Chapter 5
H^+/K^+-ATPase Inhibitors from Plants: A Potential Source for Drug Discovery

Michael Buenor Adinortey and Benoit Banga N'guessan

Abstract Apart from regulatory biomolecules, namely acetylcholine, histamine, and gastrin that stimulate gastric acid secretions, H^+/K^+-ATPase also referred to as the proton pump plays a central role in controlling gastric secretions. Any disarray in the secretions of these biomolecules can lead to an imbalance between the aggressive secretions and defense/protective factors, thereby causing hyperacidity. Several drug regimens that target these regulatory biomolecules are available, but the most frequently recommended by health practitioners have been synthetic proton pump inhibitors. The use of synthetic proton pump inhibitors (PPIs) has revolutionized the management of peptic ulcers, nevertheless, there are still various challenges associated with long-term usage that calls for pharmacotherapeutic alternatives. This chapter presents an overview of the structure of H^+/K^+-ATPase highlighting its central role as one of the most appropriate drug targets necessary for control of hyperacidity. In addition, the role of plant natural nutraceutical products as inhibitors of H^+/K^+-ATPase is presented. This review also presents evidence that compounds belonging to different classes of natural products make significant contributions to alleviate gastric acid secretion-related diseases, and thus these compounds or their derivatives could be useful "seed" compounds for developing new drugs and nutraceutical supplements for prevention and management of peptic ulcer diseases.

Keywords H^+/K^+-ATPase · Proton pump inhibitors · Peptic ulcer diseases

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5.1 Introduction

In the last three decades, many pieces of research have been carried out to expand our knowledge of the biology of gastric acid secretion and of acid-related disease. Aside from gastric acid secretion's role in the stomach, there are other functions, including gastric motility, excretion of bile salts, and others, which are beyond the scope of this chapter. One of the biological roles of the stomach is the digestion of food. Gastric acid supports digestion by ensuring an optimal pH for lipase and pepsin to catalyze breakdown of food. Gastric acid secretion is influenced by both the central and peripheral nervous systems. The process is regulated by signal transduction biomolecules, namely acetylcholine, gastrin, histamine, and somatostatin (Engevik et al. 2020). The stimulatory effect of acetylcholine and gastrin is intermediated by an upswing in cytosolic calcium, while the effect of histamine is mediated through activation of adenylate cyclase and production of a second messenger called cyclic adenosine monophosphate (cAMP). It is important to note that the foremost stimulus of gastric acid secretion is gastrin, which does not directly stimulate parietal cells, but mobilizes histamine from oxyntic mucosa through enterochromaffin-like cells (Sachs et al. 2007; Schubert and Peura 2008).

The decisive element in gastric acid secretion is the stimulation of protein H^+/K^+-ATPase also known as proton pump which controls the exchange of cytoplasmic H^+ for extracellular K^+. The protons secreted into gastric lumen by the proton pump combine with luminal Cl^- to form hydrochloric acid in the stomach. After adequate gastric acid is secreted, a feedback mechanism is used to stop it. A key inhibitor of gastric acid secretion is the hormone somatostatin. A decline in intragastric pH stimulates the release of somatostatin from antral D cells. It is clear then that somatostatin inhibits not only gastric acid secretion but also slows gastrin release (Wallmark et al. 1985; Engevik et al. 2020). Unreservedly it can be said that histamine, acetylcholine, and gastrin all function through H^+/K^+-ATPase to allow parietal cells to produce HCl as shown in Fig. 5.1. Any disarray in the secretions of these biomolecules [histamine, acetylcholine, and gastrin] can lead to an imbalance between the aggressive secretions (pepsin, gastric secretions) and defense/protective factors (bicarbonates, mucus secretions, mucosal blood flow, cellular regeneration of the epithelial layer, and endogenous protective agents such as prostaglandins and epidermal growth factor) causing hyperacidity (Chung and Shelat 2017). The gastric H^+/K^+-ATPase enzyme is a central regulatory biomolecule that controls gastric secretions and thus it is responsible for the release of H^+ into the lumen of the stomach leading to hyperacidity and gastric ulcerations. Inhibition of gastric H^+/K^+-ATPase is reported to correlate with healing and symptomatic relief in both erosive esophagitis and gastroesophageal reflux disease in patients (Herszényi et al. 2020).

Globally, several synthetic proton pump inhibitors (PPIs) such as Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, and Pantoprazole are available for managing gastric acid-related diseases. Though PPIs are among the most commonly used and overprescribed medications for PUDs (Spechler 2019), they are also the most effective prophylactic agents (Strand et al. 2017). While the short term side effects of

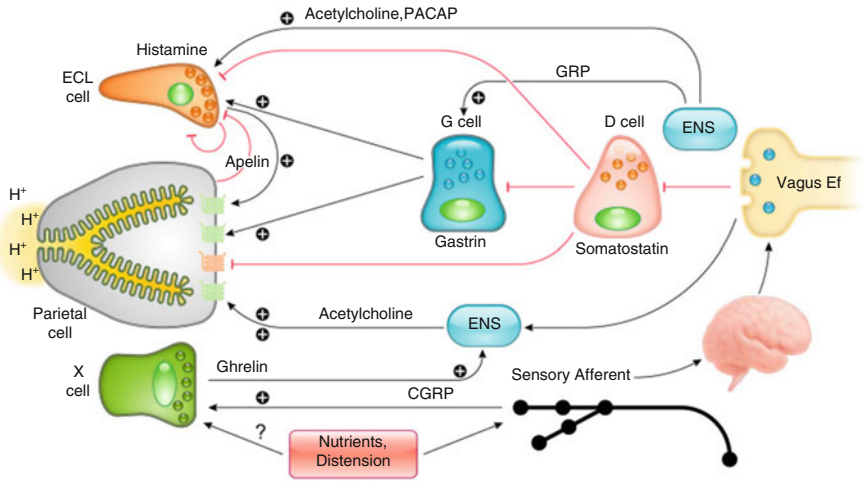


Fig. 5.1 Cellular components that control gastric acid secretions. Numerous cell types regulate gastric acid secretion. Enterochromaffin-like (ECL) cells through histamine and X cells that secrete ghrelin activate parietal cells via paracrine and neural pathways, respectively. (Adapted from Engevik et al. 2020)

PPIs usage such as headache, diarrhea, constipation, and abdominal discomfort are minor and easily managed (Hunt et al. 2015; Maes et al. 2017), systematic and large studies have suggested an association between long-term PPIs usage and several adverse effects such as higher risk of chronic kidney disease (CKD) and dementia, which has been a basis of major concern to patients and physicians (Lazarus et al. 2016; Freedberg et al. 2017; Yu et al. 2017; Moayyedi et al. 2019). This necessitates interest in alternative gastric H^+/K^+ ATPase inhibitors from natural sources which are of nutraceutical value and may be desirable for the prevention of gastric acid-related diseases. It is therefore important to identify plant food components that inhibit gastric H^+/K^+-ATPase.

A potential natural source of H^+/K^+-ATPase inhibitors is provided by the abundance of plants in nature. This chapter presents an insightful overview of the protein structure of H^+/K^+-ATPase highlighting its central role as one of the most appropriate drug targets necessary for the control of hyperacidity. In addition, the impact of different nutraceutical plant products on gastric H^+/K^+-ATPase enzyme is offered as evidence for serious consideration in the drug discovery pipeline globally. Furthermore, selected isolated compounds from plant sources of nutraceutical importance reported to possess H^+/K^+-ATPase inhibitory activity are captured with information on their potency. The pharmaceutical industrial prospects have also been elaborated on.

5.2 Structure of Gastric H^+/K^+-ATPase and Its Role as a Drug Target

The gastric H^+/K^+-ATPase is an enzyme expressed on the apical canalicular membrane of parietal cells. It belongs to P-type ATPase family. This enzyme which is an α,β-heterodimeric protein uses energy derived from ATP hydrolysis to pump intracellular hydrogen ions into the lumen, in exchange for extracellular potassium ions (Abe et al. 2018). Hydrochloric acid is formed through the interaction between Cl^- ions of arterial blood and H^+ from parietal cells.

The α subunit of the enzyme is bonded to the β subunit. The α subunit of a molecular weight (Mwt) 100 kDa contains the catalytic site. It is comprised of ten membrane spanning segments (TM1 to TM10) and three cytosolic domains, namely nucleotide binding-N, phosphorylation-P, and activation-A. The α subunit also has conserved sequences along with the other P_2 type ATPases for the ATP binding site and the phosphorylation site. The phosphorylation site is reported to be at Asp386, which is well conserved in other P-type ATPases (Abe et al. 2018). The β subunit, which has a Mwt of 35 kDa is non-covalently bonded to the α subunit in the region of the sequence Arg898 to Arg922 in the α subunit (Bamberg and Sachs 1994). It contains roughly 290 amino acid residues with a single transmembrane segment that is located at the region near the N-terminus (Shin and Sachs 1994).

Stimulation of gastric acid secretions encompasses the translocation of H^+/K^+-ATPase to the apical membrane of the parietal cell. When the cell is at rest or when unstimulated, H^+/K^+-ATPase is located in vesicles inside the cell. When the cell is stimulated, these vesicles fuse with the plasma membrane, thereby causing an increase in the surface area of the plasma membrane and the number of H^+/K^+-ATPase in the membrane (Abe et al. 2018; Engevik et al. 2020). Implicitly it is clear that gastric H^+/K^+-ATPase enzyme is a key regulatory protein that controls gastric secretions and thus it is responsible for the release of H^+ into the lumen of the stomach leading to hyperacidity and gastric ulcerations. The central role played by the H^+/K^+-ATPase enzyme (proton pump) in gastric acid secretions makes it a key drug target for controlling hyperacidity-related disorders of the stomach.

5.3 Mechanism of Action of H^+/K^+-ATPase Inhibitors

It is worth noting that early treatments of peptic ulcers and hyperacidity-related disorders started with the use of anti-acids, which act to neutralize gastric acid and acetylcholine antagonists. These classes of drugs became outdated in the early1980s by histamine receptor antagonists (H_2RAs) such as cimetidine and ranitidine. By the late 1980s, H^+/K^+ ATPase inhibitors also known as proton pump inhibitors (PPIs) began to emerge. PPIs are prodrugs, which are bioactive only after protonation. They block gastric H^+/K^+-ATPase, inhibiting gastric acid secretions. This outcome enables healing of peptic ulcers, gastroesophageal reflux disease (GERD), Barrett's

esophagus, and Zollinger–Ellison syndrome, as well as other related diseases as part of combination regimens (Sachs et al. 2000). PPIs are a class of drugs that cause a profound and prolong reduction of gastric acid production. They perform this role by irreversibly binding to and inhibiting gastric H^+/K^+-ATPase that resides on the luminal surface of the parietal cell membrane.

In humans, the stomach organ is the only acidic space with a pH lower than 4. With the recognition that the known H^+/K^+-ATPase inhibitors are weak bases with a pK_a between ~4.0 and 5.0, it implied that they would accumulate in the acidic space (Shin et al. 2004). This acid space dependent concentration of the PPIs is the first vital property that controls their therapeutic index, offering a concentration at the luminal surface of H^+/K^+-ATPase pump that is about 1000-fold that in the blood. The second vibrant phase is the low pH dependent conversion from the accumulated prodrug to the activated species that is an extremely reactive cationic thiophilic reagent. This implies that protonation of these compounds is vital for their activation to form disulfides with cysteines of H^+, K^+-ATPase. When the rate of conversion of different compounds was measured as a function of pH, it was uncovered that the pH dependence of activation reflected protonation of the benzimidazole moiety (Shin et al. 2004; Sachs et al. 2007) which explains the different activation rates among synthetic PPIs.

Subsequent to accumulation in the stimulated secretory canaliculus of the parietal cell and binding to the pump, the protonation activates it to form the thiophilic drug that reacts with luminally accessed cysteines on H^+/K^+-ATPase. It implies that the presence of acid secretion is critical for their action. This explains why in prescription, PPIs are given ~30 min before mealtime to ensure that H^+/K^+-ATPase pumps are active during peak concentrations of the PPIs in the blood (Fellenius et al. 1981; Shin et al. 2004). The protonation step results in selective accumulation in the secretory canaliculus of the parietal cell. In acid, there is an acid catalyzed conversion to the sulfenic acid and hence to the sulfenamide. Either of these can inhibit the H, K ATPase although it appears more likely that the sulfenic acid is the primary inhibitor (Sachs et al. 2000).

5.4 Plant Nutraceutical Products as Proton Pump Inhibitors

A nutraceutical product can be defined as a substance that has a physiological benefit or provides protection against chronic diseases (Hay et al. 2019). The use of natural products as nutraceuticals for the prevention of various ailments is as old as human civilization. Generally, natural products are everything produced by life such as wood, bioplastics, cornstarch, milk, and plants extract. Most of these natural products are organic compounds synthesized by a living organism via a process which more or less transforms their biological activities. The chemical constituents of plants that produce certain physiological actions on the human body are known as

phytochemicals. There are thousands of phytochemicals in plants that may not be required as essential nutrients but may enhance the health status of organisms. The important bioactive compounds obtained from plants, called phytochemicals, are terpenes, alkaloids, and phenolics such as tannins and flavonoids (Hay et al. 2019). Extensive use of these natural products as either a spice or food or medicine has several beneficial effects.

The use of plant-based nutraceuticals forms the basis of many modern pharmaceuticals. It is now considered a keystone of health care services all over the world. There is the need to make available evidence-based data on these nutraceuticals in order to promote their development into generally acceptable food supplements or drugs for prevention of diseases including peptic ulcers. Studies on plants used as food and medicine have led to the discovery of proton pump inhibitors from plant sources. Spectrophotometric analytical technique is mostly used to estimate gastric H^+/K^+ ATPase inhibitory activity in vitro and in vivo.

Increased acid secretion in part plays a role in the pathogenesis of gastric ulcers. The unavailability of data on these plant natural products in a one stop-document despite the reported evidence of efficacy necessitates the need to amass information on them and their constituents that possess proton pump inhibitory effects. This section highlights selected medicinal plants used also as food with reported gastric H^+/K^+-ATPase inhibitory activity. A list of selected plants with nutraceutical importance reported to have significant gastric H^+/K^+ ATPase inhibitory activity is shown on Table 5.1. Largely, researchers have reported on the potency of many plant extracts by determining the concentration needed to inhibit 50% (IC_{50}) of the activity of gastric H^+/K^+ ATPase. This section presented IC_{50} data available in μg/mL for easy comparison of their potencies.

There are several mechanisms involved in the inhibition of acid secretion induced by edible natural ingredients. Several studies have shown that some edible natural ingredients prevent the development of gastric ulcers via inhibition of acid secretion in various animal models. Some of these edible plants include *Solanum nigrum* aerial parts, *Arctium lappa* roots, *Garcinia* kola seeds, *Garcinia mangostana* fruit, seeds of *Azadirachta indica*. Hot water extract of *Garcinia mangostana* fruit peel recorded IC_{50} value less than 10 μg/mL compared to its ethanolic extract which showed a higher IC_{50} value of 19.96 μg/mL (Nanjarajurs et al. 2014). The leaf extract of *Carissa carandas* showed potency of 25 μg/mL (Shukla et al. 2016). Plants, namely *Acalypha wilkesiana* (Gupta and Pradeepa 2013), *Arctium Lappa* L. (Dos Santos et al. 2008), *Annona squamosa* (Yadav et al. 2012), *Decalepis hamiltonii* (Wight & Arn.) (Naik et al. 2007), *Delonix* regia (Sachan et al. 2017) *Cecropia glazioui* (Souccar et al. 2008), *Cissus quadrangularis* L. (Yadav et al. 2012), *Pongamia pinnata* (L.) Pierre (Belagihally et al. 2011), and *Tectona grandis* leaves (Lakshmi et al. 2010) exhibited an inhibition on H^+/K^+-ATPase with IC_{50} values ranging from 30 to 70 μg/mL. It is interesting to note that 50% hydroethanolic extract of *Garcinia mangostana* (Nanjarajurs et al. 2014) showed IC_{50} value of 164 μg/mL markedly different from that of 70% hydroethanolic extract. Fruits of *Xylocarpus granatum* plant (Lakshmi et al. 2010), *Hedranthera barteri* (Onasanwo et al. 2011), and *Solanum nigrum* fruits (Jainu and Devi 2006) also showed

Table 5.1 Selected plants with H^+/K^+ ATPase inhibitory activity

Plant name	Family	Part used	Extraction solvent	Study model	IC50 (μg/mL)	References
Scoparia dulcis L.	Scrophulariaceae	Aerial parts	Aqueous	In vivo	500	Mesía-Vela et al. (2007)
Arctium Lappa L.	Asteraceae	Root	Chloroform	In vitro	53	Dos Santos et al. (2008)
Cecropia glazioui	Cecropiaceae	Aerial	*n*-Butanol	In vitro	58.8	Souccar et al. (2008)
Annona squamosa	Annonaceae	Twigs	Ethanol	In vitro	31.43	Yadav et al. (2012)
		Twigs	Chloroform	In vitro	55.98	
		Twigs	Hexane	In vitro	62.24	
Acalypha wilkesiana	Euphorbiaceae	Leaf	Water	In vitro	51.5	Gupta and Pradeepa (2013)
Carissa carandas	Apocynaceae	Leaf	Methanol/acetone	In vitro	25	Shukla et al. (2016)
Cissus quadrangularis L.	Vitaceae	Tubers	Methanol	In vitro	38	Yadav et al. (2012)
Decalepis hamiltonii	Asclepiadaceae	Roots	Aqueous	In vitro	36	Naik et al. (2007)
Delonix regia	Fabaceae	Stem bark	Ethanol	In vitro	68.31	Sachan et al. (2017)
Garcinia kola Heckel.	Guttiferae	Seeds	Petroleum ether	In vitro	43.8	Onasanwo et al. (2011)
Garcinia mangostana	Guttiferae	Fruit peel	Hot water (60 °C)	In vitro	7.6	Nanjarajurs et al. (2014)
			Ethanol (70%)	In vitro	19.96	
			Alcohol (50%)	In vitro	164.58	
Hedranthera barteri	Apocynaceae	Roots	Dichloromethane	In vitro	89.69	Onasanwo et al. (2011)
Pongamia pinnata (L.)	Leguminosae	Seeds	Petroleum ether	In vitro	39.5	Belagihally et al. (2011)
Solanum nigrum	Solanaceae	Aerial parts	Aqueous	In vitro	121.81	Jainu and Devi (2006)
Tectona grandis	Verbenaceae	Leaf	Ethanol/butanol	In vitro	499.36	Lakshmi et al. (2010)
			Butanol		69.03	
Xylocarpus granatum	Meliaceae	Fruit	Chloroform	In vitro	89.37	Lakshmi et al. (2010)

substantial potencies between 71 and 200 μg/mL. Plants that exhibited poor inhibitory activity against gastric H^+/K^+-ATPase with IC_{50} value above 201 μg/mL are *Scoparia dulcis* L. (Mesía-Vela et al. 2007), ethanolic extract of *Tectona grandis* (Lakshmi et al. 2010).

Generally, the plant that showed the highest potency among all available data was hot water *Garcinia mangostana* fruit peel an indication of its potential to be considered in the discovery pipeline. It is interesting to note that most plants that showed potency between 7 and 30 μg/mL were better than the standard drugs used as a positive control in that experiment. This calls for further research into nutraceuticals with evidence-based data on proton pump inhibitory potentials.

5.5 Nutraceuticals Compounds as Proton Pump Inhibitors

Plant medicines that are pure isolated compounds have remained useful and unmatchable sources of molecules for effective prevention and treatment of disease burdens. Plant-derived polyphenols have drawn attention owing to their biological properties, including health-promoting benefits. Most pharmaceutical drugs including opium, aspirin, digitalis, and quinine, which are currently available in orthodox medicine, have a long history of use as herbal medications. Carbenoxolone, the first systemically effective anti-ulcer agent, was isolated from the plant, *Glycyrrhiza glabra*. It is the first plant that proved effective in the treatment of gastric ulcers. Gefarnate, another effective compound isolated from the juice of wild cabbage, was found to be effective against gastric ulcers. It was shown to improve the gastric defensive mechanism, by increasing mucus synthesis in the mucosa through an enhanced synthesis of prostaglandins (Damle 2014).

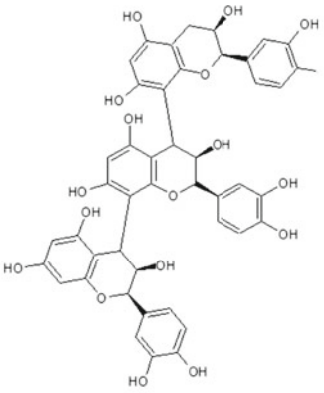
Work on new bioactive compounds from plants has led to the isolation and structure elucidation of a number of new compounds. A list of phytoconstituents having significant gastric H^+/K^+ ATPase inhibitory activity is provided on Table 5.2 and molecular structures of some of these compounds are shown in Fig. 5.2. Among compounds shown on Table 5.2, flavonoids seem to have better gastric H^+/K^+ ATPase inhibitory effects. This could be attributed to the fact that plant-derived phenolic compounds have numerous beneficial properties by virtue of their ability to act as antioxidants. In the gastric H^+/K^+ ATPase, there is a lysine 791 located in the fifth transmembrane segment that replaces a serine present in the Na^+/K^+ ATPase isoforms. This lysine of the H^+/K^+ ATPase seems to characterize the H^+/K^+-enzyme specificity for outward transport of the hydronium ion (Shin et al. 2009). Thus, the potent inhibition of the gastric H^+/K^+ ATPase enzyme might be a result of the interactions that occur between the flavonoids and the lysine residues. Further experiments such as computer-assisted homology modeling, molecular docking, and molecular dynamics simulation could be done to understand the actual mechanisms by which these flavonoids and alkaloidal compounds from a large family of plants are able to inhibit the gastric H^+/K^+ ATPase enzyme. However, the synergistic use of these phytoconstituents could also be explored.

Table 5.2 Selected nutraceutical compounds with H^+/K^+-ATPase inhibitory activities

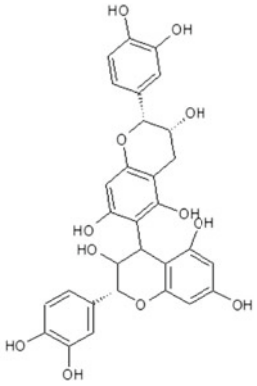
Compound	Plant	Family	IC_{50} (μg/mL)	References
Alkaloid				
Uleine	*Himatanthus lancifolius*	Amaranthaceae	197	Baggio et al. (2005)
Peganine	*Peganum harmala*	Zygophyllaceae	73.47	Singh et al. (2013)
(+)-*O*-methylarmepavine	*Annona squamosa*	Annonaceae	111.83	Yadav et al. (2012)
N-methylcorydaldine	*Annona squamosa*	Annonaceae	60.9	
Isocorydine	*Annona squamosa*	Annonaceae	88.42	
Flavonoids				
Procyanidin B5	*Cecropia glaziovii*	Cecropiaceae	36.9	Souccar et al. (2008)
Procyanidin B3 + cathechin	*Cecropia glaziovii*	Cecropiaceae	34.8	
Procyanidin B2	*Cecropia glaziovii*	Cecropiaceae	23.5	
Epicatechin	*Cecropia glaziovii*	Cecropiaceae	43.8	
Procyanidin C1	*Cecropia glaziovii*	Cecropiaceae	40.3	
Orientin	*Cecropia glaziovii*	Cecropiaceae	31	
Isoorientin	*Cecropia glaziovii*	Cecropiaceae	18.1	
Isovitexin	*Cecropia glaziovii*	Cecropiaceae	25.9	
Verbascoside	*Tectona grandis*	Verbenaceae	60.98	Singh et al. (2010)
Terpenes				
Gedunin	*Xylocarpus granatum*	Meliaceae	56.86	Lakshmi et al. (2010)
Photogedunin	*Xylocarpus granatum*	Meliaceae	66.54	
Azadiradione	*Azadirachta indica seed*	Meliaceae	87.75	Singh et al. 2015)
Anthraquinone				
Chrysophanol	*Rheum emodi*	Polygonaceae	187.13	Mishra (2016)
Emodin	*Rheum emodi*	Polygonaceae	110.30	

5.6 Conclusion

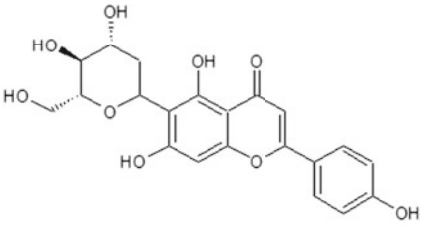
Promising plant species and numerous phytoconstituents as H^+/K^+ ATPase inhibitors are presented in this chapter. The foremost class of natural products widely reported to have H^+/K^+ ATPase inhibition potential is flavonoids. This chapter has collected data to show that edible natural products are effective for the prevention of gastric ulcers induced by hyperacidity. Because these natural products are generally safe and widely available, they could be a promising regime strategy for the prevention and management of hyperacidity-related disorders, particularly for individuals who require long-term usage of PPIs once clinical data is amassed on it.



Procyanidin C1



Procyanidin B5



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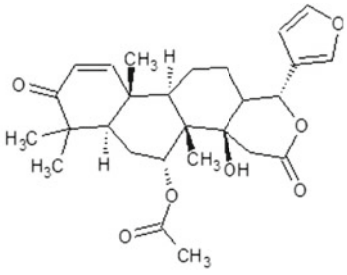

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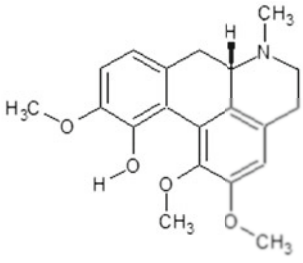

Gedunin

Fig. 5.2 Molecular structures of some selected compounds

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