International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

Proton Pump Inhibitors: Mechanisms, Clinical Applications, and Future Perspectives

Mr. Jain Sahil, Mr.Joshi Gunjan, Ms.Naik Khushi, Mr.Panda Ronak, Ms.Pandey Saumya, Ms. Nandini Banerjee*

SVB's College of Pharmacy, Sonarpada, Dombivli (E), India.

Received: 23 November 2025 Revised: 05 December 2025 Accepted: 23 December 2025

ABSTRACT

Proton pump inhibitors (PPIs) are widely prescribed for the treatment of acid-related gastrointestinal disorders, including peptic ulcers, gastroesophageal reflux disease (GERD), and Helicobacter pylori infection. Their therapeutic action is based on the irreversible inhibition of gastric H^+/K^+-ATPase, resulting in sustained acid suppression. Despite their application, PPIs exhibit several pharmacological limitations such as delayed onset of action, short plasma half-life, inter-individual metabolic variability, and inadequate nocturnal acid control, which can compromise therapeutic outcomes. To address these issues, potassium-competitive acid blockers (P-CABs) have emerged as promising alternatives, offering rapid, metal-independent acid suppression with improved pharmacodynamic profiles. This review explores the pharmacological mechanisms, clinical applications, and long-term safety concerns associated with PPIs, including nutrient malabsorption, increased infection risk, and idiosyncratic hepatotoxicity. This article emphasizes the role of computational drug design tools like molecular docking, QSAR modelling, and ADMET prediction in accelerating the discovery and optimization of next-generation acid suppressants. Case studies and experimental strategies are discussed to focus on the therapeutic potential of both PPIs and P-CABs. The article also addresses regulatory considerations, ethical implications, and future directions in precision drug design, emphasizing the need for a balanced approach to efficacy, safety, and individualized therapy in acid-related gastrointestinal diseases.

Keywords : Proton pump inhibitors (PPIs), H^+/K^+-ATPase inhibition, Mechanism of PPIs, Potassium-Competitive Acid Blockers (P-CABs), Computational drug design, Future perspectives on acid suppression therapy.

INTRODUCTION

Gastric acid secretion is a fundamental physiological process essential for digestion, nutrient absorption, and work against ingested pathogens. This function is primarily mediated by parietal cells in the stomach, which secrete hydrochloric acid (HCl) through activation of the gastric H^+/K^+-ATPase. This is commonly known as the proton pump. Although tightly regulated by neural, hormonal, and paracrine signals, dysregulation of acid secretion contributes to a wide range of gastrointestinal disorders, like gastroesophageal reflux disease (GERD), peptic ulcer disease, erosive esophagitis, and Zollinger-Ellison syndrome.

The introduction of proton pump inhibitors (PPIs) in the late 20th century marked a big step in the management of acid-related diseases. By irreversibly inhibiting the H^+/K^+-ATPase, PPIs suppress the final step of acid secretion, offering sustained acid suppression. Agents such as omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole rapidly became the basis of therapy, exceeding H_2-receptor antagonists in healing and symptom control. Today, PPIs are among the most widely prescribed drug classes globally, significantly reducing peptic disorders.

Despite their widespread use and clinical efficacy, PPIs show a wide range of limitations. Challenges include inter-individual variability due to cytochrome P450 polymorphisms, short plasma half-lives, and suboptimal control of nocturnal acid secretion. Moreover, concerns have emerged regarding long-term safety, with studies linking chronic PPI use to infections, bone fractures [1], renal impairment [2–4], micronutrient deficiencies, and even cognitive decline. The prevalence of inappropriate prescribing and over-the-counter availability further underlines the need for critical reassessment.

In response, potassium-competitive acid blockers (P-CABs) have emerged as promising alternatives [5]. These agents offer rapid, reversible inhibition of acid secretion, independent food intake, and demonstrate superior pharmacokinetic profiles [6,7]. Concurrently, advances in computer-aided drug design (CADD) like molecular docking, pharmacophore modelling, and in silico ADMET profiling are accelerating the discovery of novel acid suppressants with improved safety and efficacy.

Apart from gastroenterology, PPIs are gaining attention to other potential activities like immunomodulatory and anticancer properties [8], expanding their therapeutic applications. This article provides a comprehensive analysis of PPIs, encompassing their mechanisms, clinical applications, limitations, and safety concerns. It also explores emerging trends like P-CABs and the role of computational tools in drug development, aiming to illuminate future directions in precision acid-suppressive therapy.

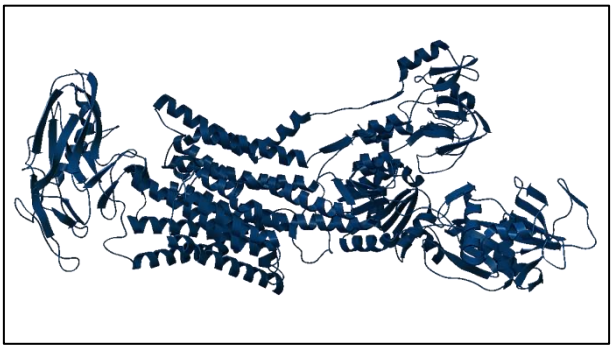

Figure 1: Cryo-EM structure of gastric H+,K+-ATPase with bound rubidium

Mechanism of Gastric Acid Secretion and Target Biology

A basic physiological function common to all vertebrates; gastric acid secretion is necessary for nutrient absorption, microbial defense, and digestion. The gastric H^+/K^+-ATPase, a proton pump found in the secretory canaliculus, is activated by the stomach's parietal cells to produce hydrochloric acid (HCl) [9]. This process is tightly regulated by neural, hormonal, and paracrine signals, and its dysregulation contributes to disorders such as GERD, peptic ulcers, and Zollinger-Ellison syndrome.

In the past, morphological research helped to clarify the cellular source of acid secretion. The secretory canaliculus growth in stimulated parietal cells was initially reported by Golgi [9]. Bayliss and Starling introduced the idea of hormonal regulation [10], while Pavlov's experiments later illustrated the function of vagal stimulation. By the 1920s, several theories had surfaced, including those based on redox and those involving hormones and neurotransmitters such as histamine, acetylcholine, and gastrin.

Both central and peripheral pathways are used to coordinate acid secretion [11]. Enteric neurons are triggered by vagal stimulation and release acetylcholine, which directly stimulates parietal cells [12]. In reaction to food and amino acids, G cells release gastrin, which attaches to enterochromaffin-like (ECL) cells' CCK-B receptors to cause the release of histamine [13,14]. Acid secretion is then increased when histamine activates parietal cells H_2 receptors. Additionally, acetylcholine activates ECL cells, enhancing histamine-mediated communication.

The interplay between G cells, ECL cells, and D cells forms a regulatory triad [15]. D cells release somatostatin, which provides negative feedback by preventing the release of histamine and gastrin. To prevent excessive acid production, somatostatin secretion is further modulated by luminal acid and peptides such as CGRP. Acid secretion is mediated by three important G protein-coupled receptors on parietal cells: CCK_2 (gastrin), M_3 (acetylcholine), and H_2 (histamine). Despite parallel pathways, histamine is thought to be the last common mediator. Acid stimulation is counteracted by inhibitory receptors such as the EGF receptor and EP_3 (prostaglandin).

The last effector of acid secretion is the H^+/K^+-ATPase. It lives in cytoplasmic tubules in cells that are at rest. The pump is moved to the canaliculus' microvilli by cytoskeletal reorganization upon stimulation [16–18], where it converts cytoplasmic H^+ into luminal K^+ [19–21]. This causes fluid secretion into the gastric lumen and produces an extremely acidic environment (pH ~0.8). Osmotic gradients and K/Cl permeability are also involved in activation.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

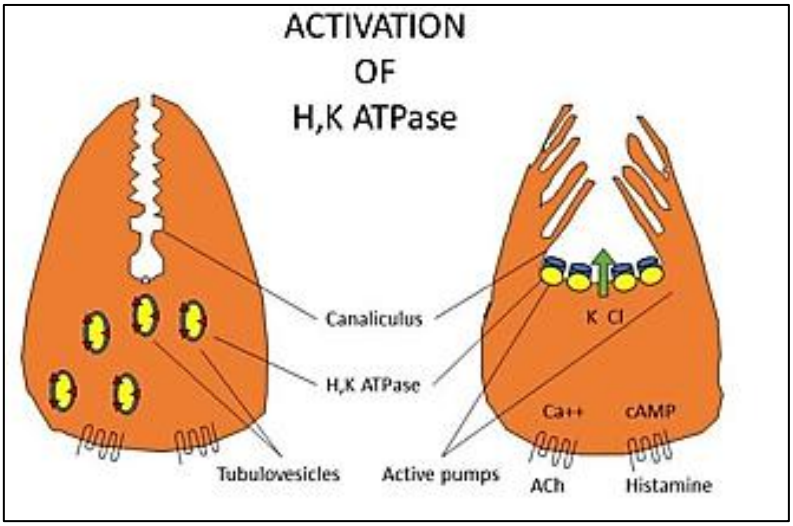

Figure 2: Activation of H+,K+-ATPase

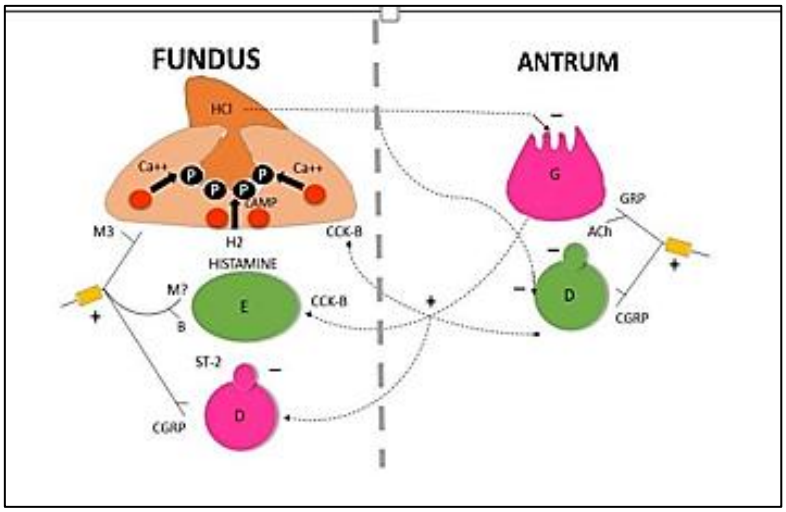

Figure 3: Regulation of gastric acid secretion

Pharmacology of Proton Pump Inhibitors (PPIs)

Omeprazole, esomeprazole, lansoprazole, Dex lansoprazole, pantoprazole, and rabeprazole are among the benzimidazole derivatives that make up most proton pump inhibitors (PPIs). A methyl sulfinyl group connects the heterocyclic pyridine and benzimidazole rings in these compounds. While tenatoprazole, a more recent imidazopyridine derivative, has shown promise in preclinical studies due to its prolonged half-life, it is still not approved for clinical use [22]. Omeprazole was the first PPI to receive clinical approval [23].

PPIs are weak bases and administered as prodrugs. The small intestine absorbs them in their inactive state, and the systemic circulation carries them to the gastric parietal cells. PPIs are protonated, and their sulfoxide bond is rearranged to form an active electrophilic species, such as sulfenamide or sulfenic acid, in the acidic environment of the secretory canaliculus (pH 1.5–3.5). The drug can covalently bind via disulfide bonds to cysteine residues on the H^+/K^+-ATPase enzyme thanks to this pH-dependent transformation, which permanently stops acid secretion until new pumps are made (usually within 36 hours).

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

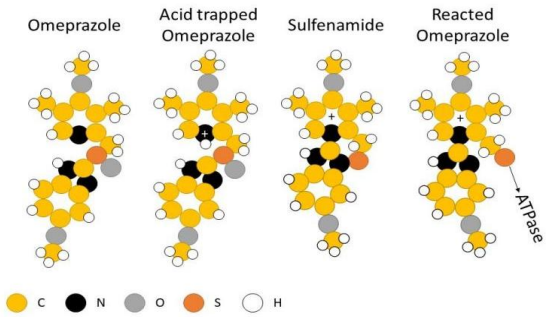

Figure 4: The mechanism of activation of omeprazole.

Cysteine Targets of PPIs

- **Omeprazole**: Cys813, Cys892
- **Esomeprazole**: Cys813
- **Lansoprazole**: Cys813, Cys822, Cys892, Cys321
- **Pantoprazole**: Cys813, Cys822 (noted for high selectivity and stable binding)
- **Rabeprazole**: Cys813, Cys892 (rapid activation due to high reactivity)

This covalent inhibition blocks the final step of acid secretion, making the H^+/K^+-ATPase a central therapeutic target in acid-related disorders.

Metabolism and Pharmacokinetics

Hepatic cytochrome P450 enzymes, particularly CYP2C19 [24], are the main enzymes responsible for the metabolism of PPIs. Drug response varies from person to person due to genetic variations in CYP2C19. People of Asian heritage, for instance, frequently have higher bioavailability, requiring lower starting doses. PPI metabolism is also impacted by aging, necessitating dose modifications for senior citizens.
Omeprazole and esomeprazole, which are heavily metabolized by CYP2C19, exhibit the most noticeable drug-drug interactions. Although they also involve CYP2C19, lansoprazole, dexlansoprazole, and rabeprazole have a strong affinity for CYP3A4, which leads to fewer interactions. Pantoprazole is mostly broken down by CYP2C19-mediated O-demethylation and sulfate conjugation, and it has the least potential for cytochrome induction or inhibition [25].

Excretion Pathways

Most PPIs are excreted renally, except for lansoprazole and dexlansoprazole, which are eliminated via the biliary route [26]. Despite their shared mechanism of action, individual PPIs differ in their pharmacokinetic profiles, metabolic pathways, and interaction potential, which can influence clinical activity and patient outcomes [27].

Table 1: Characteristics of substituted benzimidazoles

Characteristics	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Time to peak plasma level (tmax, hr)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
Half-life, hr	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
Bioavailability, %	30–40	64–90	80–85	-	77	52
Protein binding, %	95	97	97	96	98	96.3
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19 CYP3A4	CYP2C19 CYP3A4	CYP2C19
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

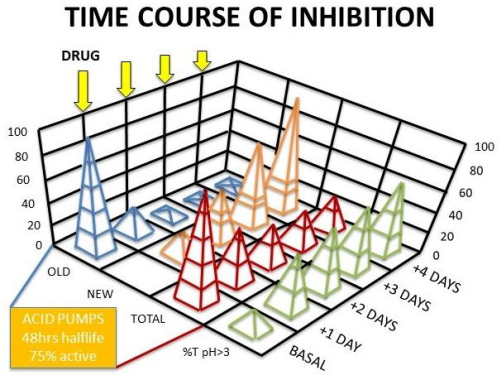

Figure 5: Time course of inhibition

Clinical Applications of Proton Pump Inhibitors (PPIs)

Because of their strong and long-lasting acid-suppressive properties, proton pump inhibitors are frequently used in the treatment of gastrointestinal disorders associated with acid reflux. Among their clinical uses are:

1. Recovery from Peptic Ulcer Disease PPIs facilitate ulcer resolution by decreasing the production of gastric acid, which aids in mucosal healing.

2. Treatment of Gastrointestinal Bleeding Associated with Peptic Ulcers In upper gastrointestinal hemorrhage, high-dose PPIs stabilize clots and lower the risk of rebleeding.

3. Helicobacter pylori eradication by raising stomach pH, PPIs improve the effectiveness of antibiotics and are essential to triple or quadruple therapy regimens.

4. Preventing Gastroduodenal Ulcers Caused by NSAIDs PPIs lower the chance of mucosal damage in patients who need long-term NSAID treatment.

5. The Syndrome of Zollinger-Ellison in gastrin-producing tumors, high-dose PPIs are used to regulate excessive acid secretion.

6. For repairing oesophageal mucosal damage brought by acid reflux, PPIs are the preferred treatment for erosive esophagitis.

7. PPIs for Nerosive Reflux Disease (NERD) reduce symptoms in patients who have reflux-related issues but no obvious oesophageal damage.

8. Dyspepsia with Function Patients with epigastric pain syndrome may benefit from PPIs, especially if acid suppression is a contributing factor [23].

Strategies to Re-engineer Irreversible into Reversible Binders

While PPIs are generally considered safe and effective, their widespread use and irreversible mechanism of action have prompted interest in developing reversible alternatives [6].

1.Overuse and Safety Profile PPIs are overprescribed and used without obvious indications because they are frequently thought of as harmless "stomach protectors." This has sparked worries about needless exposure and possible long-term hazards.

2. Principles of Rational Use PPIs should only be administered under medical supervision, at the lowest possible effective dose, and for the shortest amount of time when clinically indicated.

3. Extended Safety Issues Chronic PPI use has been linked to several possible negative consequences, such as:

- Acute interstitial nephritis and chronic kidney disease; osteoporotic fractures brought on by calcium malabsorption; and deficiencies in iron, magnesium, and vitamin B12.

- A higher chance of gastrointestinal infections, such as those caused by Clostridium difficile.
- Potential correlations between gastric neoplasia and dementia

However, most of the associations are derived from observational studies, which are prone to confounding and can be biased.

Pharmacogenomic Considerations: Genetic polymorphisms, particularly in CYP2C19 [28–32], influence PPI metabolism. Poor metabolizers may experience higher drug exposure and increased risk of adverse effects, highlighting the need for personalized dosing strategies [33].

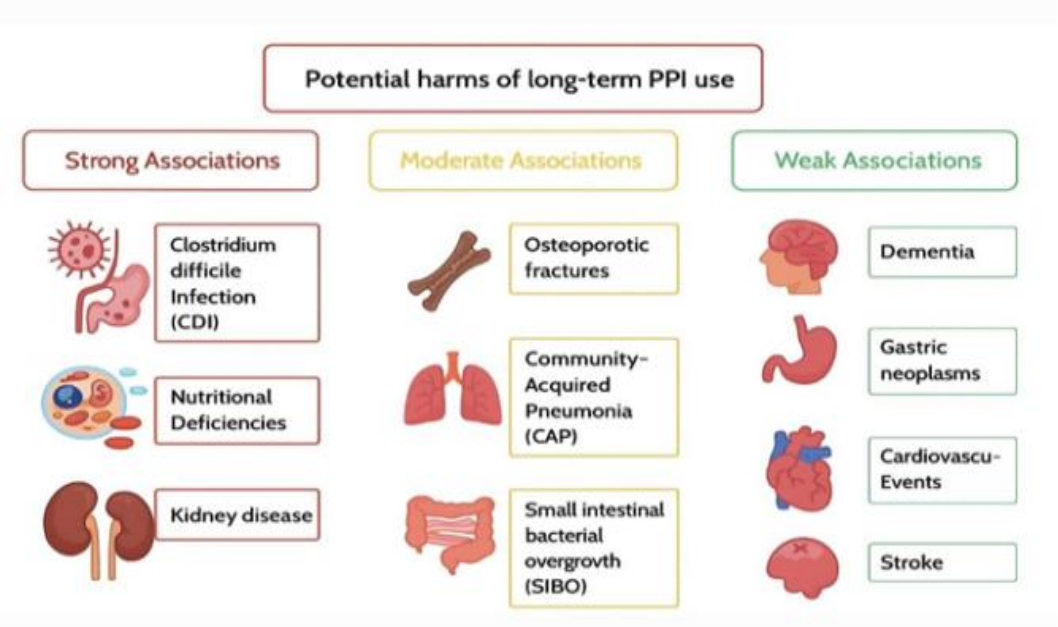

Figure 6: Potential harms of long-term use of PPIs

Role for Potassium-Competitive Acid Blockers (P-CABs)

Although proton pump inhibitors (PPIs) are frequently used to treat disorders related to acidity, they have drawbacks such as poor nocturnal acid control, meal-dependent activation, short plasma half-life, and delayed onset. It takes a few days for delayed-release PPIs (DR-PPIs) to consistently suppress acidity, and they must be activated in acidic environments [34]. The timing of meals affects how effective they are, and they frequently fall short of maintaining sufficient plasma levels during the day and night.

New a flexible dosing, and quick onset to overcome these obstacles [35]. To provide rapid, dose-dependent acid suppression without the need for acid activation or meal coordination, P-CABs reversibly bind to the H^+/K^+-ATPase at the potassium site. They work well with extended-release formulations, are acid-stable, and can be taken twice a day for best control [36]. Antisecretory drugs must provide 24-hour acid control.

PPIs are still the gold standard for treating GERD [37–40], especially erosive esophagitis (EE) [37,39], but they are not always successful, especially when it comes to atypical symptoms. P-CABs have similar safety profiles but show better healing rates and quicker symptom relief. Their pharmacokinetics provide more predictable results by avoiding CYP2C19 variability [41].

Because P-CABs [42] suppress acid, they promise improved mucosal protection for Helicobacter pylori eradication and NSAID-induced ulcer prevention. P-CABs can provide true 24-hour control [43], meeting unmet clinical needs, in contrast to PPIs, which have coverage gaps. Their function in long-term safety and primary prevention is being assessed in ongoing trials.

Table 2: Comparison P-CABs vs PPIs: Differences in the mechanism of action [35]

P-CABS	PPI
Directly (after protonation) affects the H+,K+-ATPase enzyme.	requires conversion to sulfenamide, the active form
P-CABs attach itself to the K+ binding site of H+,K+-ATPase in a competitive manner.	Sulfenamide and H+,K+-ATPase form a covalent bond.
To the proton pump, reversible binding occurs.	Permanent attachment to the proton pump.
super-concentrates in the acid space of parietal cells (100,000 times higher than in plasma).	Concentrate in the acid space of parietal cells (1000 times more than in plasma).
The duration of the effect is correlated with the drug's plasma half-life.	Effect duration is correlated with the sulfenamide-enzyme complex half-life.
Complete impact from the initial dose.	Complete effect following several doses.

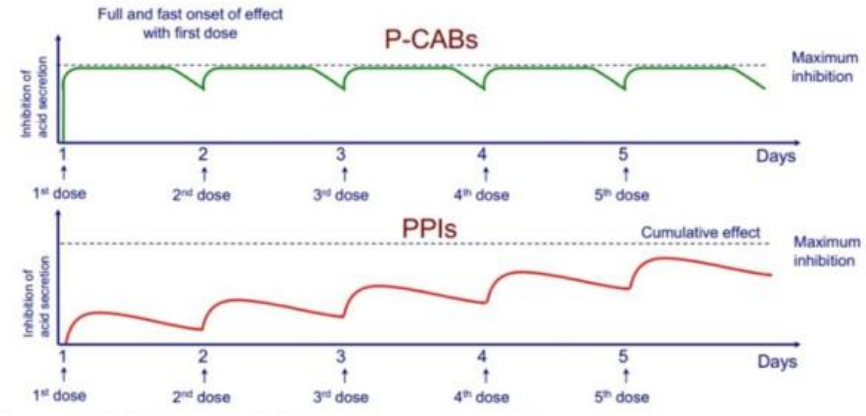

Figure 7: Time course of acid inhibition by P-CABs and PPIs

Mechanism of Action of Potassium-Competitive Acid Blockers (P-CABs)

Through a reversible, potassium-competitive mechanism, P-CABs, a class of acid-suppressing agents, inhibit gastric H^+/K^+-ATPase without the need for prior activation in acidic environments [36]. P-CABs have a faster onset, meal-independent dosing, and more reliable acid control than PPIs, which are prodrugs that require acid-mediated conversion.

These substances are weak bases, and their protonated forms preferentially gather in the parietal cells' acidic canaliculi. There, they attach to the proton pump's K-binding site and prevent the last stage of acid secretion. Their gradual rise in plasma concentration and dose-dependent action help to provide long-lasting suppression [44].

The potency of P-CABs correlates with their pKa values, which influence protonation and canalicular retention [45–47]:

- SCH28080: pKa 5.6
- Linaprazan: pKa 6.1
- Vonoprazan: pKa 9.3 (highly protonated and potent)

Computational Methods

Computational approaches have rapidly evolved as essential complements to experimental techniques for predicting protein–protein interactions (PPIs) and accelerating drug discovery [48]. Despite their accuracy, traditional experimental techniques are constrained by their high expense, labor-intensive nature, and insufficient proteome coverage [49]. Computational models, on the other hand, use sophisticated algorithms and a wealth of biological data to produce predictions that are more accurate, reproducible, and economical [48]. These techniques have made significant contributions to contemporary computer-aided drug design (CADD), which has resulted in the identification of new drug candidates that are currently undergoing clinical testing [50].

Current research also explores new electrophiles to selectively modify less reactive residues like histidine or tryptophan. Computational chemistry and activity-based protein profiling have been instrumental in designing such inhibitors and identifying new druggable sites [51,52].

COMPUTER-AIDED DRUG DESIGN (CADD)

CADD employs structure-based (SB) and ligand-based (LB) strategies to optimize drug discovery. The choice depends on the availability of a target's three-dimensional (3D) structure.

Structure-Based Drug Design (SBDD)

Utilizes experimentally derived protein structures (X-ray, NMR, or cryo-EM) to model and optimize ligand–receptor interactions. Virtual high-throughput screening, molecular docking, and energy minimization are applied to identify small molecules that best complement the binding site. Minor structural modifications enhance steric fit, van der Waals interactions, and electrostatics, improving affinity and selectivity [50,53].

Ligand-Based Drug Design (LBDD)

Used when 3D structures are unavailable. It relies on known active ligands to infer essential chemical features. Methods like pharmacophore modelling and Quantitative Structure–Activity Relationship (QSAR) analyses identify molecular patterns and physicochemical properties associated with biological activity, enabling rational design of new ligands [50,53,54].

Modeling of Pharmacophores

The fundamental spatial arrangement of chemical characteristics needed for molecular recognition by a biological target is represented by a pharmacophore. Models may be ligand-based (derived from active compounds) or structure-based (derived from receptor–ligand interactions). Pharmacophore-based virtual screening has become a key component of lead discovery due to advancements in computational tools. The design of molecules that mimic the essential characteristics that cause binding and bioactivity is guided by these models [50,53].

Relationship between Quantitative Structure and Activity (QSAR)

Biological activity and molecular descriptors (like steric parameters, electronic distribution, and lipophilicity) can be quantitatively correlated using QSAR techniques. While 3D-QSAR (such as CoMFA and CoMSIA) integrates spatial and electrostatic information, 2D-QSAR uses basic descriptors. These methods are still very useful because they enable quick predictions of pharmacokinetic behaviour, toxicity, and activity, particularly in situations where receptor structures are not available [50,53,55].

Molecular Docking

Docking predicts the optimal orientation and binding affinity of ligands within a target's active site. It serves as a core step in SBDD, enabling high-throughput virtual screening and ranking of potential inhibitors based on binding energies. Docking tools reduce large chemical libraries to smaller subsets of likely binders, providing reliable starting points for synthesis and biological validation [50,53].

In Silico ADMET and Selectivity Filters

Predicting Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties is critical for drug optimization [56]. Computational ADMET profiling accelerates development by reducing experimental workload, refining drug-likeness, and minimizing animal testing. Filters such as Lipinski's Rule of Five help pre-screen candidates for desirable physicochemical properties (e.g., molecular weight <500 Da, LogP <5, hydrogen bond donors <5, acceptors <10) [57–59].

Comprehensive platforms like SwissADME, pkCSM, and ADMETlab integrate these functions. SwissADME evaluates oral bioavailability and pharmacokinetics [57]; pkCSM uses graph-based signatures to model ADMET outcomes [57]; and ADMETlab combines over 30 predictive models with an extensive curated database for systematic evaluation [60,61]. Together, these tools form a robust pipeline for virtual screening and preclinical prioritization.

Experimental Validation

Computational predictions are validated through biochemical and cellular assays to confirm inhibitory activity and safety.

Enzymatic Assays

Used for evaluating **covalent inhibitors**, these assays measure parameters like K_i and *k_inact* to determine binding affinity and inactivation kinetics.

- **Direct observation** via mass spectrometry provides accurate measurements of enzyme–inhibitor complexes.
- **Continuous (Kitz–Wilson) assays** track real-time enzyme activity changes.
- **Discontinuous and pre-incubation assays** measure reaction endpoints or time-dependent inhibition [48].

Cell-Based Assays

PPIs such as omeprazole and lansoprazole have demonstrated anti-cancer properties by inhibiting FASN thioesterase (TE) activity. Validation involves:

- **Fluorogenic assays** using fluorescent substrates (e.g., 4-MUH) to measure enzyme inhibition.
- **Colony formation assays** to assess long-term cancer cell proliferation.
- **Apoptosis assays** (DNA fragmentation ELISA, Western blot for cleaved PARP-1) to confirm dose-dependent cell death mechanisms [49].

Safety Profiling

Comprehensive validation includes:

- **In vitro enzyme inhibition, assays** for gastric H^+/K^+ATPase to assess drug mechanism and selectivity.
- **Cytotoxicity and biomarker assays** for dose-dependent toxicity and inflammatory responses.
- **Clinical biomarker studies** (gastrin levels, calcium absorption, bone density) to monitor adverse outcomes.
- **Microbiome monitoring**, since chronic PPI use may increase infection risk through altered gut acidity [50,51].

Computational approaches have become indispensable in modern drug discovery, bridging experimental limitations with predictive modeling. By integrating CADD**,** QSAR**,** pharmacophore modeling**,** docking**,** and in silico ADMET screening, researchers can efficiently design, optimize, and validate new therapeutic agents before clinical testing. Combined with experimental assays, these strategies form a cohesive framework for accelerating the discovery of selective, safe, and effective drug candidates.

Table 3: Computational Methods in PPI Design [48,50,53,55,56,66–68]

Method	Purpose	Application in PPI Design
Molecular Docking	Predicts binding orientation and affinity of ligands to target proteins	Identifies optimal binding of sulfenamide intermediates to cysteine residues on H^+/K^+-ATPase
Pharmacophore Modeling	Defines essential chemical features required for biological activity	Helps design new benzimidazole scaffolds with improved activation and binding characteristics
Virtual Screening	Filters large compound libraries to identify potential hits	Screens prodrug candidates for acid stability and selective pump targeting
QSAR Modeling	Correlates molecular structure with biological activity	Predicts potency and guides chemical modifications of PPI analogs

Molecular Dynamics (MD)	Simulates molecular motion and stability of drug–target complexes	Evaluates conformational changes in H^+/K^+-ATPase and drug binding under acidic conditions
ADMET Prediction	Assesses absorption, distribution, metabolism, excretion, and toxicity	Optimizes pharmacokinetic profiles and minimizes CYP2C19-related variability
Density Functional Theory (DFT)	Analyzes electronic structure and reactivity	Supports understanding of sulfenamide formation and thiol reactivity
Homology Modeling	Builds 3D structures of proteins when crystal structures are unavailable	Constructs models of H^+/K^+-ATPase for docking and structure-based design
Binding Free Energy Calculations	Estimates thermodynamic favorability of ligand binding	Refines docking predictions and ranks PPI candidates based on binding strength
Machine Learning Models	Learns patterns from data to predict drug properties	Predicts efficacy, metabolism, and potential side effects of new PPI candidates

Case Studies: PPIs vs P-CABs in Clinical and Pharmacological Context

Case studies are essential for bridging theoretical pharmacology with real-world therapeutic outcomes. Given the widespread and long-term use of proton pump inhibitors (PPIs), it is critical to evaluate their broader physiological effects and compare them with emerging alternatives like potassium-competitive acid blockers (P-CABs).

- **PPIs** irreversibly inhibit H^+/K^+-ATPase via covalent binding, requiring new enzyme synthesis for recovery.

- **P-CABs** reversibly block the potassium-binding site of the same enzyme, offering rapid, potent, and meal-independent acid suppression.

Key Case Studies

H. pylori Eradication: P-CAB vs PPI

A network meta-analysis showed that a 2-week vonoprazan regimen achieved high eradication rates. While tegoprazan-based regimens showed comparable efficacy to PPIs, vonoprazan demonstrated a more consistent outcome [2].

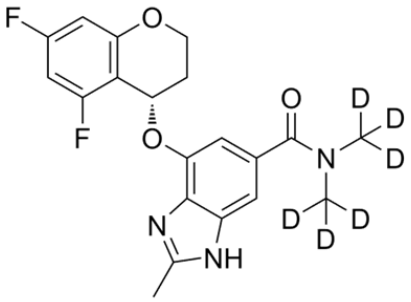

Figure 8: Tegoprazan-d6 (CJ-12420-d6) | Tegoprazan Isotope

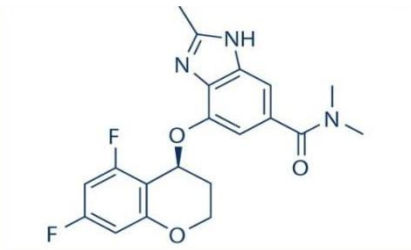

Figure 9: Tegoprazan

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

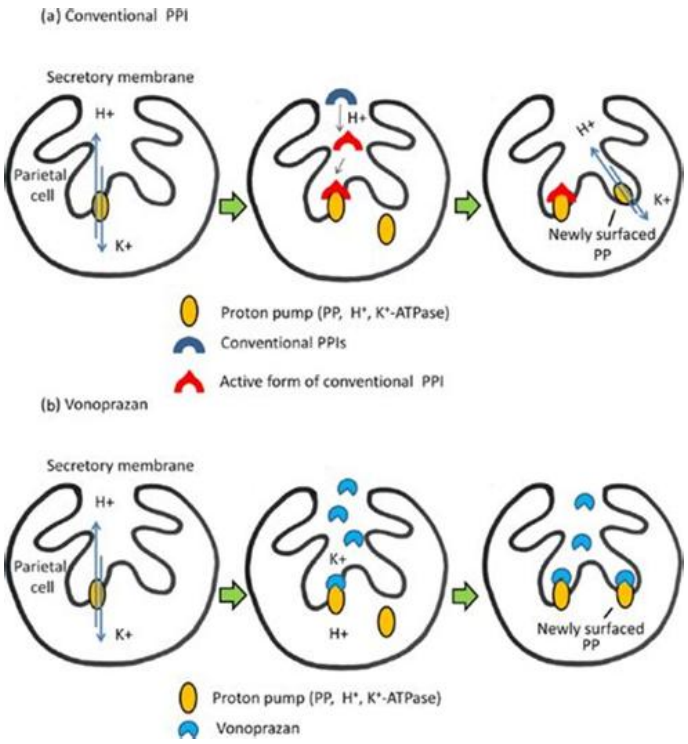

Figure 10: Tegoprazan. K-CAB

Health Care Cost Analysis in GERD

A Japanese real-world study found that PPI-first treatment incurred higher overall healthcare costs compared to P-CAB-first treatment, largely due to non-GERD-related hospitalizations. However, excluding hospitalization, PPI-first therapy was more cost-effective [3].

Potent Acid Suppression Profiles

New-generation PPIs (e.g., dexlansoprazole MR, IR-omeprazole) and P-CABs (e.g., vonoprazan) address limitations of delayed-release PPIs, such as short half-life and poor nocturnal control. P-CABs offer rapid, reversible, and food-independent acid suppression with prolonged pH elevation [4].

7- vs 14-Day Quadruple Therapy for H. pylori

A comparative study found that both 7- and 14-day P-CAB-based bismuth quadruple regimens were effective, with similar or fewer adverse effects compared to 14-day PPI-based regimens, especially in clarithromycin-resistant infections [5].

P-CABs as Next-Generation Acid Suppressants

P-CABs like vonoprazan are acid-stable, fast-acting, and effective in treating GERD, peptic ulcer disease (PUD), and H. pylori infection. Their ability to elevate gastric pH to ≥6.0 and maintain consistent suppression positions them as superior alternatives to PPIs [6].

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

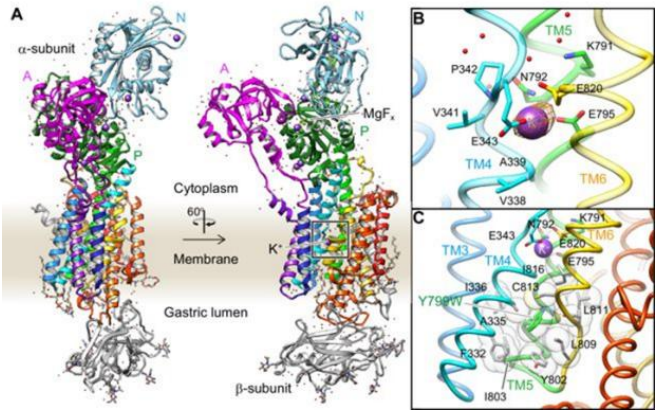

Figure 11: K+-binding site in the crystal structure

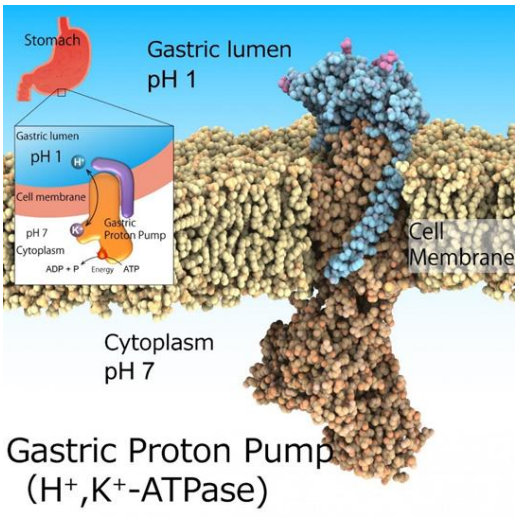

Figure 12: Gastric Proton Pump, H+,K+-ATP

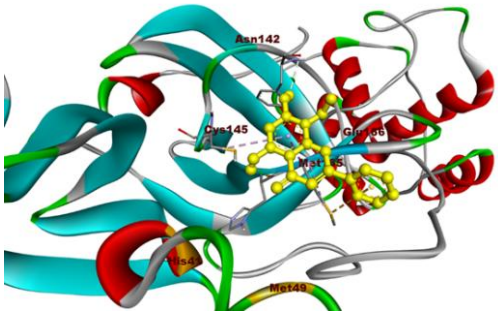

Figure 13: Molecular Docking

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

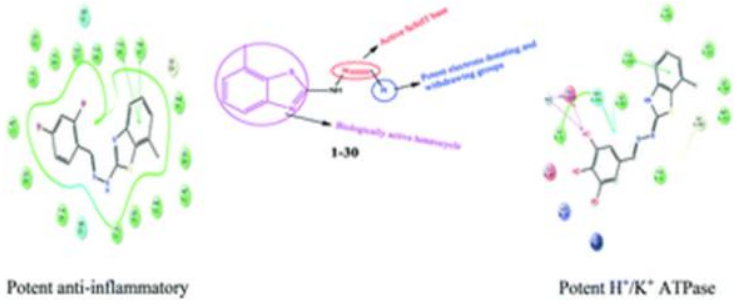

Figure 14: Synthesis of benzothiazole-hydrazone analogues

Challenges, Risks, and Ethical Considerations

Because of their established effectiveness and good safety records, proton pump inhibitors (PPIs) are among the most often prescribed drugs. However, a few clinical, legal, and ethical issues have been brought up by their extensive and frequently unsupervised use. The need for careful administration, better monitoring, and ethical compliance in both research and clinical practice is highlighted by the growing number of reports of side effects and methodological difficulties in PPI studies.

1. Idiosyncratic Hepatotoxicity: A Rare but Serious Concern

Rare cases of idiosyncratic drug-induced liver injury (DILI) have been documented, even though PPIs are usually well tolerated. This problem is demonstrated by the hepatotoxicity linked to pantoprazole: a 35-year-old man who was treated for acute gastritis experienced systemic side effects, including nephritis, pancytopenia, and generalized edema, which ultimately led to hepatic dysfunction. Such reactions, though uncommon, highlight the unpredictable nature of idiosyncratic toxicity, necessitating individualized monitoring during long-term therapy.[1]

2. Potential Long-Term Adverse Effects of PPIs

PPI therapy is still safe for short-term use, but prolonged, unsupervised use can lead to several problems. Due to self-medication and overuse, over-the-counter availability has resulted in negative consequences like hypomagnesemia, bone demineralization, and potential gastrointestinal infections. Chronic PPI use has also been linked to microscopic colitis, small intestinal bacterial overgrowth, and Clostridium difficile infection (CDI). Although evidence linking PPIs to CDI remains inconclusive, meta-analyses indicate a modest but statistically significant increase in risk (pooled OR ≈ 1.5). Thus, long-term use should be carefully considered, particularly in patients who are susceptible or have cirrhosis [2].

3. Regulatory Perspectives on Covalent Drugs

PPIs are well-known examples of covalent inhibitors and understanding how they are regulated can help us understand the larger issues this drug class faces. These days, organizations like the FDA and EMA stress the need to strike a balance between efficacy and off-target reactivity. By facilitating transient covalent bonding with target residues, developments in reversible covalent inhibition (RCI) have allayed worries about immunological reactions and indiscriminate reactivity. Future regulatory focus will likely involve improved computational modelling to identify reactive amino acids, refined reactivity guidelines, and sensitive assays to predict immunogenic or electrophilic stress responses. Research into the creation of new, trackable electrophilic warheads is still ongoing [4].

4. Chemical Reactivity–Selectivity Trade-Offs

The effectiveness of PPIs, such as omeprazole, depends on a finely tuned balance between chemical reactivity and site-specific selectivity. Omeprazole functions as a prodrug, activated only in the acidic environment of the gastric parietal cell, where it covalently inhibits H^+/K^+-ATPase and carbonic anhydrase, while also exerting cytoprotective effects. This pH-dependent activation minimizes systemic reactivity, exemplifying how rational prodrug design can optimize both selectivity and safety [5].

5. Practical Limitations in Molecular Docking Studies

Molecular docking, a crucial tool in drug discovery, continues to face difficulties despite tremendous advancements. It is necessary to address problems with protein flexibility, scoring function accuracy, and entropy or desolvation effects to accurately predict ligand

binding modes. Even though ligand sampling algorithms have significantly improved, dynamic and thermodynamic complexities are still difficult for current scoring functions to capture. Furthermore, protein conformational change modelling is still a computationally demanding and undeveloped field. Continued refinement of benchmark datasets (e.g., DUD, CSAR) and hybrid simulation approaches integrating molecular dynamics and machine learning are essential for improving docking reliability.
PPIs and covalent inhibitors are still very useful in therapeutic medicine, but careful management is necessary due to their long-term use, unpredictable idiosyncratic reactions, and methodological difficulties in computational modelling. Ethical considerations—including patient safety, informed prescribing, and responsible drug design—must guide future research and clinical application. Enhancing computational accuracy, refining toxicity prediction, and ensuring regulatory vigilance will be pivotal in minimizing risks while maximizing therapeutic benefits [6].

Future Perspectives and Recommendations

Advancements in Docking and Drug Discovery

Enhancing protein flexibility modelling, considering ligand-induced conformational changes, and employing quicker grid-based methods will be the main goals of future docking research. Charge transfer and metal coordination simulations will be more accurate thanks to quantum mechanics (QM) [76,77] and hybrid QM/MM techniques. More dependable large-scale drug screening [78] will be made possible by customized docking techniques for protein families [79] and the combination of molecular mechanics and QM.

Development of In Silico Modeling and ADMET Profiling

In order to predict drug-like properties early on, ADMET profiling is moving toward integrated in silico–in vitro–in vivo platforms [80]. Advanced data-mining tools and automated, high-throughput assays will simplify the candidate selection process and lower attrition rates [81]. With AI-driven models and visual outputs for improved interpretation, tools such as SwissADME, pkCSM, ADMET lab, and admet SAR will increase their predictive capabilities [82].

Environmental Safety in the Design of Drugs

In order to guarantee environmental safety, future drug development will place a strong emphasis on ecotoxicity assessment using tools like FAF-Drugs and admet SAR. This will encourage the development of pharmaceuticals that are both environmentally friendly and effective for people [83].

In Drug Design, Covalent Docking Covalent docking provides access to difficult protein sites, high selectivity, and long-lasting effects by simulating irreversible drug–target interactions [84,85]. This strategy is demonstrated by medications [86] such as Dacomitinib, Zanubrutinib, and Aspirin. Although accuracy varies, tools like AutoDock, GOLD, and FlexX are utilized [87–90]. It is anticipated that AI-enhanced techniques will increase prediction accuracy and broaden their applicability to intricate molecules such as peptides [91].

Conclusion

PPIs have revolutionized the treatment of acid-related disorders, but they have drawbacks regarding long-term safety, nocturnal control, and onset. Many of these gaps are filled by P-CABs, which provide faster, reversible, and more reliable acid suppression. Early-stage drug development is being revolutionized by computational drug design, which uses docking, QSAR, pharmacophore modeling, and ADMET prediction. When combined, these developments offer treatments that are safer, more efficient, and more ecologically friendly.

REFERENCES

[1] Protopapadakis Y, Shuster H, Bambach AB, Fitzgerald S, Brayman C, Ewing JA, et al. Effects of Prolonged Proton-Pump Inhibitor Use on Renal Dysfunction and Bone Fragility. Ann Pharmacother. 2025 Apr;59(4):330–6.
[2] Ang SP, Chia JE, Valladares C, Patel S, Gewirtz D, Iglesias J. Association between Proton Pump Inhibitor Use and Risk of Incident Chronic Kidney Disease: Systematic Review and Meta-Analysis. Biomedicines. 2024 Jun 25;12(7):1414.
[3] Wu CC, Liao MH, Kung WM, Wang YC. Proton Pump Inhibitors and Risk of Chronic Kidney Disease: Evidence from Observational Studies. J Clin Med. 2023 Mar 15;12(6).
[4] González-Pérez A, Martínez-Domínguez SJ, Lanas Á, Lanas A, Iñigo P, García-Rodríguez LA. Proton Pump Inhibitor Use and Worsening Kidney Function: A Retrospective Cohort Study Including 122,606 Acid-Suppressing Users. J Gen Intern Med. 2025 Mar;40(4):818–27.

[5] Ahmed S, Asghar S, Khanzada M, Soxi F, Gundala Raja H, Gul M, et al. Comparing Proton Pump Inhibitors and Emerging Acid-Suppressive Therapies in Gastroesophageal Reflux Disease: A Systematic Review. Cureus. 2025 May;17(5): e84311.
[6] Scarpignato C, Hunt RH. Potassium-competitive Acid Blockers: Current Clinical Use and Future Developments. Curr Gastroenterol Rep. 2024 Nov;26(11):273–93.
[7] Domingues G, Chinzon D, Moraes-Filho JPP, Senra JT, Perrotti M, Zaterka S. Potassium-competitive acid blockers, a new therapeutic class, and their role in acid-related diseases: a narrative review. Prz Gastroenterol. 2023;18(1):47–55.
[8] Bridoux M, Simon N, Turpin A. Proton Pump Inhibitors and Cancer: Current State of Play. Front Pharmacol. 2022; 13:798272.
[9] Prinz C, Kajimura M, Scoyt D, Helander H, Shin J, Besancon M, et al. Acid Secretion and the H,K ATPase of Stomach. Vol. 65, THE YALE JOURNAL OF BIOLOGY AND MEDICINE. 1992.
[10] Waldum HL, Hauso Ø, Fossmark R. The regulation of gastric acid secretion - clinical perspectives. Acta Physiol (Oxf). 2014 Feb;210(2):239–56.
[11] Sachs G, Shin JM, Briving C, Wallmark B, Hersey S. The pharmacology of the gastric acid pump: The H+,K+ ATPase. Vol. 35, Annual Review of Pharmacology and Toxicology. Annual Reviews Inc.; 1995. p. 277–305.
[12] Walsh JH. Gastrointestinal Hormones and peptides. 2nd ed. Vol. 1. New York: Raven Press; 1987. 181–257 p.
[13] Prinz C, Kajimura M, Scott DR, Mercier F, Helander HF, Sachs G. Histamine secretion from rat enterochromaffinlike cells. Gastroenterology. 1993 Aug;105(2):449–61.
[14] Håkanson R, Böttcher G, Ekblad E, Panula P, Simonsson M, Dohlsten M, et al. Histamine in endocrine cells in the stomach. A survey of several species using a panel of histamine antibodies. Histochemistry. 1986;86(1):5–17.
[15] Sachsa G, Prinz C, Loo D, Bamberg K, Besancon M, Moo Shin J. Gastric Acid Secretion: Activation and Inhibition. Vol. 67, YALE JOURNAL OF BIOLOGY AND MEDICINE. 1994.
[16] Helander HF. The cells of the gastric mucosa. Int Rev Cytol. 1981;70:217–89.
[17] LR Johnson, James Christensen. Functional Gastric Morphology . Physiology of the gastrointestinal tract. 1987; 1:817–36.
[18] Forte TM, Machen TE, Forte JG. Ultrastructural changes in oxyntic cells associated with secretory function: a membrane-recycling hypothesis. Gastroenterology. 1977 Oct;73(4 Pt 2):941–55.
[19] Scott DR, Helander HF, Hersey SJ, Sachs G. The site of acid secretion in the mammalian parietal cell. Biochim Biophys Acta. 1993 Feb 23;1146(1):73–80.
[20] Sachs G, Chang HH, Rabon E, Schackman R, Lewin M, Saccomani G. A nonelectrogenic H+ pump in plasma membranes of hog stomach. J Biol Chem. 1976 Dec 10;251(23):7690–8.
[21] Wolosin JM, Forte JG. Stimulation of oxyntic cell triggers K+ and Cl- conductances in apical H+-K+-ATPase membrane. Am J Physiol. 1984 May;246(5 Pt 1):C537-45.
[22] Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006 Jun;23 Suppl 2:2–8.
[23] Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: A comprehensive review. Vol. 11, Gut and Liver. Joe Bok Chung; 2017. p. 27–37.
[24] Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K, Kawasaki T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. Ann Intern Med. 1998 Dec 15;129(12):1027–30.
[25] Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2011 Jun;12(6):873–88.
[26] Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol. 2008 Oct;64(10):935–51.
[27] Williams MP, Pounder RE. Review article: the pharmacology of rabeprazole. Aliment Pharmacol Ther. 1999 Aug;13 Suppl 3:3–10.
[28] de la Coba Ortiz C, Argüelles Arias F, Martín de Argila de Prados C, Júdez Gutiérrez J, Linares Rodríguez A, Ortega Alonso A, et al. Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Española de Patología Digestiva. Revista Española de Enfermedades Digestivas. 2016;108:207–24.
[29] Lanza FL, Chan FKL, Quigley EMM. Guidelines for Prevention of NSAID-Related Ulcer Complications. Am J Gastroenterol. 2009 Mar 24;104(3):728–38.
[30] Fossmark R, Martinsen TC, Waldum HL. Adverse effects of proton pump inhibitors—evidence and plausibility. Vol. 20, International Journal of Molecular Sciences. MDPI AG; 2019.
[31] Klotz U, Schwab M, Treiber G. CYP2C19 polymorphism and proton pump inhibitors. Basic Clin Pharmacol Toxicol. 2004 Jul;95(1):2–8.
[32] Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One. 2013;8(4):e62162.
[33] Andrawes M, Andrawes W, Das A, Siau K. Proton Pump Inhibitors (PPIs)-An Evidence-Based Review of Indications, Efficacy, Harms, and Deprescribing. Medicina (Kaunas). 2025 Aug 31;61(9).
[34] Hunt R. Acid suppression for reflux disease: “off-the-peg” or a tailored approach? Clin Gastroenterol Hepatol. 2012 Mar;10(3):210–3.

[35] Scarpignato C, Hunt RH. Editorial: towards extended acid suppression--the search continues. Aliment Pharmacol Ther. 2015 Oct;42(8):1027–9.
[36] Rawla P, Sunkara T, Ofosu A, Gaduputi V. Potassium-competitive acid blockers - are they the next generation of proton pump inhibitors? World J Gastrointest Pharmacol Ther. 2018 Dec 13;9(7):63–8.
[37] Katz PO, Ginsberg GG, Hoyle PE, Sostek MB, Monyak JT, Silberg DG. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. Aliment Pharmacol Ther. 2007 Mar 1;25(5):617–28.
[38] Chapelle N, Ben Ghezala I, Barkun A, Bardou M. The pharmacotherapeutic management of gastroesophageal reflux disease (GERD). Expert Opin Pharmacother. 2021 Feb;22(2):219–27.
[39] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022 Jan 1;117(1):27–56.
[40] Maradey-Romero C, Fass R. New and future drug development for gastroesophageal reflux disease. J Neurogastroenterol Motil. 2014 Jan;20(1):6–16.
[41] Chong E, Ensom MHH. Pharmacogenetics of the proton pump inhibitors: a systematic review. Pharmacotherapy. 2003 Apr;23(4):460–71.
[42] Sachs G, Shin JM, Vagin O, Lambrecht N, Yakubov I, Munson K. The gastric H,K ATPase as a drug target: Past, present, and future. In: Journal of Clinical Gastroenterology. 2007.
[43] Scarpignato C, Hunt RH. Nonsteroidal antiinflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention. Gastroenterol Clin North Am. 2010 Sep;39(3):433–64.
[44] Inatomi N, Matsukawa J, Sakurai Y, Otake K. Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases. Pharmacol Ther. 2016 Dec;168:12–22.
[45] Matsukawa J, Hori Y, Nishida H, Kajino M, Inatomi N. A comparative study on the modes of action of TAK-438, a novel potassium-competitive acid blocker, and lansoprazole in primary cultured rabbit gastric glands. Biochem Pharmacol. 2011 May 1;81(9):1145–51.
[46] Graham DY, Dore MP. Update on the Use of Vonoprazan: A Competitive Acid Blocker. Gastroenterology. 2018 Feb;154(3):462–6.
[47] Shinozaki S, Osawa H, Hayashi Y, Sakamoto H, Miura Y, Lefor AK, et al. Vonoprazan treatment improves gastrointestinal symptoms in patients with gastroesophageal reflux disease. Kaohsiung J Med Sci. 2017 Dec;33(12):616–22.
[48] Xian L, Wang Y. Advances in Computational Methods for Protein–Protein Interaction Prediction. Electronics (Basel). 2024 Mar 12;13(6):1059.
[49] Piehler J. New methodologies for measuring protein interactions in vivo and in vitro. Curr Opin Struct Biol. 2005 Feb;15(1):4–14.
[50] Prada-Gracia D, Huerta-Yépez S, Moreno-Vargas LM. Application of computational methods for anticancer drug discovery, design, and optimization. Bol Med Hosp Infant Mex. 2016;73(6):411–23.
[51] Liu Y, Lv S, Peng L, Xie C, Gao L, Sun H, et al. Development and application of novel electrophilic warheads in target identification and drug discovery. Biochem Pharmacol. 2021 Aug;190:114636.
[52] Mehta N V, Degani MS. The expanding repertoire of covalent warheads for drug discovery. Drug Discov Today. 2023 Dec;28(12):103799.
[53] Lin X, Li X, Lin X. A Review on Applications of Computational Methods in Drug Screening and Design. Molecules. 2020 Mar 18;25(6).
[54] Leelananda SP, Lindert S. Computational methods in drug discovery. Beilstein journal of organic chemistry. 2016;12:2694–718.
[55] Vucicevic J, Nikolic K, Mitchell J B. Rational Drug Design Of Antineoplastic Agents Using 3D-QSAR, Cheminformatics and Virtual Screening- Approaches. Curr Med Chem . 2019;26:387.
[56] Gheidari D, Mehrdad M, Karimelahi Z. Virtual screening, ADMET prediction, molecular docking, and dynamic simulation studies of natural products as BACE1 inhibitors for the management of Alzheimer's disease. Sci Rep. 2024 Nov 2;14(1):26431.
[57] Mvondo JGM, Matondo A, Mawete DT, Bambi SMN, Mbala BM, Lohohola PO. In Silico ADME/T Properties of Quinine Derivatives using SwissADME and pkCSM Webservers. Int J Trop Dis Health. 2021 Aug 3;1–12.
[58] Moroy G, Martiny VY, Vayer P, Villoutreix BO, Miteva MA. Toward in silico structure-based ADMET prediction in drug discovery. Drug Discov Today. 2012 Jan;17(1–2):44–55.
[59] Ahmed AH, Alkali YI. In silico pharmacokinetics and molecular docking studies of lead compounds derived from diospyros mespiliformis. PharmaTutor. 2019;7:31–7.
[60] Dong J, Wang NN, Yao ZJ, Zhang L, Cheng Y, Ouyang D, et al. Admetlab: A platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. J Cheminform. 2018;10(1).
[61] Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: An integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res. 2021 Jul 2;49(W1):W5–14.
[62] Mader LK, Borean JE, Keillor JW. A practical guide for the assay-dependent characterisation of irreversible inhibitors. RSC Med Chem. 2024 Nov 1;

[63] Fako VE, Wu X, Pflug B, Liu JY, Zhang JT. Repositioning proton pump inhibitors as anticancer drugs by targeting the thioesterase domain of human fatty acid synthase. J Med Chem. 2015 Jan 22;58(2):778–84.
[64] Dipasquale V, Cicala G, Spina E, Romano C. A Narrative Review on Efficacy and Safety of Proton Pump Inhibitors in Children. Front Pharmacol. 2022;13:839972.
[65] Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol. 2010 May 21;16(19):2323–30.
[66] Thomas M., Tahsin F. Kellici. Rational Drug Design . Methods in Molecular Biology. 2018;1824:403–17.
[67] A. M, DE S. Integrating in silico molecular docking, ADMET analysis of C.verticillata with diabetic markers and in vitro anti-inflammatory activity. Futur J Pharm Sci. 2024 Jan 5;10(1).
[68] Wang D, Jin J, Shi G, Bao J, Wang Z, Li S, et al. ADMET evaluation in drug discovery: 21. Application and industrial validation of machine learning algorithms for Caco-2 permeability prediction. J Cheminform. 2025 Dec 1;17(1).
[69] Jiang Y, Zhang R, Fang Y, Zhao R, Fu Y, Ren P, et al. P-CAB versus PPI in the eradication of Helicobacter pylori: a systematic review and network meta-analysis. Therap Adv Gastroenterol. 2024;17:17562848241241224.
[70] Miwa H, Shiotani A, Takeda M, Eda M, Kato T, Yajima T. Health Care Cost Analysis of PPI or P-CAB-First Treatment in Patients With Gastroesophageal Reflux Disease. J Clin Gastroenterol. 2023 Apr 1;57(4):370–9.
[71] Khurmatullina AR, Andreev DN, Kucheryavyy YA, Sokolov FS, Beliy PA, Zaborovskiy A V, et al. The Duration of Proton Pump Inhibitor Therapy and the Risk of Small Intestinal Bacterial Overgrowth: A Systematic Review and Meta-Analysis. J Clin Med. 2025 Jul 3;14(13).
[72] Oh CK, Lim H, Seo SI, Lee SP, Bang CS, Shin WG, et al. Efficacy comparison of 7- and 14-day P-CAB based bismuth-containing quadruple regimen with PPI based bismuth-containing quadruple regimen for Helicobacter pylori infection: rationale and design of an open-label, multicenter, randomized controlled trial. BMC Gastroenterol. 2023 Dec 1;23(1).
[73] Liu J, Hahn J. Clinical pharmacokinetics of potassium competitive acid blockers: a systematic review and meta-analysis. Front Pharmacol. 2025 Jul 8;16.
[74] Aslan M, Celik Y, Karadas S, Olmez S, Cifci A. Liver hepatotoxicity associated with pantoprazole: a rare case report. Wien Klin Wochenschr. 2014 Jun;126(11–12):390–2.
[75] Corleto VD, Festa S, Di Giulio E, Annibale B. Proton pump inhibitor therapy and potential long-term harm. Curr Opin Endocrinol Diabetes Obes. 2014 Feb;21(1):3–8.
[76] Patel D, Huma ZE, Duncan D. Reversible Covalent Inhibition─Desired Covalent Adduct Formation by Mass Action. ACS Chem Biol. 2024 Apr 19;19(4):824–38.
[77] Lindberg P, Brändström A, Wallmark B, Mattsson H, Rikner L, Hoffmann KJ. Omeprazole: the first proton pump inhibitor. Med Res Rev. 1990;10(1):1–54.
[78] Huang SY, Zou X. Advances and challenges in protein-ligand docking. Int J Mol Sci. 2010 Aug 18;11(8):3016–34.
[79] Ginex T, Vázquez J, Estarellas C, Luque FJ. Quantum mechanical-based strategies in drug discovery: Finding the pace to new challenges in drug design. Curr Opin Struct Biol. 2024 Aug;87:102870.
[80] Sheng X, Himo F. The Quantum Chemical Cluster Approach in Biocatalysis. Acc Chem Res. 2023 Apr 18;56(8):938–47.
[81] Yuriev E, Agostino M, Ramsland PA. Challenges and advances in computational docking: 2009 in review. J Mol Recognit. 2011;24(2):149–64.
[82] Hartshorn MJ, Verdonk ML, Chessari G, Brewerton SC, Mooij WTM, Mortenson PN, et al. Diverse, high-quality test set for the validation of protein-ligand docking performance. J Med Chem. 2007 Feb 22;50(4):726–41.
[83] Yadav J, El Hassani M, Sodhi J, Lauschke VM, Hartman JH, Russell LE. Recent developments in in vitro and in vivo models for improved translation of preclinical pharmacokinetics and pharmacodynamics data. Drug Metab Rev. 2021 May;53(2):207–33.
[84] Kar S, Leszczynski J. Open access in silico tools to predict the ADMET profiling of drug candidates. Expert Opin Drug Discov. 2020 Dec;15(12):1473–87.
[85] Venkataraman M, Rao GC, Madavareddi JK, Maddi SR. Leveraging machine learning models in evaluating ADMET properties for drug discovery and development. ADMET DMPK. 2025;13(3):2772.
[86] Grabarczyk Ł, Mulkiewicz E, Stolte S, Puckowski A, Pazda M, Stepnowski P, et al. Ecotoxicity screening evaluation of selected pharmaceuticals and their transformation products towards various organisms. Environ Sci Pollut Res Int. 2020 Jul;27(21):26103–14.
[87] Bandyopadhyay A, Gao J. Targeting biomolecules with reversible covalent chemistry. Curr Opin Chem Biol. 2016 Oct;34:110–6.
[88] Kumalo HM, Bhakat S, Soliman MES. Theory and applications of covalent docking in drug discovery: merits and pitfalls. Molecules. 2015 Jan 27;20(2):1984–2000.
[89] Shibata Y, Chiba M. The role of extrahepatic metabolism in the pharmacokinetics of the targeted covalent inhibitors afatinib, ibrutinib, and neratinib. Drug Metab Dispos. 2015 Mar;43(3):375–84.
[90] Daoud NEH, Borah P, Deb PK, Venugopala KN, Hourani W, Alzweiri M, et al. ADMET Profiling in Drug Discovery and Development: Perspectives of In Silico, In Vitro and Integrated Approaches. Curr Drug Metab. 2021;22(7):503–22.
[91] Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009 Dec;30(16):2785–91.

[92] Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. J Mol Biol. 1997 Apr 4;267(3):727–48.
[93] Rarey M, Kramer B, Lengauer T, Klebe G. A fast flexible docking method using an incremental construction algorithm. J Mol Biol. 1996 Aug 23;261(3):470–89.
[94] Schmidt S, Röck K, Sahre M, Burkhardt O, Brunner M, Lobmeyer MT, et al. Effect of protein binding on the pharmacological activity of highly bound antibiotics. Antimicrob Agents Chemother. 2008 Nov;52(11):3994–4000.

How to cite this article:
Nandini Banerjee et al. Ijppr.Human, 2026; Vol. 32 (1): 349-366.
Conflict of Interest Statement: All authors have nothing else to disclose.