International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 1 | Jan – Feb 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i1.25

Molecular Biomarkers of NSAID-induced Gastritis

Wisik Candra Padmasari[1] , Willy Sandhika[1,2*]

[1]Immunology Study Program, Postgraduate School,
Universitas Airlangga, Indonesia

[2]Department of Anatomic Pathology, Faculty of Medicine,
Universitas Airlangga, Surabaya, Indonesia

E-mail: wisik.can.padmasari-2021@pasca.unair.ac.id; willysand@fk.unair.ac.id

*Corresponding author detail: Willy Sandhika; willysand@fk.unair.ac.id

ABSTRACT

Nonsteroidal anti-inflammation drug (NSAID) has been commonly used by people to treat myalgia and arthritis. Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) can cause chronic gastritis due to its topical and systemic effects. The topical effects of NSAID comprise cytotoxic and apoptotic effects on gastric mucosa which involve many apoptosis biomarkers while systemic effects are associated with cyclooxygenase (cox) inhibition in the reduction of prostaglandins production that plays a role in gastric mucosa's protectors. Apoptosis biomarkers that are involved in NSAID-induced gastritis comprise tumor necrosis factor-alpha (TNF-α) as well as cytochrome-c and SMAC which act as apoptosis inducers via extrinsic and intrinsic pathways respectively, caspase-8, caspase-9, caspase-3 in apoptosis pathway, Apoptosis Inducing Factor (AIF), longevity of apoptotic inhibitor proteins and NF-kB activity, resulting in apoptosis and cytotoxic effect to develop gastritis. This review will help us to understand the safety of NSAID drugs and to find effective treatments to regulate its mediators and not just suppress gastric acid secretion.

Keywords: chronic disease; gastritis; drug safety; nonsteroidal anti-inflammation drug; tumor necrosis factor.

INTRODUCTION

Nonsteroidal anti-inflammation drugs (NSAID) can induce gastritis aside from its main use in managing pain, fever, and inflammation. Long-term use of NSAIDs can cause chronic diseases in the form of chronic gastritis. NSAID can go through several mechanisms to cause gastritis which can be categorized as two main mechanisms. These mechanisms are topical mechanism that occurs through apoptosis, and systemic mechanisms that occur through COXs inhibitions and disruption of prostaglandin production. These mechanisms cause the imbalance of aggressive factors and protective factors, resulting in gastritis [1]. Preventive measures should be taken to mitigate this adverse effect.

1. TOPICAL MECHANISM

Topical mechanism can occur through direct irritation of gastric mucosa by acidic nature or direct contact in damaging epithelial cells, and disruption of the mucus-bicarbonate barrier by mucus-bicarbonate reduction and bicarbonate secretion decrease after NSAID administrations. NSAID causes direct irritation to gastric mucosa by its non-ionized formation in an acidic environment, allowing it to penetrate deeper into the barrier. The ion trapping theory also explains how the acidic pH of the gastric environment facilitates the diffusion of the non-ionized to lipid-soluble NSAIDs that conversed to lipophobic form that may induce toxicity within the neutral pH environment of the cytosolic gastric mucosa [2].

NSAID can also cause damage by directly in contact with the epithelial cells of the gastric mucosa. This process mainly involves apoptosis and thus plays a major role in the topical mechanism of NSAID-induced gastritis. Apoptosis is one of programmed cell deaths that occurs naturally in the body to remove old or damaged cells. This program is highly happening in cellular eukaryotic cells that can be stimulated by extrinsic and intrinsic factors [3]. NSAID induces apoptosis in the stomach lining can happen via the reduction of prostaglandin and several molecular interactions after NSAID intakes. Several molecular biomarkers in this mechanism involve comprising TNF-α, cytochrome-c, SMAC (second mitochondria-derived activator caspases), caspase-3, caspase-8, caspase-9, AIF (Apoptosis Inducing Factor), and survivin to manifest NSAID-induced gastritis.

1.1 Tumor Necrosis Factor-alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) plays a significant role in the development of NSAID-induced gastritis, where it contributes to inflammation, mucosal injury, and ulcer formation in the stomach.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain and inflammation relief, but they can cause gastric damage by interfering with the protective mechanisms of the gastric mucosa. Here's how TNF-α contributes to NSAID-induced gastritis:

Promotion of Inflammatory Response: TNF-α is a pro-inflammatory cytokine that becomes elevated in response to NSAID use. NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), which reduces prostaglandin production. Prostaglandins are essential for maintaining gastric mucosal protection, and their reduction leads to increased gastric acid secretion and decreased mucus and bicarbonate production. As a result, the gastric lining becomes more vulnerable to damage, and TNF-α release is triggered in response to this stress, leading to an inflammatory cascade [4, 5].

Recruitment and Activation of Immune Cells: TNF-α attracts immune cells, such as neutrophils and macrophages, to the site of injury in the gastric mucosa. The attractant such as cytokine-induced neutrophil chemoattractant-1 (CINC-1) of gastric epithelial cells can be stimulated by TNF-α to attract immune cells [6]. These immune cells release additional inflammatory mediators, including interleukins (e.g., IL-1β) and reactive oxygen species (ROS), which further damage the gastric lining and increase inflammation. This amplifies the gastric injury caused by NSAIDs.

Induction of Apoptosis in Gastric Cells: TNF-α can promote apoptosis (programmed cell death) of gastric epithelial cells by activating pro-apoptotic signaling pathways, particularly through receptors like TNF receptor 1 (TNFR1). TNF receptor 1 (TNFR1) senses TNF-α around the epithelial cells and leads to several pathways such as complex IIb, and complex IIa, and is associated with caspase 8 to trigger caspase 3 [7]. These caspases then execute apoptosis as a cell death program and contribute to gastric epithelial cell loss, compromising the integrity of the gastric mucosa, further weakening its protective barrier, and increasing susceptibility to acid and other irritants.

Microcirculation Impairment: TNF-α contributes to microcirculatory disturbances by increasing vascular permeability and promoting endothelial cell damage, which can impair blood flow to the gastric mucosa. TNF-α induced endothelial cell injury and reduced several tight junction proteins such as ZO-1 and Claudin-5 thus increasing the permeability of the blood vessel barrier [8]. This causes impairment of the blood vessels barrier leading to the reduction of blood flow. Reduced blood flow limits the delivery of oxygen and nutrients necessary for healing and maintaining mucosal integrity, exacerbating the damage caused by NSAIDs.

1.2 Cytochrome-c

Cytochrome-c plays a critical role in NSAID-induced gastritis primarily through its involvement in the mitochondrial pathway of apoptosis in gastric mucosal cells.

NSAID-induced gastritis occurs due to the disruption of the gastric mucosal barrier and the induction of cell death in gastric epithelial cells, leading to mucosal damage and ulcer formation. Here's how cytochrome-c is involved in this process:

Mitochondrial Damage and Cytochrome-c Release: NSAIDs, by inhibiting cyclooxygenase enzymes (COX-1 and COX-2), reduce the production of protective prostaglandins in the gastric mucosa, making the cells more susceptible to damage from gastric acid and other stressors. NSAIDs can also directly impact mitochondria, causing mitochondrial membrane permeability changes such as through depolarization and increased membrane transition pores [9]. This membrane disruption allows cytochrome-c to escape from the mitochondrial intermembrane space into the cytosol.

Activation of the Apoptotic Pathway: Once in the cytosol, cytochrome-c binds to apoptotic protease activating factor-1 (Apaf-1), forming a complex known as the apoptosome [10]. This complex then activates caspase-9, which in turn activates downstream effector caspases like caspase-3. These caspases execute apoptosis by cleaving cellular proteins, leading to programmed cell death. Apoptosis of gastric epithelial cells compromises the mucosal barrier, increasing susceptibility to further damage and contributing to NSAID-induced gastritis and ulcer formation [11].

Induction of Oxidative Stress: Cytochrome-c release is associated with increased oxidative stress. NSAIDs can generate reactive oxygen species (ROS) within the mitochondria, which can further damage mitochondrial membranes and other cellular components. Cytochrome-c contributes to ROS formation of mitochondrial cargo as it leaks from damaged mitochondria, further exacerbating oxidative damage within the gastric mucosa [12]. This can result in weakening the integrity of the gastric mucosa barrier.

1.3 Second mitochondria-derived activator of caspases (SMAC)

The Second Mitochondria-Derived Activator of Caspases (Smac), also known as Diablo, plays a significant role in NSAID-induced gastritis by regulating apoptosis in gastric mucosal cells. Smac is a mitochondrial protein released into the cytosol following mitochondrial stress or injury, which can be triggered by NSAIDs. Here's how Smac contributes to NSAID-induced gastritis:

Promotion of Apoptosis: In the context of NSAID use, mitochondrial stress occurs due to the loss of protective prostaglandins, which weaken the gastric mucosa. NSAIDs can induce mitochondrial damage, causing the release of Smac into the cytosol along with other pro-apoptotic factors like cytochrome-c. Once in the cytosol, Smac inhibits inhibitors of Apoptosis Proteins (IAPs), such as XIAP (X-linked inhibitor of apoptosis protein), which normally suppress caspase activation.

By binding to and neutralizing IAPs, Smac facilitates the activation of caspase-9 and downstream caspases (e.g., caspase-3), promoting apoptosis in gastric epithelial cells [13].

Synergistic Role with Cytochrome-c: Smac works in tandem with cytochrome-c to amplify the apoptotic response in NSAID-induced gastritis. While cytochrome-c forms the apoptosome complex to initiate caspase activation, Smac ensures that IAPs do not interfere with this process, allowing apoptosis to proceed efficiently. This synergistic effect enhances cell death in the gastric mucosa, compromising the protective barrier of the stomach lining [14].

Exacerbation of Mucosal Damage: The loss of IAP function after Smac release can effectively allow the promotion of apoptosis [15]. The promotion of apoptosis by Smac release contributes to the loss of gastric epithelial cells, weakening the mucosal layer that serves as a barrier against stomach acid and other irritants. This loss exacerbates gastric damage, leading to symptoms of NSAID-induced gastritis and, potentially, ulcer formation as the mucosal defense is further compromised.

1.4 Survivin

Survivin, a member of the inhibitor of apoptosis (IAP) family, plays a complex role in NSAID-induced gastritis by helping to regulate cell survival and apoptosis in the gastric mucosa. NSAIDs disrupt the protective mechanisms of the stomach lining, leading to increased cell death, inflammation, and potential ulceration. Survivin is typically involved in promoting cell survival and preventing apoptosis, but its role in NSAID-induced gastritis can vary depending on how NSAIDs impact Survivin levels and activity. Here's an outline of its role:

Prevention of Apoptosis: Survivin is an anti-apoptotic protein that inhibits caspase activation, helping cells resist apoptosis. In NSAID-induced gastritis, where the gastric mucosal cells undergo stress and are more prone to apoptosis due to mitochondrial damage and increased pro-apoptotic signaling, Survivin expression may help some gastric epithelial cells resist this stress. Survivin binds to SMAC/diablo and forms a complex that restrains SMAC/diablo from binding with cIAP1/2 or XIAP thus further effectively blockading caspase activity [16]. By inhibiting caspases (particularly caspase-3 and caspase-7), Survivin reduces cell death, helping to preserve the integrity of the gastric mucosal barrier.

Response to NSAID-Induced Damage: In the setting of NSAID-induced gastritis, however, Survivin levels may be altered. Some studies suggest that NSAID treatment can downregulate Survivin expression in gastric mucosal cells, which removes this anti-apoptotic protection [17, 18, 19]. NSAID downregulates survivin through involvement in survivin degradation and inhibition of STAT3 and HSF-1 which can bind to survivin promoters and function as transcriptional activators of survivin genes [18, 20, 21]. Reduced Survivin levels allow apoptosis to proceed, leading to increased cell loss and weakening of the gastric mucosa, exacerbating the damage caused by NSAIDs. This makes the stomach lining more susceptible to acid and other irritants, promoting gastritis and ulcer formation.

Survivin in NSAID-induced gastritis may help protect gastric cells from apoptosis and support mucosal integrity. However, NSAIDs can disrupt this protective function by downregulating Survivin, leading to increased cell death, impaired repair, and worsening of gastritis [16, 18, 22]. Survivin's dual roles in both apoptosis inhibition and cell proliferation highlight its importance in maintaining gastric mucosal health under NSAID-induced stress.

1.5 Apoptosis Inducing Factor (AIF)

Apoptosis-inducing factor (AIF) is a mitochondrial protein involved in caspase-independent cell death, and it plays an important role in NSAID-induced gastritis by contributing to the apoptosis of gastric epithelial cells. NSAIDs cause stress and damage to the gastric mucosa, leading to cell death and inflammation. Here's how AIF contributes to NSAID-induced gastritis:

Mitochondrial Damage and AIF Release: NSAIDs cause oxidative stress and mitochondrial injury in gastric epithelial cells by inhibiting protective prostaglandins. NSAID induction enhances the formation of permeabilization of the outer mitochondrial membrane (MOMP) and depolarization, leading to mitochondrial dysfunction [23, 24]. This MOMP allows AIF to translocate from the mitochondria to the cytosol and, subsequently, to the nucleus.

Induction of Caspase-Independent Apoptosis: Once AIF is released into the cytosol and enters the nucleus, it triggers a caspase-independent pathway of apoptosis [25]. AIF binds to DNA in the nucleus and causes large-scale DNA fragmentation and chromatin condensation, leading to cell death. This process is independent of caspase activation, which distinguishes it from the caspase-dependent apoptotic pathways often associated with NSAID-induced injury (e.g., via cytochrome-c release) [26].

Contribution to Gastric Mucosal Damage: AIF-mediated apoptosis contributes to the loss of gastric epithelial cells, weakening the gastric mucosal barrier. As AIF promotes cell death in the gastric mucosa, it increases the tissue's vulnerability to acid and other irritants, exacerbating NSAID-induced gastritis. The cumulative loss of cells disrupts the mucosal lining, impairing its ability to protect the underlying tissue.

AIF plays a pro-apoptotic role in NSAID-induced gastritis by promoting caspase-independent apoptosis in gastric epithelial cells. High AIF expressions are found to be related to high caspase-3 expressions, contributing to the breakdown of the gastric mucosal barrier [27].

Its role in oxidative stress by causing increased cellular ROS and cell death makes it a critical factor in the pathogenesis of NSAID-induced gastric injury [28].

1.6 Caspases

Caspases are crucial in the development of NSAID-induced gastritis, as they mediate apoptosis (programmed cell death) in the gastric epithelial cells, contributing to mucosal damage and inflammation. NSAIDs disrupt the gastric mucosal barrier by inhibiting protective prostaglandins, which makes the mucosa more susceptible to injury. Here's how caspases are involved in NSAID-induced gastritis:

Activation of Apoptotic Pathways: NSAIDs can trigger apoptosis in gastric mucosal cells through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Caspases are central to both pathways:

- Intrinsic Pathway: NSAID-induced mitochondrial stress leads to the release of cytochrome-c, which forms a complex with apoptotic protease activating factor-1 (Apaf-1) to activate caspase-9. NSAID also attenuates SIRT3, allowing caspase-9 release [[29]]. Caspase-9 then activates downstream caspases, such as caspase-3, which execute apoptosis by cleaving cellular proteins and DNA.
- Extrinsic Pathway: NSAIDs can upregulate pro-inflammatory cytokines like TNF-α, which bind to death receptors on gastric epithelial cells and trigger the activation of caspase-8 [30, 31]. Caspase-8 binds with the Fas-associated death domain (FADD) and later forms a death-inducing signaling complex (DISC) upon DED-DED interaction [32, 33]. Caspase-8 activates downstream effector caspases, such as caspase-3 and caspase-7, leading to cell death.

Execution of Apoptosis: Caspase-3, known as the "executioner caspase," plays a direct role in executing apoptosis by breaking down cellular components and structural proteins, ultimately leading to cell death. Caspase-3 activation cleaves poly ADP-ribose polymerase-1 (PARP1), and cleaves DFNA5 that later produces DFNA5-N fragment [34, 35]. The activation of caspase-3 is a crucial step in NSAID-induced apoptosis in gastric mucosal cells, as it leads to DNA fragmentation, membrane blebbing, and loss of cellular integrity.

1.7 Nuclear Factor Kappa B (NF-kB)

Nuclear Factor kappa B (NF-κB) plays a significant role in NSAID-induced gastritis by mediating inflammation, cell survival, and immune responses in the gastric mucosa. NF-κB is a transcription factor that regulates the expression of various pro-inflammatory cytokines, chemokines, and molecules involved in immune responses. Here's how NF-κB is involved in NSAID-induced gastritis:

Induction of Inflammatory Response: NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), reducing the production of protective prostaglandins in the gastric mucosa. This inhibition disrupts the mucosal barrier and promotes inflammation. In response to this damage, NF-κB is activated and translocates to the nucleus, where it upregulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [36]. These cytokines recruit and activate immune cells, amplifying inflammation and worsening mucosal injury.

Promotion of Gastric Epithelial Cell Apoptosis: NSAID-induced NF-κB activation can lead to the production of pro-apoptotic molecules in the gastric mucosa. For example, NF-κB promotes the expression of Fas ligand and TNF-α, which can bind to death receptors on the surface of gastric epithelial cells, triggering apoptosis [37, 38]. Increased apoptosis contributes to the weakening of the gastric mucosal barrier, making it more susceptible to injury from gastric acid and other irritants.

Regulation of Oxidative Stress: NF-κB also regulates the expression of enzymes involved in oxidative stress responses, such as inducible nitric oxide synthase (iNOS) and NADPH oxidase, which produce reactive oxygen species (ROS) [[39]]. Elevated ROS levels contribute to oxidative stress, damaging cellular structures, including mitochondria and DNA, which further trigger NF-κB activation. This creates a feedback loop where NF-κB activation leads to oxidative stress, which, in turn, promotes further NF-κB activity and inflammation in the gastric mucosa.

Involvement in Immune Cell Recruitment: NF-κB activation leads to the production of chemokines, such as IL-8, which attract immune cells (e.g., neutrophils and macrophages) to the site of injury. The released IL-8 interacts with chemokine receptors such as CXCR2 on neutrophils and CXCR4 on macrophages, recruiting these immune cells to the site [40, 41]. These immune cells release additional pro-inflammatory mediators, including proteases and more ROS, which exacerbate tissue damage and inflammation, further contributing to NSAID-induced gastritis.

NF-κB plays a crucial role in NSAID-induced gastritis by promoting inflammation, apoptosis, oxidative stress, and immune cell recruitment in the gastric mucosa. Its activation exacerbates the damage caused by NSAIDs, contributing to the development and persistence of gastritis.

2. SYSTEMIC MECHANISM

NSAIDs, while primarily causing local effects in the gastric mucosa, can also have systemic effects that contribute to gastritis and other gastrointestinal complications. These systemic effects occur because NSAIDs circulate throughout the body and affect various physiological processes, especially those related to inflammation and cell signaling. Here's how NSAIDs exert systemic effects that contribute to gastritis:

Systemic Inhibition of COX Enzymes:

- NSAIDs inhibit both COX-1 and COX-2 enzymes throughout the body, reducing prostaglandin synthesis in multiple tissues, including gastric mucosa. This inhibition happens selectively and nonselectively, having a significant impact on homeostasis [42]. Inhibition of COXs by NSAIDs causes the increase of mucosal vulnerability toward irritant and aggressive factors.
- Prostaglandins, especially those produced by COX-1, play a critical role in maintaining gastric mucosal protection. Systemic inhibition of COX-1 decreases prostaglandin levels in the stomach lining, reducing mucus production, bicarbonate secretion, and blood flow, making the stomach more vulnerable to damage. The impaired function of the mucosal lining such as the intestinal barrier allows bacteria to invade mucosa and trigger more inflammatory cascades [42].

Reduction in Mucosal Defense Mechanisms:

- The systemic reduction of prostaglandins compromises various defense mechanisms in the gastrointestinal tract. NSAIDs reduce prostaglandin levels not only in the stomach but also in other parts of the gastrointestinal tract, leading to decreased mucus production and bicarbonate secretion. The occurrence of mucosal breaks causes more damage and severe complications [43].
- This systemic effect makes the entire digestive tract more susceptible to injury from digestive acids and enzymes, increasing the risk of gastritis, enteropathy, and ulcers [44].

2.1 Cyclooxygenase (Cox)

Cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, play a central role in NSAID-induced gastritis by affecting the balance of protective and inflammatory processes in the gastric mucosa. Nonsteroidal anti-inflammatory drugs (NSAIDs) target these enzymes to reduce pain and inflammation, but this inhibition can also compromise the protective mechanisms in the stomach. Here's how COX enzymes are involved in NSAID-induced gastritis:

COX-1 and Gastric Mucosal Protection:

A. COX-1 is constitutively expressed in most tissues, including the gastric mucosa, where it plays a key role in producing protective prostaglandins (mainly prostaglandin E2, or PGE2). These prostaglandins help maintain gastric integrity by:
   - Stimulating mucus and bicarbonate secretion creates a protective layer on the stomach lining and helps neutralize stomach acid.
   - Enhancing mucosal blood flow, which supplies nutrients and oxygen, aiding in mucosal repair.
   - Modulating the secretion of gastric acid, ensuring it stays within safe levels.

B. When NSAIDs inhibit COX-1, the production of these protective prostaglandins decreases, compromising the stomach's defenses against the acidic environment. Inhibition of COX-1 by NSAID also results in the reduction of stimulation to mucus/bicarbonate secretion, demolishing stabilization and protective function of the stomach barrier, allowing more exposure of gastric acid to gastric epithelial cells, and leading to various inflammatory processes and apoptosis in contributing to cell irritation and cell damage [45]. Taken together, inhibition of COX-1 increases the risk of mucosal injury, gastritis, and ulceration.

COX-2 and Inflammation:

- COX-2 is an inducible enzyme, typically expressed in response to inflammation and tissue injury, including gastric injuries. COX-2 helps produce prostaglandins that mediate inflammation, pain, and fever.
- While COX-2 inhibition is the primary target of NSAIDs to relieve pain and inflammation, it also plays a role in the stomach by facilitating mucosal healing after injury.
- COX-2 is required for the synthesis of prostaglandin E2 which plays a crucial role in various cell regeneration and healing processes [46, 47]. Inhibition of COX-2 by NSAIDs can, therefore, impair the gastric mucosa's ability to repair itself after minor injuries, which can worsen gastritis or ulceration in the presence of preexisting mucosal damage.

Selective vs. Non-Selective NSAIDs:

- Non-selective NSAIDs inhibit both COX-1 and COX-2, which maximizes their anti-inflammatory effects but also leads to increased gastrointestinal side effects, such as gastritis and ulcer formation, due to reduced protective prostaglandins from COXs inhibition. COXs inhibition by NSAID can lead to several apoptosis, resulting in further gastric mucosal damage. COX enhances Akt phosphorylation, and its inhibition can block Akt activation, resulting in apoptosis induction [48, 49, 50].
- COX-2 selective inhibitors (e.g., celecoxib) aim to reduce inflammation and pain without affecting COX-1 and the protective gastric effects it mediates. However, while they are generally associated with a lower risk of gastric injury than non-selective NSAIDs, they are not completely without risk, as COX-2 also plays a role in mucosal healing. COX-2 selective inhibition enhances apoptosis in gastric mucosal healing via blocking in the Akt pathway, thus delaying healing in gastric mucosa [48].

Role in Mucosal Healing:

- In cases of gastric injury, COX-2 expression can increase as part of the body's natural healing process, promoting the production of prostaglandins that aid in the repair and recovery of the gastric lining. NSAIDs, by inhibiting COX-2, may hinder this repair process, leading to prolonged or worsened mucosal injury.

- This effect is particularly relevant in chronic NSAID use, where constant inhibition of COX-2 may lead to delayed healing of any existing gastritis or ulcers.

COX enzymes are critical in NSAID-induced gastritis, where COX-1 inhibition reduces protective prostaglandins, compromising gastric mucosal defenses, and COX-2 inhibition can delay mucosal healing.

2.2 Prostaglandin

Prostaglandins play a crucial protective role in the gastric mucosa, and their reduction due to NSAID use is a primary factor in NSAID-induced gastritis. Prostaglandins, especially prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2), are synthesized by the action of cyclooxygenase-1 (COX-1) and contribute to maintaining gastric mucosal integrity. Here's how prostaglandins protect the gastric lining and how their reduction leads to NSAID-induced gastritis:

Stimulation of Mucus and Bicarbonate Secretion:

- Prostaglandins stimulate the production of mucus and bicarbonate in the gastric mucosa. The mucus forms a protective gel layer that shields the stomach lining from the acidic gastric contents, while bicarbonate neutralizes the acid near the mucosal surface. Bicarbonate ions can also chelate calcium (Ca2+), alongside pH neutralization near the mucosa, resulting in mucin linearization and remodeling [51, 52, 53].
- This combination helps maintain a pH gradient that protects epithelial cells from damage. When NSAIDs inhibit COX-1, prostaglandin levels drop, leading to reduced mucus and bicarbonate secretion, weakening this protective layer and exposing the mucosa to acid and digestive enzymes.

Enhancement of Gastric Mucosal Blood Flow:

- Prostaglandins increase blood flow to the gastric mucosa, which is essential for providing oxygen, nutrients, and a steady supply of bicarbonate. This blood flow also aids in the repair and regeneration of epithelial cells, helping the stomach recover from minor injuries. Prostaglandins through their receptors induce vasodilatation, reduce cell death, and protect tight junctions near endothelial cells that are important to maintain blood vessel integrity [54, 55, 56].
- When prostaglandin synthesis is reduced by NSAIDs, mucosal blood flow decreases, impairing the stomach's ability to repair itself and making it more susceptible to injury from acidic and mechanical stress.

Modulation of Gastric Acid Secretion:

- Prostaglandins help regulate gastric acid secretion, maintaining it within safe levels that do not harm the stomach lining. By acting on parietal cells, prostaglandins prevent excessive acid production [57].
- With NSAID-induced reduction in prostaglandins, there is less regulation of acid secretion, leading to higher acid levels in the stomach, which can further irritate and damage the gastric mucosa. NSAID exposure can be an active substance that induces gastric acid secretion through increased nitric oxide (NO) production and activates the H+, K+-ATPase to the apical membrane of parietal cells [58]. Because NSAIDs reduce the production of prostaglandins, and increase the activity of H+, K+-ATPase to induce gastric acid, the gastric condition becomes more acidic and easily irritates the weakened gastric protective layer, damaging mucosal barrier increasing the opportunity for bacterial infection to pass through the mucosal layer and causing further infections.

Anti-inflammatory and Cytoprotective Effects:

- Prostaglandins exhibit anti-inflammatory properties that help protect the stomach lining from inflammatory responses that can result from minor injuries or irritants. Prostaglandins reduce the pro-inflammatory activity of some immune cells through their receptors such as inhibiting NET formation through cAMP production [59, 60]. Thus, prostaglandins enhance cell survival and protect against oxidative damage.
- The loss of these cytoprotective effects with NSAID use makes the gastric mucosa more vulnerable to inflammation, apoptosis, and injury from reactive oxygen species (ROS) and inflammatory mediators.

Consequences of Prostaglandin Reduction in NSAID-Induced Gastritis:

- A significant decrease in prostaglandin levels compromises all of these gastric protective functions with COX inhibition by NSAIDs being the main causative factor. On the other hand, this decrease also further increases the activity of aggressive factors such as activation of H+, K+-ATPase that leads to excessive gastric acid production. This further leads to an imbalance between aggressive factors (acid, pepsin, ROS) and defensive factors (mucus, bicarbonate, blood flow), resulting in mucosal injury, inflammation, and gastritis.
- This can lead to clinical manifestations of NSAID-induced gastritis, such as epigastric pain, nausea, and an increased risk of gastric ulcers, which can bleed or perforate in severe cases [61, 62].

Prostaglandins are essential for gastric mucosal protection, helping to regulate mucus and bicarbonate production, blood flow, and acid secretion. The reduction of prostaglandins due to NSAID use removes these protective mechanisms, leading to increased susceptibility to gastritis and gastric injury.

CONCLUSION

Gastritis induced by NSAID can go through two categorized mechanisms that affect cytotoxic, and apoptotic effects, as well as COXs inhibition cascade effects involving several molecular biomarkers that require attention on its treatment. By understanding the mechanism of gastritis caused by NSAIDs, hopefully, the public can also understand the side effects of NSAID use, thereby encouraging the achievement of drug safety in the use of NSAIDs.

REFERENCES

[1] E. Gugliandolo et al., "Protective effect of snail secretion filtrate against ethanol-induced gastric ulcer in mice," Sci Rep, vol. 11, no. 1, p. 3638, Feb. 2021, doi: 10.1038/s41598-021-83170-8.

[2] S. Bindu, S. Mazumder, and U. Bandyopadhyay, "Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective," Biochem Pharmacol, vol. 180, p. 114147, Oct. 2020, doi: 10.1016/j.bcp.2020.114147.

[3] J. Fang et al., "An apoptosis-inducing factor controls programmed cell death and laccase expression during fungal interactions," Appl Microbiol Biotechnol, vol. 108, no. 1, p. 135, Dec. 2024, doi: 10.1007/s00253-023-12988-1.

[4] E. Wu et al., "Gastric alarmin release: A warning signal in the development of gastric mucosal diseases," Front Immunol, vol. 13, Oct. 2022, doi: 10.3389/fimmu.2022.1008047.

[5] R. S. Aziz, A. Siddiqua, M. Shahzad, A. Shabbir, and N. Naseem, "Oxyresveratrol ameliorates ethanol-induced gastric ulcer via downregulation of IL-6, TNF-α, NF-κB, and COX-2 levels, and upregulation of TFF-2 levels," Biomedicine & Pharmacotherapy, vol. 110, pp. 554–560, Feb. 2019, doi: 10.1016/j.biopha.2018.12.002.

[6] Z. L. Durham, J. L. Hawkins, and P. L. Durham, "Tumor necrosis factor-Alpha stimulates cytokine expression and transient sensitization of trigeminal nociceptive neurons.," Arch Oral Biol, vol. 75, pp. 100–106, Mar. 2017, doi: 10.1016/j.archoralbio.2016.10.034.

[7] M. K. Preedy, M. R. H. White, and V. Tergaonkar, "Cellular heterogeneity in TNF/TNFR1 signalling: live cell imaging of cell fate decisions in single cells," Cell Death Dis, vol. 15, no. 3, p. 202, Mar. 2024, doi: 10.1038/s41419-024-06559-z.

[8] W. Zhou, G. Shi, J. Bai, S. Ma, Q. Liu, and X. Ma, "Colquhounia Root Tablet Protects Rat Pulmonary Microvascular Endothelial Cells against TNF- α -Induced Injury by Upregulating the Expression of Tight Junction Proteins Claudin-5 and ZO-1," Evidence-Based Complementary and Alternative Medicine, vol. 2018, pp. 1–11, Nov. 2018, doi: 10.1155/2018/1024634.

[9] L. Brandolini et al., "NSAIDs-dependent adaption of the mitochondria-proteasome system in immortalized human cardiomyocytes," Sci Rep, vol. 10, no. 1, p. 18337, Oct. 2020, doi: 10.1038/s41598-020-75394-x.

[10] C.-C. Wu et al., "The Apaf-1 apoptosome induces formation of caspase-9 homo- and heterodimers with distinct activities," Nat Commun, vol. 7, no. 1, p. 13565, Nov. 2016, doi: 10.1038/ncomms13565.

[11] J. Fuentes et al., "Protection against indomethacin-induced loss of intestinal epithelial barrier function by a quercetin oxidation metabolite present in onion peel: In vitro and in vivo studies," J Nutr Biochem, vol. 100, p. 108886, Feb. 2022, doi: 10.1016/j.jnutbio.2021.108886.

[12] K. Magierowska et al., "Mitochondria-targeted hydrogen sulfide donors versus acute oxidative gastric mucosal injury," Journal of Controlled Release, vol. 348, pp. 321–334, Aug. 2022, doi: 10.1016/j.jconrel.2022.05.051.

[13] H. Zhu, Y. Li, Y. Liu, and B. Han, "Bivalent SMAC Mimetics for Treating Cancer by Antagonizing Inhibitor of Apoptosis Proteins," ChemMedChem, vol. 14, no. 23, pp. 1951–1962, Dec. 2019, doi: 10.1002/cmdc.201900410.

[14] S. M. Ghufran, S. Sharma, S. Ghose, and S. Biswas, "Divergent effect of Birinapant, and BV6 SMAC mimetic on TNFα induced NF-κB signaling and cell viability in activated hepatic stellate cells," Mol Biol Rep, vol. 50, no. 3, pp. 2107–2117, Mar. 2023, doi: 10.1007/s11033-022-08210-6.

[15] P. Wolf, "Inhibitor of apoptosis proteins as therapeutic targets in bladder cancer," Front Oncol, vol. 13, Feb. 2023, doi: 10.3389/fonc.2023.1124600.

[16] M. Santhanam et al., "Interaction of SMAC with a survivin-derived peptide alters essential cancer hallmarks: Tumor growth, inflammation, and immunosuppression," Molecular Therapy, vol. 32, no. 6, pp. 1934–1955, Jun. 2024, doi: 10.1016/j.ymthe.2024.04.007.

[17] N. Bilani, H. Bahmad, and W. Abou-Kheir, "Prostate Cancer and Aspirin Use: Synopsis of the Proposed Molecular Mechanisms," Front Pharmacol, vol. 8, Mar. 2017, doi: 10.3389/fphar.2017.00145.

[18] S.-K. Chiou and S. Mandayam, "NSAIDs enhance proteasomic degradation of survivin, a mechanism of gastric epithelial cell injury and apoptosis," Biochem Pharmacol, vol. 74, no. 10, pp. 1485–1495, Nov. 2007, doi: 10.1016/j.bcp.2007.07.024.

[19] N. Sakoguchi-Okada et al., "Celecoxib inhibits the expression of survivin via the suppression of promoter activity in human colon cancer cells," Biochem Pharmacol, vol. 73, no. 9, pp. 1318–1329, May 2007, doi: 10.1016/j.bcp.2006.12.033.

[20] H.-J. Moon, S.-Y. Park, S.-H. Lee, C.-D. Kang, and S.-H. Kim, "Nonsteroidal Anti-inflammatory Drugs Sensitize CD44-Overexpressing Cancer Cells to Hsp90 Inhibitor Through Autophagy Activation," Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics, vol. 27, no. 7, pp. 835–847, Jul. 2019, doi: 10.3727/096504019X15517850319579.

[21] X. Chen, N. Duan, C. Zhang, and W. Zhang, "Survivin and Tumorigenesis: Molecular Mechanisms and Therapeutic Strategies.," J Cancer, vol. 7, no. 3, pp. 314–23, 2016, doi: 10.7150/jca.13332.

[22] C. Sanhueza, S. Wehinger, J. Castillo Bennett, M. Valenzuela, G. I. Owen, and A. F. G. Quest, "The twisted survivin connection to angiogenesis," Mol Cancer, vol. 14, no. 1, p. 198, Dec. 2015, doi: 10.1186/s12943-015-0467-1.

[23] L. Brandolini et al., "NSAIDs-dependent adaption of the mitochondria-proteasome system in immortalized human cardiomyocytes," Sci Rep, vol. 10, no. 1, p. 18337, Oct. 2020, doi: 10.1038/s41598-020-75394-x.

[24] P. N. Thai et al., "Chronic Diclofenac Exposure Increases Mitochondrial Oxidative Stress, Inflammatory Mediators, and Cardiac Dysfunction," Cardiovasc Drugs Ther, vol. 37, no. 1, pp. 25–37, Feb. 2023, doi: 10.1007/s10557-021-07253-4.

[25] M. Abdellatif and G. Kroemer, "Exercise-induced sudden cardiac death is caused by mitochondrio-nuclear translocation of AIF," Cell Death Dis, vol. 12, no. 4, p. 383, Apr. 2021, doi: 10.1038/s41419-021-03677-w.

[26] H. A. M. I. Khalifa, N. Z. H. Eleiwa, and H. A. Nazim, "Royal Jelly, A Super Food, Protects Against Celecoxib-Induced Renal Toxicity in Adult Male Albino Rats," Can J Kidney Health Dis, vol. 11, Jan. 2024, doi: 10.1177/20543581241235526.

[27] K. Surya Negara et al., "The role of caspase-dependent and caspase-independent pathways of apoptosis in the premature rupture of the membranes: A case-control study," International Journal of Reproductive BioMedicine (IJRM), Jul. 2020, doi: 10.18502/ijrm.v13i6.7285.

[28] T. Li et al., "AIF Overexpression Aggravates Oxidative Stress in Neonatal Male Mice After Hypoxia–Ischemia Injury," Mol Neurobiol, vol. 59, no. 11, pp. 6613–6631, Nov. 2022, doi: 10.1007/s12035-022-02987-0.

[29] Y. Yang, W. Wang, Y. Tian, and J. Shi, "Sirtuin 3 and mitochondrial permeability transition pore (mPTP): A systematic review," Mitochondrion, vol. 64, pp. 103–111, May 2022, doi: 10.1016/j.mito.2022.03.004.

[30] D. Stöhr, A. Jeltsch, and M. Rehm, "TRAIL receptor signaling: From the basics of canonical signal transduction toward its entanglement with ER stress and the unfolded protein response," 2020, pp. 57–99. doi: 10.1016/bs.ircmb.2020.02.002.

[31] M. Edagawa et al., "Role of Activating Transcription Factor 3 (ATF3) in Endoplasmic Reticulum (ER) Stress-induced Sensitization of p53-deficient Human Colon Cancer Cells to Tumor Necrosis Factor (TNF)-related Apoptosis-inducing Ligand (TRAIL)-mediated Apoptosis through Up-regulation of Death Receptor 5 (DR5) by Zerumbone and Celecoxib," Journal of Biological Chemistry, vol. 289, no. 31, pp. 21544–21561, Aug. 2014, doi: 10.1074/jbc.M114.558890.

[32] L. K. Hillert et al., "Dissecting DISC regulation via pharmacological targeting of caspase-8/c-FLIPL heterodimer," Cell Death Differ, vol. 27, no. 7, pp. 2117–2130, Jul. 2020, doi: 10.1038/s41418-020-0489-0.

[33] P. Davidovich, C. A. Higgins, Z. Najda, D. B. Longley, and S. J. Martin, "cFLIPL acts as a suppressor of TRAIL- and Fas-initiated inflammation by inhibiting assembly of caspase-8/FADD/RIPK1 NF-κB-activating complexes," Cell Rep, vol. 42, no. 12, p. 113476, Dec. 2023, doi: 10.1016/j.celrep.2023.113476.

[34] R. Li et al., "Biological function, mediate cell death pathway and their potential regulated mechanisms for post-mortem muscle tenderization of PARP1: A review," Front Nutr, vol. 9, Dec. 2022, doi: 10.3389/fnut.2022.1093939.

[35] C. Rogers, T. Fernandes-Alnemri, L. Mayes, D. Alnemri, G. Cingolani, and E. S. Alnemri, "Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death," Nat Commun, vol. 8, no. 1, p. 14128, Jan. 2017, doi: 10.1038/ncomms14128.

[36] C. Yu et al., "Protective effect of Lizhong Pill on nonsteroidal anti-inflammatory drug-induced gastric mucosal injury in rats: Possible involvement of TNF and IL-17 signaling pathways," J Ethnopharmacol, vol. 318, p. 116991, Jan. 2024, doi: 10.1016/j.jep.2023.116991.

[37] G. Carrà, M. F. Lingua, B. Maffeo, R. Taulli, and A. Morotti, "P53 vs NF-κB: the role of nuclear factor-kappa B in the regulation of p53 activity and vice versa," Cellular and Molecular Life Sciences, vol. 77, no. 22, pp. 4449–4458, Nov. 2020, doi: 10.1007/s00018-020-03524-9

[38] H. Patel, M. S. Sheikh, and Y. Huang, "ECRG2, a novel transcriptional target of p53, modulates cancer cell sensitivity to DNA damage," Cell Death Dis, vol. 11, no. 7, p. 543, Jul. 2020, doi: 10.1038/s41419-020-2728-1.

[39] Q. Guo et al., "NF-κB in biology and targeted therapy: new insights and translational implications," Signal Transduct Target Ther, vol. 9, no. 1, p. 53, Mar. 2024, doi: 10.1038/s41392-024-01757-9.

[40] X. Tian, G. Xie, H. Xiao, F. Ding, W. Bao, and M. Zhang, "CXCR4 knockdown prevents inflammatory cytokine expression in macrophages by suppressing activation of MAPK and NF-κB signaling pathways," Cell Biosci, vol. 9, no. 1, p. 55, Dec. 2019, doi: 10.1186/s13578-019-0315-x.

[41] C. Sun et al., "Neutrophils in glioma microenvironment: from immune function to immunotherapy," Front Immunol, vol. 15, May 2024, doi: 10.3389/fimmu.2024.1393173.

[42] J. Kuczyńska and B. Nieradko-Iwanicka, "The effect of ketoprofen lysine salt on mucosa of rat stomach after ethyl alcohol intoxication," Biomedicine & Pharmacotherapy, vol. 141, p. 111938, Sep. 2021, doi: 10.1016/j.biopha.2021.111938.

[43] I. Tachecí et al., "NSAID-Induced Enteropathy in Rheumatoid Arthritis Patients with Chronic Occult Gastrointestinal Bleeding: A Prospective Capsule Endoscopy Study," Gastroenterol Res Pract, vol. 2013, pp. 1–10, 2013, doi: 10.1155/2013/268382.

[44] F. Di Vincenzo, A. Del Gaudio, V. Petito, L. R. Lopetuso, and F. Scaldaferri, "Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review," Intern Emerg Med, vol. 19, no. 2, pp. 275–293, Mar. 2024, doi: 10.1007/s11739-023-03374-w.

[45] K.-A. Gwee, V. Goh, G. Lima, and S. Setia, "Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits," J Pain Res, vol. Volume 11, pp. 361–374, Feb. 2018, doi: 10.2147/JPR.S156938.

[46] M. M. Menger et al., "Diclofenac, a NSAID, delays fracture healing in aged mice," Exp Gerontol, vol. 178, p. 112201, Jul. 2023, doi: 10.1016/j.exger.2023.112201.

[47] G. Bueno et al., "The essential oil from Baccharis trimera (Less.) DC improves gastric ulcer healing in rats through modulation of VEGF and MMP-2 activity," J Ethnopharmacol, vol. 271, p. 113832, May 2021, doi: 10.1016/j.jep.2021.113832.

[48] R. Brea et al., "Beneficial effects of hepatic cyclooxygenase-2 expression against cholestatic injury after common bile duct ligation in mice," Liver International, vol. 44, no. 9, pp. 2409–2423, Sep. 2024, doi: 10.1111/liv.16004.

[49] X. Peng et al., "COX-1/PGE2/EP4 alleviates mucosal injury by upregulating β-arr1-mediated Akt signaling in colitis," Sci Rep, vol. 7, no. 1, p. 1055, Apr. 2017, doi: 10.1038/s41598-017-01169-6.

[50] R. Liu et al., "PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers," Cell Death Dis, vol. 11, no. 9, p. 797, Sep. 2020, doi: 10.1038/s41419-020-02998-6.

[51] D. Amaral Silva et al., "Simulated, biorelevant, clinically relevant or physiologically relevant dissolution media: The hidden role of bicarbonate buffer," European Journal of Pharmaceutics and Biopharmaceutics, vol. 142, pp. 8–19, Sep. 2019, doi: 10.1016/j.ejpb.2019.06.006.

[52] J. He et al., "Ca2+ signaling in HCO3− secretion and protection of upper GI tract," Oncotarget, vol. 8, no. 60, pp. 102681–102689, Nov. 2017, doi: 10.18632/oncotarget.21840.

[53] G. W. Hughes, C. Ridley, R. Collins, A. Roseman, R. Ford, and D. J. Thornton, "The MUC5B mucin polymer is dominated by repeating structural motifs and its topology is regulated by calcium and pH," Sci Rep, vol. 9, no. 1, p. 17350, Nov. 2019, doi: 10.1038/s41598-019-53768-0.

[54] H. Xu et al., "Endothelial cell prostaglandin E2 receptor EP4 is essential for blood pressure homeostasis," JCI Insight, vol. 5, no. 13, Jul. 2020, doi: 10.1172/jci.insight.138505.

[55] K. M. DeMars, A. O. McCrea, D. M. Siwarski, B. D. Sanz, C. Yang, and E. Candelario-Jalil, "Protective Effects of L-902,688, a Prostanoid EP4 Receptor Agonist, against Acute Blood-Brain Barrier Damage in Experimental Ischemic Stroke," Front Neurosci, vol. 12, Feb. 2018, doi: 10.3389/fnins.2018.00089.

[56] B. A. Carboneau, J. A. Allan, S. E. Townsend, M. E. Kimple, R. M. Breyer, and M. Gannon, "Opposing effects of prostaglandin E 2 receptors EP3 and EP4 on mouse and human β-cell survival and proliferation," Mol Metab, vol. 6, no. 6, pp. 548–559, Jun. 2017, doi: 10.1016/j.molmet.2017.04.002.

[57] G. Adebayo-Gege et al., "Molecular docking and anti-ulcerative potential of Cucumis (L. Inodorous) on ibuprofen induced gastric ulceration in male wistar animals," Biomedicine & Pharmacotherapy, vol. 161, p. 114531, May 2023, doi: 10.1016/j.biopha.2023.114531.

[58] A. M. Kitay, F. S. Ferstl, A. Link, and J. P. Geibel, "Induction of Secretagogue Independent Gastric Acid Secretion via a Novel Aspirin-Activated Pathway," Front Physiol, vol. 10, Oct. 2019, doi: 10.3389/fphys.2019.01264.

[59] K. Shishikura et al., "Prostaglandin E2 inhibits neutrophil extracellular trap formation through production of cyclic AMP," Br J Pharmacol, vol. 173, no. 2, pp. 319–331, Jan. 2016, doi: 10.1111/bph.13373.

[60] O. O. Oyesola and E. D. Tait Wojno, "Prostaglandin regulation of type 2 inflammation: From basic biology to therapeutic interventions," Eur J Immunol, vol. 51, no. 10, pp. 2399–2416, Oct. 2021, doi: 10.1002/eji.202048909.

[61] M. Louis, M. Cawthon, B. Gibson, and B. Kuhn, "Management of NSAID-Induced Penetrating Gastric Ulcer Complicated by Hemorrhagic Cholecystitis: The Role of Percutaneous Transhepatic Biliary Drainage," Radiol Case Rep, vol. 19, no. 9, pp. 4059–4065, Sep. 2024, doi: 10.1016/j.radcr.2024.06.032.

[62] E. Nesiama, L. Mirembe, K. Weber, S. Isaac, D. Trammell, and I. Obokhare, "Massive Gastrointestinal Bleeding Related to NSAID Use in a Patient with Ileorectal Anastomosis," Case Rep Surg, vol. 2024, no. 1, Jan. 2024, doi: 10.1155/2024/4619458.