the epithelium covering the mucosa and has a neutral pH due to bicarbonate ion secretions by epithelial cells. Lastly, the abundant vascular supply of the stomach mucosa removes acid that has re-diffused into the lamina propria while also delivering nutrients, oxygen, and bicarbonate. Any disruption to one of the defensive systems might lead to the development of chronic or acute gastritis (Elseweidy et. al., 2017)

Categorization of Inflammation

Gastritis may be chronic or acute.

i) Intense gastritis

Acute gastritis is a brief episode of mucosal inflammation that can cause varying degrees of nausea, vomiting, and epigastric discomfort, or it might be asymptomatic.Degradation, ulceration, bleeding, or, in extreme circumstances, significant blood loss, may transpire

(Lenti et. al., 2020). Usually, acute gastroenteritis is hemorrhagic and erosive. Neutron phils are the main cells that make up the external epithelium (Duplan et. al., 2022).

ii) Gastritis chronic

The initial phase of chronic gastritis is known as external gastritis (Kayacetin and Guresci 2014).The most frequent cause of persistent gastritis is an infection with Helicobacter pylori. On the other hand, chronic gastritis finally forces the afflicted individual to seek therapy, but acute H. pylori infection does not exhibit sufficient symptoms to warrant medical care (Lenti et. al., 2020).

The following are a few factors that might lead to both acute and chronic gastritis:

A Helicobacter pylori infection

b) Substantial alcohol intake

c) The administration of medications, such as anti-inflammatory ones

d) Trauma to the Naso Gastrin tube

e) Repeat the exposure to edra diation.

f) Immune system abnormalities (Elseweidy, 2017.

a) Ulcerative reflux disease

Open sores known as ulcers usually appear on the skin or mucous membrane. The duodenum, the first segment of the intestine, the stomach as gastric ulcers, and the oesophagus as esophageal ulcers are the most prevalent locations for ulcers. Helicobacter pylori (H pylori), an acid-resistant stomach infection bacteria, is frequently the cause of peptic ulcers. Bacteria with a helical form, known as Helicobacter pylori. Humans have it in their stomachs, and as people age, their chance of infection rises. Due to the presence of pepsin and acid in the stomach juice, peptic ulcers are defined by a persistent discontinuity in the overall thickness of the gastric mucosa. The stomach enzyme pepsin, which facilitates the breakdown of proteins, is referred to as peptic (Emgevik et. al. 2020).

The reason for a peptic ulcer

- Peptic ulcers are most frequently caused by H. pylori, however there are other causes as well, such as aspirin and non-steroidal anti-inflammatory medicines (NSAIDs).
- Gastrectomy (Zollinger Ellison Syndrome)
- Severe stress (such as burns or trauma)
- Pancreatic enzyme reflux
- Radiation
- Viral or bacterial infection
- H. pylori infection.

The pathogenesis of ulcers discharge of gastric acid

Gastric acid secretors must be present at a minimum for peptic ulcers to develop. Therefore, when using non-steroidal anti-inflammatory medications or having an H. pylori infection, stomach acid functions as a cofactor. Usually, a patient with a duodenal ulcer secretes more acid at night or during the basal phase. Higher parietal cell mass, higher basal secretion, and increased post-prandial secretion are some of the causes of acid hypersecretion. An H. pylori infection might also result in excessive acid production (Scapini et. al., 2005).

Pepsin

It seems that pepsin plays a crucial role in the proteolytic process that causes ulcers. Gastric mucosal cells release two types of proteolytic pro enzymes. While pepsinogen II is present in the antral mucosa, pepsinogen I is restricted to the mucous neck cells of the acid-secreting mucosa. Conversion to pepsin occurs at acidic pH levels; this protein is reversibly inactivated at pH 4 and permanently removed at pH 7. There exists a direct proportionality between the rate of acid secretion and the rate of pepsinogen I secretion (Engevik et. al., 2020).

Groups at high risk for peptic ulcers

Growing older

The primary factor influencing the consequences of peptic ulcers is age. Compared to lower age groups, people over 60 had a 10-fold higher risk of complications from peptic ulcers. The bulk of deaths resulting from complications from peptic ulcers also happen in older age groups; the mortality rate for individuals over 60 is 50 times higher than that of those under 60. Although PU-related deaths in individuals under 60 are incredibly uncommon, there is some randomness to this age cut-off. Although it is advised for people over 60, gastro protection is not expected to be cost-effective for younger age groups (Graham, 2014).

Anti-inflammatory non-steroidal medications

The link between NSAIDs and peptic ulcer disease is widely established. By interfering with the cyclooxygenase (COX) enzymes, NSAIDs prevent prostaglandin synthesis and produce analgesic effects. While COX-2 is created by inflammation and is present in only a few tissues, COX-1 is present in most cells. The gastrointestinal toxicity of NSAIDs is mediated by COX-1, and the resulting drop in GI prostaglandin leads to a loss of cytoprotective effects and an elevated risk of peptic ulcers.

There is some COX-1 and COX-2 inhibitory activity in all classic NSAIDS, but the amounts differ, which is the primary cause of the variations in gastrointestinal toxicity. The least dangerous drugs are piroxicam and ketoprofen, which have an RR of eight for developing peptic ulcer disease, naproxen, which has an RR of four, and diclofenac and ibuprofen, which have an RR of roughly two (Figure 1) (Graham, 2014).

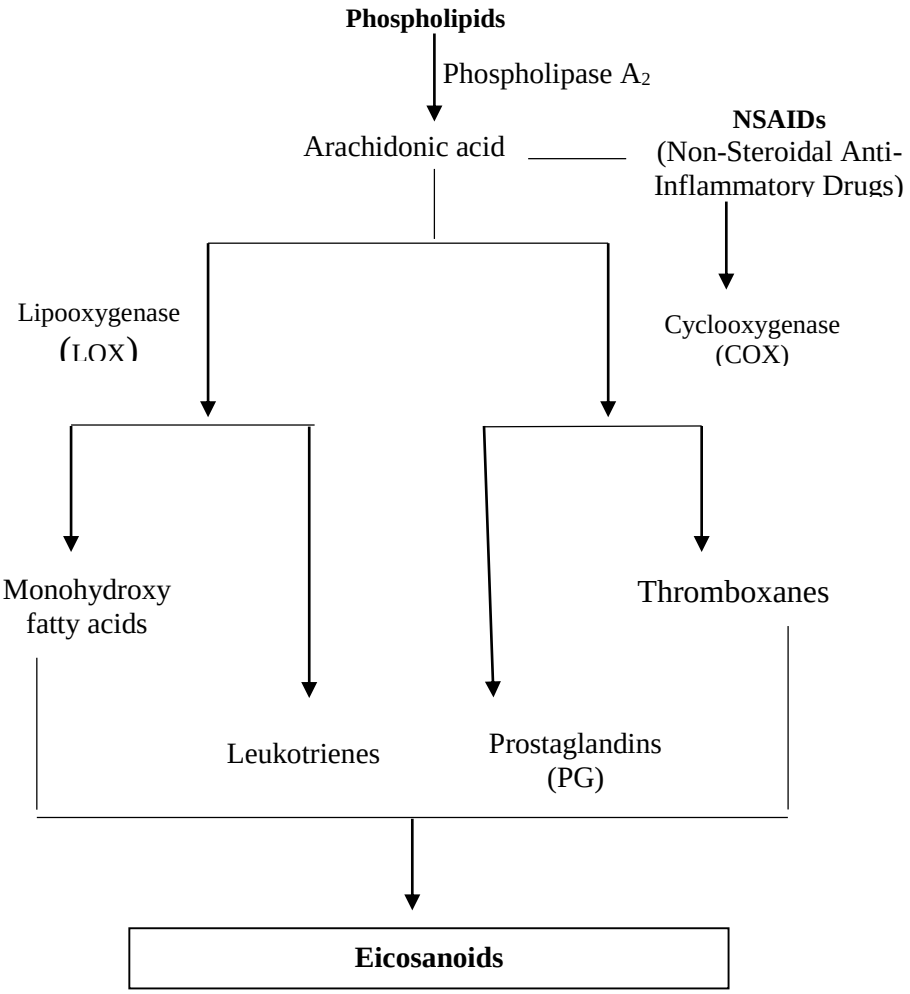

Figure1: Schematic diagram of inhibition of prostaglandin (PG) synthesis by NSAIDS (Non-steroidal Anti-inflammatory drugs)

1) Permeabilization of Membranes.

It has even been demonstrated that NSAIDs directly cause ulcers and damage to the mucosal cells of the stomach by cytotoxic effects (Gemici et. al., 2015). Certain investigations claim that COX inhibition is not necessary for direct cytotoxicity (Bindu et. al., 2020). Acidic NSAIDs, like aspirin, have been shown to cause this kind of topical damage,

which leads to the accumulation of ionized NSAIDs—a phenomenon called "ion trapping" (Tomisato et. al., 2004). It is advised that NSAIDs break down the epithelial barrier by causing membrane permeabilization (Jagannathan and Tucker 2016). In gastric mucosal cells, NSAIDs may also induce necrosis and apoptosis (Tanikawa et. al., 2012).

b) Synthesis of Extra Inflammatory Mediators.

Because NSAIDs prevent the production of PG, the Lipoxygenase pathway is activated and the synthesis of leukotrienes is boosted concurrently (Scapini et. al., 2005). The stomach mucosa is harmed by leukotrienes because they induce tissue ischemia and inflammation (LoGuidice et. al., 2010). Concomitantly, there has been a rise in the synthesis of pro-inflammatory mediators including tumor necrosis factors (Scapini et. al., 2005). This additionally illustrates the blockage of stomach microvessels, leading to a reduction in gastric blood flow and the release of free radicals derived from oxygen (Winkler, 2003). Lipid peroxidation and tissue injury are the results of the reaction between free oxygen radicals and mucosal polyunsaturated fatty acids (Birkedal, 1993).

c) Antiplatelet medication

Because they lower the risk of subsequent coronary events for at least a year, clopidogrel and other adenosine diphosphate-receptor inhibitors are frequently given following acute coronary syndromes and percutaneous coronary stenting. In addition, 1.3% of the individuals in the trial that shown the advantages of dual antiplatelet therapy with clopidogrel and ASA in acute coronary syndromes also reported gastrointestinal bleeding during the following nine months. Like all NSAIDs, the mechanisms by which ASA damages gastrointestinal mucosa are well known; however, it is less clear how antiplatelet treatment induces bleeding from peptic ulcers. If you try to stop platelet activity in a hemorrhaging peptic ulcer, it will make the ulcer worse and might cause new bleeding peptic ulcers that would have stayed "silent." Angiogenesis is facilitated by platelet-derived growth factors and is necessary for ulcer repair (Graham, 2014). The disruption of these growth factors by clopidogrel may impede the healing process of peptic ulcers and result in further problems.

d) Anticoagulant medication

Anticoagulants are usually used to prevent thrombo embolic occurrences in patients with mechanical heart valves, atrial fibrillation, or venous thrombo embolism. The risk of bleeding that comes with using vitamin K antagonist anticoagulants like warfarin is well known to both clinicians and patients (Preskorn and Stanga, 2004).

e) Corticosteroid medication

Among the many diverse ways that corticosteroids work is by significantly modulating the immune system. They are used to treat infections, osteoporosis, obesity, type 2 diabetes, and a number of autoimmune and inflammatory diseases. Since corticosteroids also prevent wounds from healing, it makes sense that they could impede the healing of peptic ulcers and raise the risk of ulcer complications. Physicians are aware of this and typically offer gastro protection and ulcer prophylaxis to patients receiving corticosteroid medication (Graham, 2014).

f) Serotonin reuptake inhibitors that are selective

Selective serotonin reuptake inhibitors (SSRIs), which have been authorized for a number of mental and medical problems, are the most often prescribed antidepressants. Compared to conventional antidepressants, they have a lower adverse event profile, although they may raise the risk of gastrointestinal bleeding. SSRIs can reduce platelet aggregation by lowering platelet serotonin. One study found that patients on SSRIs were more likely than non-users to experience an upper gastrointestinal bleeding (Scally et. al., 2018).

g) The Helicobacter pylori

The most common cause of peptic ulcer disease in the globe is H. pylori, and this infection can lead to problems in some cases of gastric and duodenal ulcers. An increased incidence of bleeding from peptic ulcers was found in a systematic review associated with H. pylori infection (Graham, 2014)

h) Healing of Ulcers

When the mucosa's natural defense systems are unable to prevent further injury, an ulcer might develop. A wound that pierces the muscle mucosa is called an ulcer. The production of granulation tissue at the base of the ulcer, angiogenesis (the development of new blood vessels), cell proliferation,

and the spread of inflammation are all components of the intricate and controlled process of ulcer healing. A distinct kind of cell appears at the ulcer margin when ulceration recurs, releasing a significant amount of EGF (epithelial growth factor) (Holzer, 2011) and serving as a strong stimulant for re-epithelialization. The mucosal and epithelial microcirculation structures are progressively rebuilt. At least in part, platelets contribute significantly to ulcer healing by supplying several growth factors that can promote angiogenesis and the accumulation of epithelial cells (Tarnawski, 2005). Naturally, platelets are important for maintaining hemostasis, and ulcer bleeding is a serious issue. Additional advantages of medications that inhibit gastric acid secretion may be associated with the facilitation of platelet accumulation; at a pH of -5.4, platelet accumulation will not take place (Szabo and Vincze 2000).

Management and avoidance of stomach disorders

I) NSAID and Gastroprotective Agent Combination Therapy

a) PG Analogues

When used with NSAIDs, PG analogues help restore any PG that has been lost due to the medication. It has been discovered that the widely used PG analog misoprostol considerably lessens NSAID-induced gastroduodenal ulceration (Preskorn et. al., 2004). Nevertheless, its effectiveness is limited as it is unable to manage dyspepsia and other unfavorable GI outcomes (Scally et. al., 2018). There are now single-tablet forms of misoprostol and diclofenac that have proven to be helpful in treating NSAID-induced gastropathy and arthritis (Okabe and Amagase, 2005).

b) Acid suppressants Agents

Acid suppressants mitigate the mucosal damage caused by NSAIDs and the stomach absorption of acidic NSAIDs. Proton pump inhibitors (PPIs) and H2-receptor antagonists are frequently utilized because they lower acid secretion, raise stomach pH, and aid in the scavenging of free radicals (Agrawal et. al., 1985). The first medications to be used as a preventative measure against NSAID-induced peptic ulcers were H2-receptor antagonists (Kangwan et. al., 2014). They were discovered to be long-lastingly beneficial in preventing stomach ulcers (Van leerdam and Rauws 2001).

Nevertheless, there has been improvement in cases of gastrointestinal bleeding (Oh et. al., 2008), therefore it is now not advised to use these medications over the long term. PPIs influence acid suppression and peptic ulcer prevention when paired with NSAIDs.

Current Developments in NSAID Therapy

Pro-NSAID medications:

Anticholinergic and acetyl cholinesterase action, site-specific targeting and delivery, nitric oxide and hydrogen sulfide release, antioxidant activity, and water solubility and dissolution can all be enhanced by NSAID pro medications (Abdelgawad et. al., 2017).

a. NSAIDs that release nitric oxide.

It has been demonstrated that nitric oxide (NO) increases blood flow, mucus formation, and bicarbonate secretion in the gastrointestinal mucosa to provide gastroprotection (Melcame et. al., 2016). (NO) Nitric oxide synthase activity reduces neutrophil endothelial adhesion and enhances mucus and bicarbonate secretion in addition to microcirculation. Among them include asprin, naproxen, and diclofenac (Elliott et. al., 1995).

b) Hydrogen Sulfide NSAID release.

In addition to its gastroprotective qualities, hydrogen sulfide (H2S) can heal pre-existing ulcers. It has been reported that compounds of naproxen, diclofenac, and indomethacin can emit H2S (Bezozowski et. al., 2001). To find out how NSAID-induced GI toxicity is affected, phosphatidyl choline-associated NSAIDs, as well as those that release NO and H2S, are being thoroughly tested in preclinical settings (Wallace et. al., 2007).

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