ISSN- 0301-1216
Indian J. Prev. Soc. Med. Vol. 56, No.1, 2025

Indomethacin: A multifaceted therapeutic agent with potential applications

Prabhat[1], Jagriti[2], MD. Abu Bashar[3]

ABSTRACT

Background: Indomethacin, a well-established non-steroidal anti-inflammatory drug (NSAID), exhibits remarkable therapeutic versatility across diverse medical applications. While traditionally recognized for its potent anti-inflammatory and analgesic properties, recent studies underscore its potential in oncology, virology, neurology, and cardiovascular health. Its primary mechanism involves cyclooxygenase (COX) inhibition, reducing prostaglandin synthesis, and modulating immune responses. Beyond this, non-COX-mediated effects, such as autophagy regulation and mitochondrial modulation, expand its therapeutic scope. **Objective:** This study aims to explore the broad therapeutic potential of indomethacin beyond its conventional use as an anti-inflammatory agent, focusing on its applications in oncology, virology, neurology, and other medical fields. **Materials and Methods:** A comprehensive review of preclinical and clinical studies was conducted to evaluate the mechanisms, therapeutic benefits, and limitations of indomethacin. Research findings on its role in cancer therapy, viral infections, neuroprotection, and inflammatory disorders were analyzed, along with advancements in drug formulations to mitigate adverse effects. **Results:** Preclinical studies demonstrate that Indomethacin restores apoptotic pathways by targeting anti-apoptotic Bcl-2 proteins, enhancing the efficacy of immuno-therapies and chemotherapies in breast, colon, and prostate cancers. In vitro and clinical studies reveal its dual antiviral action against SARS-CoV-2, canine coronavirus, and rotavirus, achieved by inhibiting viral replication and suppressing cytokine storms. Clinical evidence highlights its ability to lower intracranial pressure (ICP) in traumatic brain injury (TBI) and manage refractory migraines. Additionally, animal models suggest neuroprotective effects in Alzheimer's disease, including reduced amyloid-beta plaque formation. Furthermore, experimental studies validate its potential to mitigate inflammation in rheumatoid arthritis and ankylosing spondylitis, while clinical trials in neonatology confirm its efficacy in reducing intraventricular hemorrhage (IVH) severity. **Conclusion:** Despite its broad therapeutic utility, indomethacin's gastrointestinal (GI) toxicity remains a limitation. Advancements in drug formulations, including phospholipid conjugates (e.g., DP-155), hydrogen sulfide-based derivatives, and nano-particles, have shown promise in reducing adverse effects. Future research directions include large-scale clinical trials to validate its efficacy in under explored therapeutic domains, mechanistic studies on non-COX pathways, and innovative combination therapies. Indomethacin exemplifies the potential of repurposed drugs to address complex medical challenges. By leveraging its restorative, synergistic, and multitargeted effects, alongside innovative delivery strategies, indomethacin can continue to play a transformative role in modern medicine.

Keywords: Indomethacin; Cyclooxygenase inhibition; Cancer therapy; Antiviral activity; Prostaglandin synthesis; Cytokine storm; Gastrointestinal toxicity; Traumatic brain injury; Preterm labor; Personalized medicine; Drug repurposing; Nonsteroidal anti-inflammatory drugs (NSAIDs).

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drug classes worldwide due to their proven efficacy in managing pain, inflammation, and fever. Chemically derived from indole-acetic acid (1-(p-chlorobenzene)-5-methoxy-2-methylindole-3-acetic acid), indomethacin is a key component in the management of various rheumatic and inflammatory conditions, including osteoarthritis, ankylosing spondylitis, collagen diseases, and gout. Indomethacin's therapeutic relevance extends far beyond its traditional roles.

1. Associate Professor, Department of Biochemistry, All India Institute of Medical Sciences, Kunraghat, Gorakhpur, Uttar Pradesh: 273008, **Email:** drprabhat12811281@yahoo.in; Phone: 8318793132
2. Ph.D. Student (Medical Biochemistry), Department of Biochemistry, All India Institute of Medical Sciences, Kunraghat, Gorakhpur, Uttar Pradesh: 273008, **Email:** jagsri43200@gmail.com; Mobile: 7379653599
3. Assistant Professor, Department of Community and Family Medicine, All India Institute of Medical Sciences, Kunraghat, Gorakhpur, Uttar Pradesh: 273008**, Email:** imback20006@yahoo.in; Phone: 9501576052

Corresponding Address: Jagriti, Ph.D. Student, Department of Biochemistry, All India Institute of Medical Sciences, Gorakhpur, Kunraghat, Uttar Pradesh: 273008, India.; **Email:** jagsri43200@gmail.com

Submission	20.12.2024	Revision	05.01.2025	Accepted	18.02.2025	Printing	31.03.2025

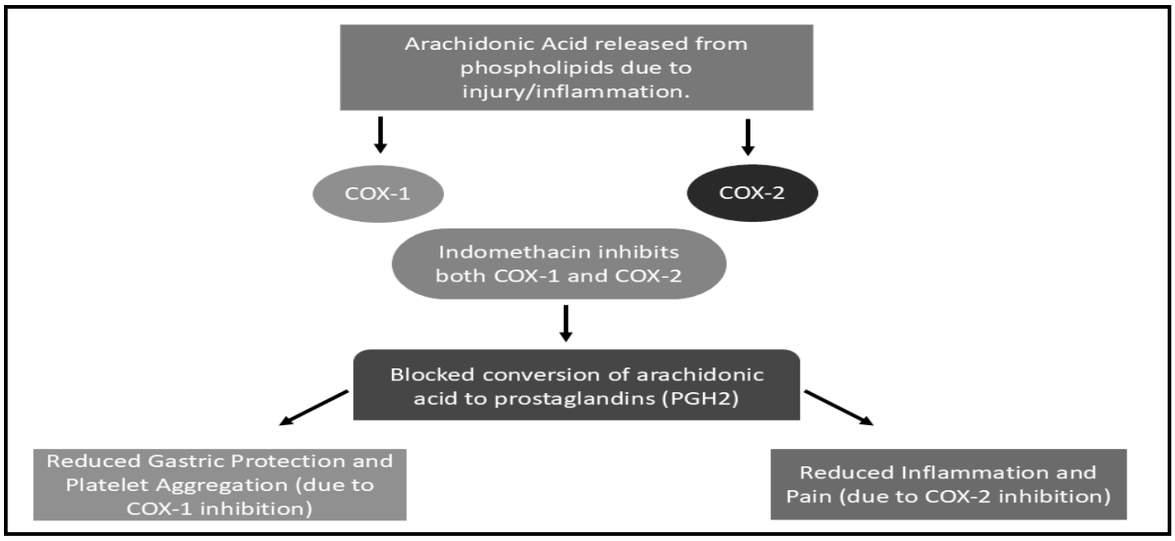
Prior Publication*: Nil*; Source of Funding:* Nil; *Conflicts of Interest*: None, *Article # 598/814

Emerging evidence reveals its potential as a versatile therapeutic agent with applications spanning oncology, virology, neuroprotection, and obstetrics. These effects are attributed to its well-documented cyclooxygenase (COX) inhibition and its under explored non-COX-mediated mechanisms.[1,2]

Pharmacologically, indomethacin possesses unique physicochemical properties. It is photosensitive, slightly soluble in alcohol, and water-insoluble, with a logarithmic acid dissociation constant (pKa) of 3 - 4.5.[3,4] At the cellular level, indomethacin influences processes by altering microenvironments within membranes, further expanding its potential applications. Clinically, it has proven effective in managing arthritic pain, fever, headache syndromes, and dysmenorrhea, and is widely utilized in neonatal medicine for the closure of the patent ductus arteriosus in preterm infants. Given the increasing prevalence of chronic inflammatory and immune-mediated diseases worldwide, exploring NSAIDs like indomethacin for broader applications is both timely and essential for addressing unmet medical needs. Furthermore, advancements in drug delivery technologies, such as nanoparticle-based formulations, hydrogel systems, and prodrugs, offer opportunities to enhance indomethacin's efficacy while mitigating its side effects. These innovations, coupled with an understanding of its mechanisms, pave the way for repositioning indomethacin as a multifaceted therapeutic agent.[5,6]

Despite its extensive use, significant gaps remain in understanding the molecular mechanisms underlying its non-COX-mediated actions, as well as its long-term safety profile in chronic conditions. Additionally, the potential of indomethacin in emerging therapeutic areas such as oncology, virology, and neuro-protection necessitate further exploration through focused clinical trials and mechanistic studies. Addressing these gaps could reveal new applications and improve its therapeutic index.[7,8] This review explores both the established and under explored pharmacological properties of indomethacin, emphasizing its synergistic and restorative effects across various disease contexts. By critically analyzing emerging evidence, identifying research gaps, and highlighting innovative approaches, we aim to provide a comprehensive overview of indomethacin's mechanisms and applications. This analysis underscores its promise as a multidimensional therapeutic agent, paving the way for future research and clinical innovation.

Figure-1: Indomethacin's Inhibition of COX-1 and COX-2 Enzymes: Indomethacin inhibits both COX-1 (blue) and COX-2 (red), blocking the conversion of arachidonic acid to prostaglandins. COX-1 inhibition reduces gastric protection and platelet aggregation, while COX-2 inhibition decreases inflammation, pain, and fever.



1. Indomethacin as an Anticancer Drug: Apoptosis, or programmed cell death, is a multigene-regulated process essential for maintaining cellular homeostasis. Dysregulation of apoptosis is a hallmark of cancer, as it enables tumor cells to evade destruction and resist therapies. Key regulators of apoptosis include anti-apoptotic proteins (e.g., Bcl-XL, Mcl-1, Bcl-2, Bcl-W, A1) and pro-apoptotic proteins (e.g., BH1-3 and BH-3 proteins) from the Bcl-2 family. Over-

expression of anti-apoptotic Bcl-2 proteins contributes to apoptosis resistance in cancer, presenting a major obstacle in treatment. In preclinical studies using cell lines, indomethacin, with its strong affinity for Bcl-2 proteins, offers a therapeutic avenue by inhibiting their expression, thereby restoring apoptotic mechanisms in cancer cells. This ability allows indomethacin to synergize with conventional anticancer therapies, overcoming drug resistance and improving efficacy.

1.1 ***Role in Breast Cancer*****:** Breast cancer, the most prevalent malignancy in women, is often associated with elevated COX-2 activity, which contributes to tumor progression by generating prostaglandin E2 (PGE2). This compound suppresses immune responses by inhibiting the activation of cytotoxic natural killer cells, CD8+ T lymphocytes, and dendritic cells, leading to immune evasion. Elevated COX-2 levels are linked to larger, more aggressive tumors with reduced immune cell functionality. Preclinical studies using cell lines and animal models show that indomethacin, as a COX-2 inhibitor, mitigate these effects and reduce tumor growth.

Recent research highlights the potential of combining MUC1-specific peptide vaccines with COX-2 inhibitors like indomethacin to enhance immunotherapy outcomes. In cell line studies, indomethacin also shows analgesic effects and protects against treatment-related hepatotoxicity and nephrotoxicity. In estrogen-sensitive breast cancer cell lines, it inhibits proliferative responses, further emphasizing its potential role as an adjunct in breast cancer therapy [9,10].

1.1 ***Effects on Colon Cancer:*** Indomethacin induces apoptosis in colon cancer cells by reducing the activation of the peroxisome proliferator-activated receptor delta (PPARδ). This receptor plays a significant role in cancer cell proliferation. Animal model studies show that by modulating the tumor microenvironment, indomethacin enhances T-cell responses and suppresses cancer cell proliferation. Additionally, it increases arginase expression at both the RNA and protein levels, which affects the availability of L-arginine in the tumor microenvironment. L-arginine depletion inhibits the immune evasion strategies of cancer cells, enhancing T-cell-mediated tumor destruction. [11-13]

1.2 ***Addressing Virus-Induced Cancers:*** Certain viruses, such as hepatitis B, hepatitis C, and human papilloma virus (HPV), are linked to oncogenesis. Cell- based studies demonstrate that indomethacin exerts antiviral properties by activating Protein Kinase R (PKR), which rapidly phosphorylates eukaryotic translation initiation factor 2 (eIF2α). This action inhibits protein synthesis, blocking viral replication and protecting host cells. Such antiviral mechanisms may indirectly reduce the risk of virus-associated cancers.

1.3 ***Non-COX-Dependent Mechanisms:*** Indomethacin's anticancer effects extend beyond COX inhibition. In-vitro studies show that non-COX-dependent mechanisms, such as interference with tubulin and heat shock protein 27 (Hsp27), disrupt cellular machinery crucial for cancer cell survival, inducing apoptosis or necrosis. These properties make indomethacin an attractive candidate for anticancer drug development, especially when combined to minimize cardiovascular risks associated with traditional COX inhibitors. Additionally, indomethacin has been shown to impede autophagic processes in cancer cells by increasing levels of autophagy substrates such as p62, LC3-II, and NBR1. By suppressing autophagy, indomethacin disrupts cancer cells' ability to adapt to stress, sensitizing them to chemotherapy.[7,14,15]

[1.4] ***Prostate Cancer:*** Prostate cancer (PC) frequently progresses to castration-resistant prostate cancer (CRPC), a lethal condition that arises from over-reliance on androgen deprivation therapy (ADT) or AR-targeted treatments. Preclinical studies using CRPC cell lines and animal models demonstrate that indomethacin derivatives, such as CZ-212-3, have demonstrated efficacy in degrading androgen receptor (AR) variants and AR proteins in CRPC cells. This mechanism effectively suppresses tumor growth, showcasing the restorative properties of indomethacin and its derivatives.[16, 17]

Table-1: Indomethacin in Combination Therapy for Cancer Treatment

Cancer Type	Combination Therapy	Mechanism of Action	Outcome/Benefits
Breast Cancer	Indomethacin + MUC1-specific vaccine	COX-2 inhibition, enhancement of immune response	Increased tumor regression, enhanced immune response
Colon Cancer	Indomethacin + Chemo-therapy (e.g., Paclitaxel)	Induces apoptosis via Bcl-2 inhibition, COX-2 inhibition	Increased sensitivity to chemo-therapy, reduced tumor growth
Prostate Cancer	Indomethacin + AR-targeted therapy	COX-2 inhibition, degradation of androgen receptors	Suppression of castration-resistant prostate cancer (CRPC) growth
Gastric Cancer	Indomethacin + Radiation Therapy	Anti-inflammatory effects, reduction of COX-2 and PGE2	Improved response to radiation, reduced tumor growth

The table- 1 summarizes the use of indomethacin in combination with other therapies for the treatment of various types of cancer. It outlines the synergistic mechanisms of action, including COX-2 inhibition and immune system modulation, and highlights the resulting benefits, such as enhanced tumor regression, increased sensitivity to chemotherapy, and improved therapeutic outcomes.

2. Indomethacin as an Antiviral Drug: Indomethacin, primarily recognized as a potent anti-inflammatory agent, has demonstrated significant antiviral properties since its initial documentation in 2006. Its antiviral activity stems from a dual mechanism: direct inhibition of viral replication and modulation of host immune responses. This combination positions indomethacin as a promising therapeutic candidate against viral infections, particularly those associated with hyper inflammatory states like COVID-19.

2.1 ***Mechanisms of Antiviral Action***:

1. **Direct Inhibition of Viral Replication:** Indomethacin exerts antiviral effects by targeting key enzymes and pathways involved in viral replication:

   - ***SARS-CoV-2 and Coronavirus Family Viruses:*** Preclinical studies using cell lines demonstrate that indomethacin directly inhibits the activity of trans-membrane serine protease and angiotensin-converting enzyme 2 (ACE2), which are critical for viral entry. By down regulating ACE2 expression, indomethacin reduces viral binding and replication in lung type II alveolar cells, enterocytes, and bladder urothelial cells.
   - ***Key Protease Blockage:*** Cell-based studies reveal that indomethacin interferes with proteases like 3C-like cysteine proteases (Mpro), Ppro, and RNA-dependent RNA polymerase (RdRp), disrupting viral transcription and replication processes.
   - ***Reduction of Viral RNA Synthesis:*** Studies on canine coronavirus (CCoV) and SARS-CoV, primarily conducted in cell lines and animal models, demonstrate over a 1,000-fold decrease in viral RNA production upon treatment with indomethacin. Similar efficacy has been observed in rotavirus infections, where it inhibits viral protein production in human intestinal cells.[18, 19]

2. **Activation of Host Antiviral Defenses:** Indomethacin activates protein kinase R (PKR) in an interferon- and double-stranded RNA-independent manner. Cell-based experiments show that PKR rapidly phosphorylates eukaryotic translation initiation factor 2 (eIF2α), effectively halting viral protein synthesis and replication. This mechanism provides a robust antiviral response, independent of the immune system's typical pathways.

2.2 Impact on COVID-19 and Cytokine Storms

1. ***Suppression of Hyper inflammation*** COVID-19 is characterized by a "cytokine storm," an uncontrolled release of pro-inflammatory cytokines like IL-6, IL-17, and IL-1, which exacerbate disease severity.[20, 21]. Indomethacin addresses this hyper inflammatory state by:

    - ***Inhibiting IL-6 Production:*** Preclinical studies using human cell lines indicate that indomethacin reduces cytokine release induced by lipopolysaccharides (LPS), indomethacin mitigates systemic inflammation.
    - ***Blocking Cathepsin L Activity:*** In vitro models suggest that indomethacin inhibits Cathepsin L activity, decreases SARS-CoV-2 entry into cells by approximately 76%.
    - ***Targeting Bradykinin Pathways:*** Indomethacin alleviates dry coughs and inflammatory effects associated with high bradykinin levels.

2. ***Clinical Evidence in COVID-19 Treatment***

    - ***Combination Therapy:*** In clinical studies involving hospitalized COVID-19 patients, indomethacin used alongside standard ICMR protocols significantly reduced disease severity, duration, and progression to pneumonia.[22] Patients also reported faster symptomatic relief compared to those receiving paracetamol-based regimens.
    - ***Comparison with NSAIDs:*** Unlike other NSAIDs, clinical data indicate that indomethacin uniquely suppresses Cathepsin L activity and exhibits direct antiviral effects, making it a distinctive candidate for COVID-19 therapy.
    - ***Potential as a Paracetamol Replacement:*** Given its dual antiviral and anti-inflammatory properties, clinical observation suggest indomethacin as a compelling alternative to paracetamol for symptom management in viral infections.[23,24]

2.3 Future Directions in Research

While indomethacin demonstrates significant antiviral potential, further studies are necessary to fully elucidate its mechanisms and optimize its use:

- ***Preclinical Studies:*** Investigate indomethacin’s effects on viral replication and host immune responses in various viral infections.
- ***Clinical Trials:*** Conduct large-scale clinical trials to evaluate the efficacy and safety of indomethacin as a standalone or adjunctive therapy in diseases such as COVID-19, influenza, and rotavirus.
- ***Novel Delivery Mechanisms:*** Develop targeted delivery systems, such as nano-particles, to enhance tissue-specific action and reduce systemic side effects.

3. Indomethacin as a CNS Drug

Indomethacin, a potent non-steroidal anti-inflammatory drug (NSAID), has demonstrated significant potential in the treatment of various central nervous system (CNS) disorders. Its unique properties as a cerebral vasoconstrictor and neuroprotective agent make it a promising candidate for managing conditions characterized by elevated intracranial pressure (ICP), traumatic brain injury (TBI), migraines, and neurodegenerative diseases such as Alzheimer’s.

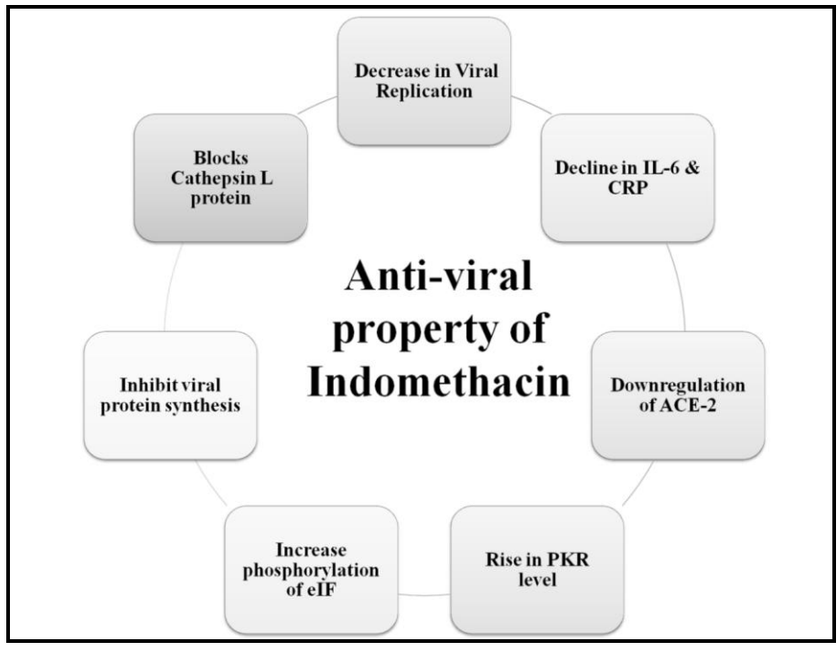
3.1 ***Role in Traumatic Brain Injury (TBI):*** Traumatic brain injury is a leading cause of disability and death globally, with mortality rates reaching 11% in severe cases. Secondary complications, such as post-traumatic cerebral edema and elevated ICP, exacerbate brain damage by reducing cerebral perfusion and oxygenation.

Clinical studies have shown that indomethacin effectively reduces ICP and improves cerebral perfusion pressure (CPP) offering a therapeutic advantage in managing TBI.

- **Mechanisms of Action:**
  While the exact pathways through which indomethacin lowers ICP remain unclear, several mechanisms have been proposed:

  - ***Cerebral Vasoconstriction*:** Observed in clinical and preclinical studies, indomethacin inhibits cyclooxygenase (COX) enzymes and blocks prostacyclin receptors, indomethacin directly reduces cerebral blood flow, alleviating swelling and lowering ICP.

***Blood-Brain Barrier (BBB) Integrity*:** Animal model studies suggest that indomethacin modulates capillary permeability, reducing BBB breakdown and preventing fluid influx that exacerbates cerebral edema.



- **Figure 2:** Indomethacin affects viral replication by regulating prostaglandin, interleukin-6 (IL-6), and C-reactive protein (CRP). The other antiviral property is the suppression of the angiotensin-converting enzyme (ACE-2) pathway, phosphorylation of elongation initiation factor (eIF), and blocking of cathepsin-L protein.

- ***Non-Prostaglandin-Mediated Neuroprotection*:** Emerging evidence from preclinical studies suggests neuroprotective effects independent of prostaglandin pathways, possibly through modulation of signaling cascades.

Clinical trials have demonstrated that indomethacin is effective in managing refractory ICP in patients unresponsive to conventional therapies. By breaking the vicious cycle of elevated ICP (>25 mmHg), indomethacin restores perfusion and improves oxygenation, mitigating the risk of ischemia.[25, 26]

3.2 Prevention of Intraventricular Hemorrhage (IVH) in Premature Infants:

In neonatology, indomethacin has been widely used to prevent patent ductus arteriosus (PDA) in preterm infants. Beyond this role, it has shown efficacy in reducing the incidence and severity of intraventricular hemorrhage (IVH), a major complication in premature infants that can lead to significant neurological sequelae.

- **Mechanisms in IVH Prevention:**
  - Cerebral Blood Flow Stabilization: Clinical and experimental studies that indomethacin reduces cerebral blood flow fluctuations and stabilizes the fragile vasculature in preterm infants, preventing hemorrhages.
  - Synergistic Effects: Clinical observations suggest that indomethacin enhances the integrity of the germinal matrix, reducing the risk of bleeding.

Experimental and clinical studies have highlighted indomethacin's ability to mitigate IVH severity, improving long-term neurological outcomes in preterm infants.

3.3 Treatment of Headaches and Migraines

Indomethacin has long been recognized as an effective treatment for certain headache disorders, including those classified as "indomethacin-responsive headaches," such as paroxysmal hemicrania and hemicrania continua.

- **Nitric Oxide Pathways:**
  - In preclinical studies, indomethacin blocks nitric oxide (NO)-induced vasodilation, which is a key contributor to headaches and migraines.
  - Clinical reports confirm that by preventing the effects of NO's on cerebral blood vessels, indomethacin alleviates headache symptoms.
- **Synergistic Effects in Migraines:**
  - Through its COX inhibition and modulation of prostaglandin pathways, preclinical and clinical studies show that indomethacin reduces inflammation and pain.
  - Its efficacy in refractory migraine cases positions it as a valuable therapeutic option for patients unresponsive to standard treatments.[27, 28]

3.4 Role in Neurodegenerative Diseases

Indomethacin has shown promise in addressing neurodegenerative disorders such as Alzheimer's disease through its anti-inflammatory and neuroprotective properties.

- **Reduction of Amyloid Plaques:**
  - Preclinical studies demonstrate that indomethacin decreases the production of amyloid-β peptide (Aβ42), a key component of the plaques associated with Alzheimer's disease.
  - By mitigating plaque formation, indomethacin helps reduce neurotoxicity and supports neuronal survival.
- **Endocannabinoid System Modulation:**
  - Experimental research indicated that indomethacin's structural similarity to cannabinoid receptor ligands suggests its potential as an allosteric modulator of CB1R (cannabinoid receptor type 1).

- The endocannabinoid system, which includes receptors (CB1R, CB2R), endogenous ligands (anandamide and 2-AG), and metabolic enzymes, plays a critical role in regulating pain, mood, and neuroprotection.
- Indomethacin's interaction with this system could inform the development of selective drugs targeting neurodegenerative conditions.[29-31]

3.5 Concerns and Considerations in CNS Applications

Despite its therapeutic promise, the use of indomethacin in CNS disorders requires careful consideration due to potential risks:

- **Cerebral Ischemia:** While clinical studies confirm indomethacin's vasoconstrictive effects lower ICP, excessive vasoconstriction may raise concerns about reduced cerebral blood flow (CBF) and ischemia. However, studies suggest that this risk can be mitigated with appropriate dosing.
- **Side Effects:** Neurological side effects are rare (<1%), but clinical evidence indicates that gastrointestinal and cardiovascular risks remain, necessitating patient-specific assessments.

3.6 Future Directions and Research Opportunities

Indomethacin's multifaceted effects in the CNS warrant further investigation to optimize its therapeutic potential:

- **Mechanistic Studies:**
  - Investigate the non-prostaglandin-mediated mechanisms underlying its neuroprotective effects using preclinical models.
  - Explore its interaction with the endocannabinoid system for potential applications in pain and depression management.
- **Clinical Trials:**
  - Conduct large-scale clinical trials evaluating indomethacin's role in TBI, IVH prevention, and neurodegenerative diseases.
  - Assess long-term outcomes in migraine and Alzheimer's patients treated with indomethacin.
- **Novel Drug Derivatives:**
  - Develop indomethacin analogs with enhanced selectivity for CNS targets and reduced systemic side effects.

4. Indomethacin as an Anti-Inflammatory Drug

Inflammation is a physiological response of body tissues to injury, infection, or harmful stimuli such as pathogens and irritants. This process is critical for eliminating harmful stimuli and initiating tissue repair.[1] However, chronic inflammation can result in excessive production of pro-inflammatory cytokines, prostaglandins (PGs), and reactive oxygen species (ROS), leading to tissue damage and the progression of various diseases.

Preclinical and clinical studies have shown that indomethacin is a potent nonsteroidal anti-inflammatory drug (NSAID) that inhibits the activity of cyclooxygenase (COX) enzymes, primarily COX-1 and COX-2, which are essential for PG synthesis. Its potency in reducing inflammation surpasses other NSAIDs, including naproxen, ibuprofen, phenylbutazone, and aspirin. By blocking COX activity, indomethacin suppresses neutrophil recruitment, reduces the production of lipoxins and resolvins (key mediators in inflammatory resolution), and decreases the accumulation of cytokines and ROS. This mechanism ensures effective inflammation control and prevents further tissue damage.

Indomethacin's role in resolving inflammation extends beyond its COX inhibition. In vitro and preclinical studies have demonstrated its ability to modulate the immune response by inhibiting nuclear factor kappa B (NF-kB), a key transcription factor involved in the regulation of inflammatory genes such as tumor necrosis factor-alpha (TNF-α) and interleukins. This dual mechanism highlights indomethacin's potential not only in managing acute inflammation but also in mitigating chronic inflammatory conditions, such as rheumatoid arthritis, ankylosing spondylitis, and gout.[33-35]

5. Role of Indomethacin in Preterm

Indomethacin has demonstrated significant therapeutic potential in managing pregnancy-related disorders, particularly preterm labor (PTL). Clinical studies define PTL as labor occurring before 37 weeks of gestation, often associated with elevated levels of prostaglandins in maternal plasma and amniotic fluid. By crossing the placental barrier, indomethacin inhibits PG synthesis in embryonic tissues, exerting tocolytic effects and reducing uterine contractility.[36]

5.1 Mechanisms of Action

[a] Prostaglandin Synthesis Inhibition: Clinical studies have shown that indomethacin reduces the maternal serum levels of prostaglandin metabolites, thereby delaying labor and extending pregnancy. However, its effects on uterine contractility are not solely attributed to COX inhibition.

[b] Modulation of NF-kB Pathway:

- Preclinical studies indicate that NF-kB, a transcription factor involved in labor onset, upregulates pro-inflammatory mediators such as TNF-α, IL-6, and IL-8. These mediators promote uterine contractions and cervical ripening.
- Indomethacin inhibits NF-kB activity, reducing the expression of these pro-labor genes, including COX-2, and countering their anti-progesterone effects. This dual action helps in maintaining uterine quiescence and delaying preterm delivery. [37-41]

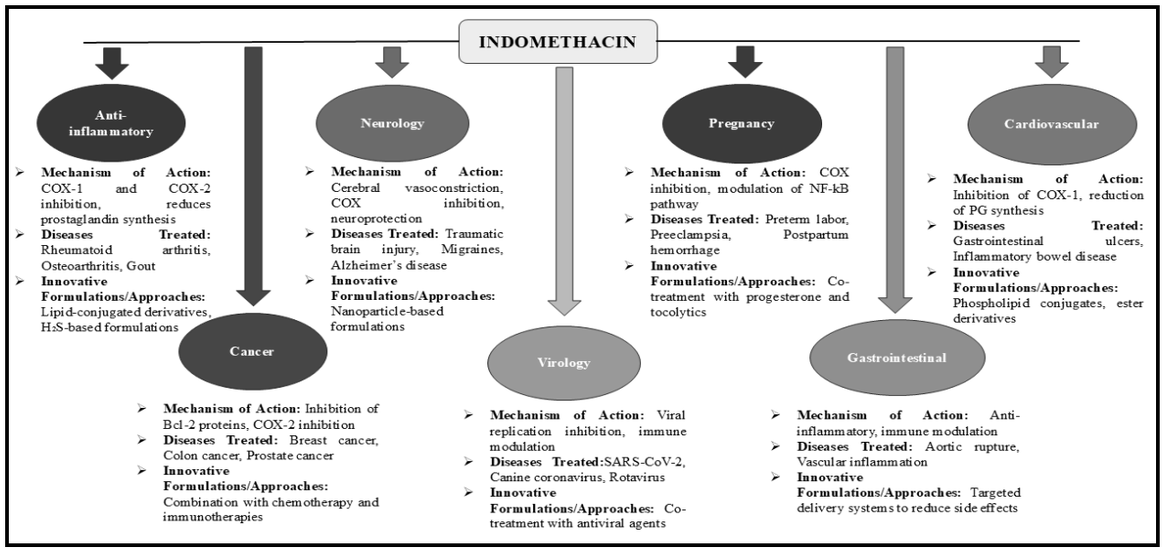
5.2 Applications and Outcomes

- **Tocolysis:** Clinical evidence supports the use of indomethacin as a widely accepted tocolytic agent for managing preterm labor. By reducing PG synthesis and inflammatory pathways, indomethacin exhibits synergistic effects that enhance the efficacy of other tocolytic therapies.
- **Pregnancy Complications:** Observational studies suggest that conditions such as hypothyroidism, gestational diabetes, and pre-eclampsia, often associated with PTL, are linked to elevated PG and NF-kB activity. By targeting these pathways, indomethacin provides a therapeutic strategy to mitigate these complications.
- **Fetal Safety and Risks:** While clinical studies highlight indomethacin's efficacy in prolonging pregnancy, its use requires careful monitoring due to potential risks such as premature closure of the fetal ductus arteriosus and reduced fetal renal perfusion.[42]

5.3 Emerging Insights and Future Directions

- **Combination Therapies:** Preclinical research explores combining indomethacin with other anti-inflammatory agents or progesterone therapies may enhance its efficacy while reducing potential adverse effects.
- **Mechanistic Studies:** Further experimental studies on alternative pathways, such as NF-kB and non-COX targets, could optimize its therapeutic applications in pregnancy and inflammation.
- **Personalized Medicine:** Clinical research focused on identifying biomarkers that predict responsiveness to indomethacin may help tailor treatments for high-risk pregnancies and inflammation-related conditions.

Figure-3: Multidisciplinary therapeutic applications of indomethacin. The diagram illustrates its diverse roles across oncology, neurology, virology, and inflammation domains. Key mechanisms, diseases treated, and innovative drug formulations are highlighted to showcase its versatility as a therapeutic agent.



6. Role of Indomethacin in Burning Scrotum Syndrome (BSS)

Burning scrotum syndrome (BSS) is a rare and poorly understood condition characterized by dysesthesia, erythema, and localized pain in the scrotum. The etiology is unclear but may involve vasodilation, neurogenic inflammation, erythromelalgia, or corticosteroid-induced rebound effects.

7. Role of Indomethacin in Preterm

Indomethacin has demonstrated significant therapeutic potential in managing pregnancy-related disorders, particularly preterm labor (PTL). Clinical studies define PTL as labor occurring before 37 weeks of gestation, often associated with elevated levels of prostaglandins in maternal plasma and amniotic fluid. By crossing the placental barrier, indomethacin inhibits PG synthesis in embryonic tissues, exerting tocolytic effects and reducing uterine contractility[36].

Therapeutic Role of Indomethacin: Evidence from case studies and experimental observations suggests that indomethacin has shown efficacy in treating BSS due to its vaso-constrictive and anti-inflammatory properties:

- **Vasoconstrictive Effects:** Indomethacin's influence on mesenteric blood flow in animal models suggests it could exert similar effects on testicular arteries, reducing localized inflammation and vasodilation.
- **Restorative and Synergistic Properties:** The drug's ability to modulate localized blood flow and address neurogenic inflammation underpins its role in managing the symptoms of BSS.[43-44]

While limited clinical evidence exists, these findings provide a rationale for further exploration of indomethacin's role in this condition.

8. Indomethacin as a Gastrointestinal Drug

Indomethacin, like many nonsteroidal anti-inflammatory drugs (NSAIDs), effectively mitigates inflammation by inhibiting cyclooxygenase (COX) enzymes. However, its therapeutic use is often limited by significant gastrointestinal (GI) side effects[45]. These include mucosal damage, ulcers, and bleeding, primarily due to the suppression of COX-1-dependent mucosal-protective prostaglandins (PGs).

Advancements in GI Safety: Recent advancements in drug formulation and alternative strategies have shown promise in enhancing the safety profile of indomethacin while retaining its therapeutic efficacy:

- **Phospholipid Conjugates: Preclinical studies** indicate that conjugating indomethacin with phospholipids (e.g., DP-155) can preserve its anti-inflammatory properties while reducing mucosal damage.
- **Hydrogen Sulfide (H_2S)-Based Approaches: Animal models** demonstrate that combining indomethacin with H_2S donors reduces oxidative stress and improves mucosal defense mechanisms, mitigating ulcerogenic effects.
- **Prodrugs and Ester Derivatives:** New formulations, including ester derivatives of indomethacin, have been developed in **experimental studies** to enhance its GI safety profile [2,46].

These innovations underscore the potential of indomethacin as a GI drug when combined with targeted delivery mechanisms or co-treatments to address side effects.

Conclusion

Indomethacin, a well-established NSAID, exemplifies its therapeutic versatility across multiple domains, including oncology, virology, neurology, and inflammation management. Beyond its well-documented COX inhibition, its ability to engage non-COX-mediated pathways, such as autophagy regulation and mitochondrial modulation, underscores its potential to address complex and multifaceted diseases. These mechanisms expand their utility in treating chronic inflammatory conditions, neurodegenerative disorders, and certain cancers.

Despite its wide-ranging applications, indomethacin's gastrointestinal toxicity has been a persistent limitation. However, advancements in drug formulation strategies, including phospholipid conjugates, H_2S-based derivatives, and ester-linked analogs, have shown promise in mitigating these side effects while preserving therapeutic efficacy. Emerging evidence also highlights its potential for integration with advanced drug delivery systems and combination therapies, enhancing its precision and impact.

Future research should prioritize large-scale clinical trials to validate its efficacy in underexplored domains, deeper mechanistic studies on non-COX-mediated effects, and the development of personalized therapeutic approaches. Such efforts will refine its safety profile and unlock new opportunities for its application in addressing contemporary medical challenges.

Indomethacin's multifaceted properties, synergistic effects, and adaptability position it as a transformative therapeutic agent with the potential to reshape its role in modern medicine. Its evolution through innovation and research solidifies its place as a pillar of next-generation therapeutic interventions, addressing the dynamic needs of a rapidly changing healthcare landscape.

References

1. Panchal NK, Prince Sabina E. Non-steroidal anti-inflammatory drugs (NSAIDs): A current insight into its molecular mechanism eliciting organ toxicities. Food Chem Toxicol. 2023 Feb 1;172: 113598.
2. Gliszczyńska A, Nowaczyk M. Lipid Formulations and Bioconjugation Strategies for Indomethacin Therapeutic Advances. Molecules. 2021 Mar 12; 26 (6):1576.
3. Comer J, Judge S, Matthews D, Towes L, Falcone B, Goodman J, et al. The intrinsic aqueous solubility of indomethacin. ADMET DMPK. 2014 Apr 1; 2:18–32.
4. Temussi F, Cermola F, Dellagreca M, Iesce M, Passananti M, Previtera L, et al. Determination of photostability and photodegradation products of indomethacin in aqueous media. Vol. 56, Journal of Pharmaceutical and Biomedical Analysis. 2013.
5. Mazumder S, De R, Debsharma S, Bindu S, Maity P, Sarkar S, et al. Indomethacin impairs mitochondrial dynamics by activating the PKCζ–p38–DRP1 pathway and inducing apoptosis in gastric cancer and normal mucosal cells. J Biol Chem. 2019 May 17; 294 (20): 8238–58.
6. Zhou Y, Hancock JF, Lichtenberger LM. The Nonsteroidal Anti-Inflammatory Drug Indomethacin Induces Heterogeneity in Lipid Membranes: Potential Implication for Its Diverse Biological Action. PLoS ONE. 2010 Jan 21; 5 (1):e8811.

7. Abdellatif KRA, Abdelall EKA, Elshemy HAH, El-Nahass ES, Abdel-Fattah MM, Abdelgawad YYM. New indomethacin analogs as selective COX-2 inhibitors: Synthesis, COX-1/2 inhibitory activity, anti-inflammatory, ulcerogenicity, histopathological, and docking studies. Arch Pharm (Weinheim). 2021 Apr; 354 (4): e2000328.
8. Uehara Y, Murata Y, Shiga S, Hosoi Y. NSAIDs diclofenac, indomethacin, and meloxicam highly upregulate expression of ICAM-1 and COX-2 induced by X-irradiation in human endothelial cells. Biochem Biophys Res Commun. 2016 Oct 28; 479 (4): 847–52.
9. Rundstadler TK, Eskandari A, Norman SM, Suntharalingam K. Polypyridyl Zinc(II)-Indomethacin Complexes with Potent Anti-Breast Cancer Stem Cell Activity. Mol Basel Switz. 2018 Sep 4;23(9):2253.
10. Segovia-Mendoza M, Camacho-Camacho C, Rojas-Oviedo I, Prado-Garcia H, Barrera D, Martínez-Reza I, et al. An organotin indomethacin derivative inhibits cancer cell proliferation and synergizes the antiproliferative effects of lapatinib in breast cancer cells. Am J Cancer Res. 2020;10 (10):3358–69.
11. Zhang G, Tu C, Zhang G, Zhou G, Zheng W. Indomethacin induces apoptosis and inhibits proliferation in chronic myeloid leukemia cells. Leuk Res. 2000 May;24 (5):385–92.
12. Ahmed MAE, Mohanad M, Ahmed AAE, Aboulhoda BE, El-Awdan SA. Mechanistic insights into the protective effects of chlorogenic acid against indomethacin-induced gastric ulcer in rats: Modulation of the cross talk between autophagy and apoptosis signaling. Life Sci. 2021 Jun 15; 275: 119370.
13. Gebril SM, Ito Y, Abu-Dief EE, Hussein MRA, Elsayed HM, Mohammad AN, et al. Ultra-structural study of the indomethacin-induced apoptosis and autophagy in rat gastric parietal cells. Ultrastruct Pathol. 2020 May 3;44(3):300–13.
14. Ganduri V, Rajasekaran K, Duraiyarasan S, Adefuye MA, Manjunatha N. Colorectal Carcinoma, Cyclooxygenases, and COX Inhibitors. Cureus. 2022 August,14 (8):e28579.
15. Rodrigues P, Bangali H, Hammoud A, Mustafa YF, Al-Hetty HRAK, Alkhafaji AT, et al. COX 2-inhibitors; a thorough and updated survey into combinational therapies in cancers. Med Oncol Northwood Lond Engl. 2024 Jan 2;41(1):41.
16. Yang JC, Xu P, Ning S, Wasielewski LJ, Adomat H, Hwang SH, et al. Novel inhibition of AKR1C3 and androgen receptor axis by PTUPB synergizes enzalutamide treatment in advanced prostate cancer. Oncogene. 2023 Feb; 42 (9):693–707.
17. Arabiyat S, Alzoubi A, Al-Daghistani H, Al-Hiari Y, Kasabri V, Alkhateeb R. Evaluation of Quinoline-Related Carboxylic Acid Derivatives as Prospective Differentially Antiproliferative, Antioxidative, and Anti-Inflammatory Agents. Chem Biol Drug Des. 2024 Oct;104 (4):e14615.
18. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. Int J Clin Pract. 2020 Sep;74 (9):e13535.
19. Desantis J, Bazzacco A, Eleuteri M, Tuci S, Bianconi E, Macchiarulo A, et al. Design, synthesis, and biological evaluation of first-in-class indomethacin-based PROTACs degrading SARS-CoV-2 main protease and with broad-spectrum antiviral activity. Eur J Med Chem. 2024 Mar 15; 268: 116202.
20. Abu Esba LC, Al-Abdulkarim HA, Alrushidan A, Al Harbi M. Pharmacy and Therapeutics Committee Preparedness Plan for COVID-19. Glob J Qual Saf Healthc. 2020 May; 3 (2):55–64.
21. Au L, Fendler A, Shepherd STC, Rzeniewicz K, Cerrone M, Byrne F, et al. Cytokine release syndrome in a patient with colorectal cancer after vaccination with BNT162b2. Nat Med. 2021 Aug;27 (8):1362–6.
22. Brizawasi A, Ahirwar AK, Prabhat, Kaim K, Ahirwar P, Kumawat R, et al. COVID-19: a viewpoint from hepatic perspective. Horm Mol Biol Clin Investig. 2023 Mar 1; 44 (1):97–103.
23. Shekhar N, Kaur H, Sarma P, Prakash A, Medhi B. Indomethacin: an exploratory study of antiviral mechanism and host-pathogen interaction in COVID-19. Expert Rev Anti Infect Ther. 2022 Mar; 20 (3):383–90.
24. Krymchantowski AV, Silva-Néto RP, Jevoux C, Krymchantowski AG. Indomethacin for refractory COVID or post-COVID headache: a retrospective study. Acta Neurol Belg. 2022 Apr;122(2):465–9.
25. Kuczynski A, Crawford S, Bodell L, Dewey D, Barlow KM. Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their response to treatment: a prospective cohort. Dev Med Child Neurol. 2013 Jul;55(7):636–41.
26. Godoy DA, Alvarez E, Manzi R, Piñero G, Di Napoli M. The physiologic effects of indomethacin test on CPP and ICP in severe traumatic brain injury (sTBI). Neurocrit Care. 2014 Apr;20(2):230–9.

27. Villar-Martínez MD, Moreno-Ajona D, Chan C, Goadsby PJ. Indomethacin-responsive headaches-A narrative review. Headache. 2021 May;61(5):700–14.
28. Myers KA, Barmherzig R, Raj NR, Berrahmoune S, Ingelmo P, Saint-Martin C, et al. The spectrum of indomethacin-responsive headaches in children and adolescents. Cephalalgia Int J Headache. 2022 Jul; 42 (8):793–7.
29. Karkhah A, Saadi M, Pourabdolhossein F, Saleki K, Nouri HR. Indomethacin attenuates neuro-inflammation and memory impairment in an STZ-induced model of Alzheimer's like disease. Immunopharmacol Immunotoxicol. 2021 Dec;43(6):758–66.
30. Stopschinski BE, Weideman RA, McMahan D, Jacob DA, Little BB, Chiang HS, et al. Microglia as a cellular target of diclofenac therapy in Alzheimer's disease. Ther Adv Neurol Disord. 2023;16: 17562864231156674.
31. McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res Brain Res Rev. 1995 Sept; 21(2):195–218.
32. P, Bhattacharjee J. Correlation of NFκB and Adiponectin levels with HOMA-IR in patients with Gestational Diabetes mellitus. Glob J Pharm Res. 2022 Oct 10;
33. Ziesenitz VC, Welzel T, van Dyk M, Saur P, Gorenflo M, van den Anker JN. Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years. Paediatr Drugs. 2022 Nov;24(6):603–55.
34. Maruyama K, Goto K, Hiramoto K, Tanaka S, Ooi K. Indomethacin, a Non-steroidal Anti-inflammatory Drug, Induces Skin Dryness via PPARγ in Mice. Biol Pharm Bull. 2022 Jan 1;45(1):77–85.
35. Savjani J, Variya B, Patel S, Mulamkattil S, Amin H, Butani S, et al. Drug Design, Synthesis and Biological Evaluation of Heterocyclic Molecules as Anti-Inflammatory Agents. Mol Basel Switz. 2022 Feb 14;27(4):1262.
36. Jain A, Prabhat F. Prenatal Screening for Genetic Disorders: Indian Scenario. Indian J Med Biochem. 2023 Jan 3;26(1):iv–v.
37. Pillai VC, Shah M, Rytting E, Nanovskaya TN, Wang X, Clark SM, et al. Prediction of maternal and fetal pharmacokinetics of indomethacin in pregnancy. Br J Clin Pharmacol. 2022 Jan;88(1):271–81.
38. D'Ambrosio V, Vena F, Scopelliti A, D'Aniello D, Savastano G, Brunelli R, et al. Use of non-steroidal anti-inflammatory drugs in pregnancy and oligohydramnios: a review. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2023 Dec;36(2):2253956.
39. Entezari B, Akbaba H, Gurer-Orhan H. Modulation of adipogenesis and lipogenesis by indomethacin and pantoprazole. Toxicol Vitro Int J Publ Assoc BIBRA. 2024 Oct;100:105895.
40. Amir M, Yimer N, Hiew M, Yusoff SM, Hussen B, Quddus A. Effect of indomethacin on embryo implantation and histomorphology of uterus, ovary, kidney, and liver of rats. Saudi J Biol Sci. 2023 Dec;30 (12):103837.
41. Rovers JFJ, Thomissen IJC, Janssen LCE, Lingius S, Wieland BV, Dieleman JP, et al. The relationship between antenatal indomethacin as a tocolytic drug and neonatal outcomes: a retrospective cohort study. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2021 Sep; 34 (18): 2945–51.
42. PJ, Banerjee A, Bansal A, Gogoi J. Lipoprotein Ratios: Correlations with Glycated Hemoglobin among Type 2 Diabetes Mellitus Patients. Cureus. 2024 Feb 5; 16.
43. Sloan B. Indomethacin for burning scrotum syndrome: September 2021. J Am Acad Dermatol. 2021 Sep; 85 (3):568.
44. Hwang AS, Costello CM, Yang YW. Rapid improvement of burning scrotum syndrome with indomethacin. JAAD Case Rep. 2021 Jun; 12:32–3.
45. Emery H, Johnston R, Rowley AF, Coates CJ. Indomethacin-induced gut damage in a surrogate insect model, Galleria mellonella. Arch Toxicol. 2019 Aug; 93 (8):2347–60.
46. Dhapola R, Hota SS, Sarma P, Bhattacharyya A, Medhi B, Reddy DH. Recent advances in molecular pathways and therapeutic implications targeting neuro-inflammation for Alzheimer's disease. Inflammopharmacology. 2021 Dec;29(6): 1669–81

Citation: Prabhat, Jagriti, Bashar A. Indomethacin: A Multifaceted Therapeutic Agent with Potential Applications**.** Indian J Prev Soc Med, 2025; 56 (1): **51-63.**