Chapter 7

Natural Products as a Potential Enzyme Inhibitors from Medicinal Plants

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67376

Abstract

Enzyme inhibitory agents are attractive because of their application in treating different ailments. The absence of enzymes produce a number of diseases. Medicinal plants are a rich source of producing secondary metabolites which showed broad-spectrum enzyme inhibitory potential. The position of enzyme inhibitors as new drugs is vast since these compounds have been used for the treatment of various physiological disorders. Bioactive secondary metabolites can deliver excellent pharmacophore patterns for drugs related to numerous illnesses. This book chapter is planned to document the enzyme inhibitory potential of natural compounds, medicinal plant extract, and its isolated compounds.

Keywords: natural products, enzyme inhibitors, medicinal plants

1. Introduction

Medicinal plants are a rich source of producing bioactive natural products in most precise and selective way. Since the mid-nineteenth century, many natural products have been purified from plants, and most of them exist to be used as active elements of the modern medication. The search of excellence, real, inexpensive, and simply accessible natural compound enzyme inhibitor is one of the drug finding and strategy investigation works in the study organizations through the world [1].

Medicinal plants, extracts, and its fractions are used by 80% of the world population for their simple health necessities. The association among human, medicinal plants, and derived drugs from medicinal plants defines the past of men. Medicinal plants are the significant basis of natural drug molecules. The medicinal plants are expected to comprise secondary metabolites which have properties to use in modern medication for the cure of

various diseases which are not treatable. Throughout the historical period, old-style systems of medicine have developed a topic of global significance. Present approximations recommended that in numerous emerging republics a huge population trusts seriously on traditional specialist and medicinal plants to chance the main health care wants, though modern drug may be obtainable in these countries. Herbal medicines must frequently preserved approval for important and national reasons. Presently, several people in the advanced countries have initiated to go to another or complementary treatments, containing therapeutic herbs [2]. Ayurvedic medication for drug adjustment switches to medicinal plants. Ayurvedic medicine is a combination of numerous elements which is ready from medicinal plants, but the active compounds when purified from that medicinal natural plant source fail to provide the wanted activity. In the nonappearance of pharmacological data on several medicinal plants and isolated compounds which is not likely to regulate the vigorous compounds consuming wanted biological potency. Earlier trainings presented the poisonous properties of chemotherapy and radiation in handling of cancer by decrees by Ayurvedic medication, and wound curing might be complete by using Ayurvedic medicine. Modern discipline production is an important part in this procedure, to grow natively establishing materials for wanted quality [3].

Enzyme inhibitors are mainly bioactive secondary metabolites that bind with an enzyme and decrease its bioactivity. Subsequently, blocking enzyme activity can kill a pathogen or correct a metabolic imbalance; many drug molecules are enzyme inhibitors, and mainly enzyme activators connect to various enzymes, increase their enzymatic actions, and subtract link and subsequently distort to products in the catalytic cycle of the enzymes. The linking of inhibitors can finish a substrate from the enzyme-active site and stays the enzyme in catalyzing in chemical reaction. Enzyme inhibition is both an irreversible and reversible process. The irreversible inhibitors react with enzyme and adjust it chemically by a covalent likening formation. Then, these inhibitors adjust important amino acid remnants wanted from an enzymatic reversible inhibitors which are non-covalently bonded; different types of inhibition are shaped depending on whether inhibitors link non-covalently, and dissimilar types of inhibition are shaped depending on whether these inhibitors bind to the enzyme and produced enzyme substrate complex or both [4].

Many natural products are enzyme inhibitors; the finding and development are dynamic areas of pharmacology and biochemistry. Medicinal enzyme inhibitors are frequently mediated by its specificity and its effectiveness that designated the absorption desirable to inhibit the enzyme. Great specificity and potency confirm that a medicinal drug will have few side effects and possess low toxicity. Natural enzyme inhibitors are involved in the guideline of much metabolic procedure. Actually, enzyme is a metabolic pathway which can be inhibited by many downstream yields. These types of bad response slow the manufacture line when product activates to shape up and a significant way to reservation homeostasis in cell. An additional cellular enzyme inhibitor is protein which specially binds and inhibits an enzyme objective. These help regulator enzymes which may be harmful to cell alike proteases. The well-categorized example of this is the ribonuclease inhibitor that link ribonucleases in the tightest recognized protein contact. Many natural enzyme inhibitors may also be poisonous and are used as defenses besides predators as habits of killing several preys [4].

http://dx.doi.org/10.5772/67376

2. Discovery and design of new enzyme inhibitors

Discovery of new drugs is actually the product of a very long drug growth procedure; the first step among which is the discovery of new enzyme inhibitors. In the past time, the only way to discover new drugs was a trial-and-error method, which proceeds to screen enormous libraries of chemical constituents against a marked enzyme and expect that maybe some valuable lead drugs will arise. This physical force method is still fruitful and has been lengthy by combinatorial chemistry methods that rapidly yield huge statistics of new, known, and novel molecules and high-throughput screening expertise to quickly screen these enormous chemical libraries for valuable new inhibitors [5].

Recently, it is reported that an alternative approach has been documented: rational new drug uses the three-dimensional chemical structure of an enzyme-active position to expect which compound potency to be the new inhibitors [6]. These predictions are then screening, and some of these screenings of compounds may be proven as novel inhibitors. These new inhibitors are then used to attempt to get a chemical structure of enzyme in an inhibitor/enzyme complex to show how the chemical constituents are connecting to the active position, presenting alteration to be complete to the inhibitor to try to optimize binding. This test and recovered cycle are then repeated until a suitably strong inhibitor is formed [7]. The computer-based methods of expecting the attraction of an inhibitor for an enzyme are also existence advanced; these are molecular docking [8] and molecular mechanics.

3. Main uses of enzyme inhibitors

The enzyme inhibitors are abundantly original in nature and considered as well as produced as a main part of pharmacology and biochemistry. Natural poisons are frequently enzyme inhibitors which have grown to defend a plant or animal against predators. These natural toxins comprised certain known poisonous compounds. Artificial inhibitors are mostly used as new drugs but also be used as insecticides such as malathion, herbicides, or glyphosate and may be used as disinfectants like triclosan. Some other artificial enzyme inhibitors block acetylcholinesterase, an enzyme which disrupts dejected acetylcholine, and are used as nerve agents in chemical warfare [9]. Pistagremic acid and di-naphthodiospyrol are isolated compounds having enzyme inhibitory activity (**Figure 1**). Coenzyme folic acid is also linked to the anticancer drug methotrexate (**Figure 2**).

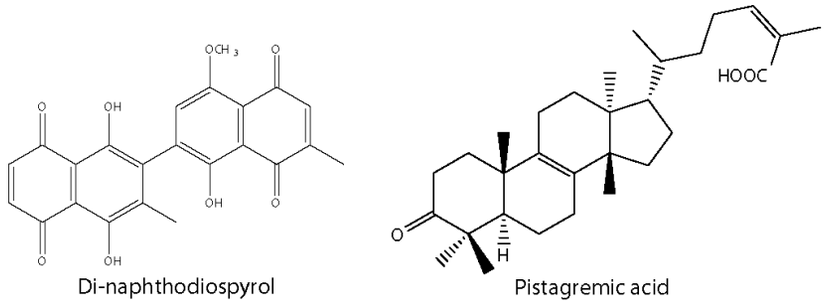

Figure 1. The chemical structure of natural enzyme inhibitor.

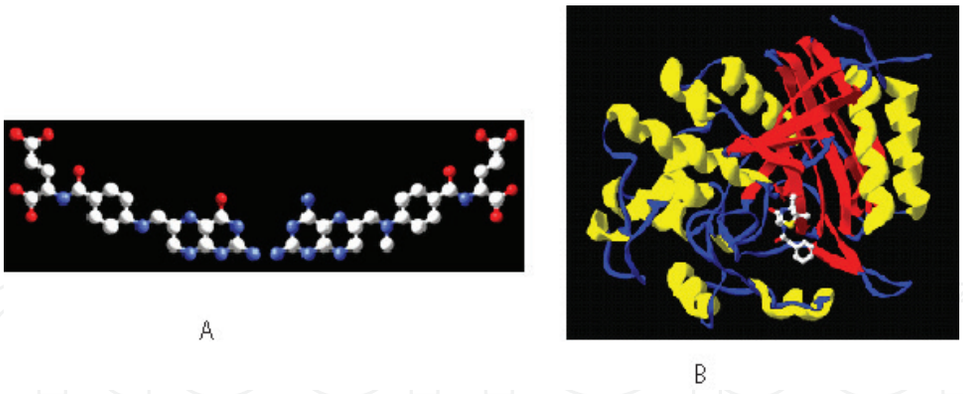

Figure 2. (A) Chemical structure of coenzyme folic acid (left side) associated to the anticancer drug methotrexate (right side). (B) The chemical structure of a complex between penicillin G and *Streptomyces* transpeptidase (produced from DB).

4. Results and discussion

Compounds isolated from medical plants and its extract and frication have potential enzyme inhibitor. Natural products derived from plants have excellent enzymatic action.

4.1. Natural products as urease inhibitors

For global nitrogen cycle, which can occur in medicinal plants, fungi and various bacteria urease (EC 3.5.1.5) are leading enzymes. Such type of hydrolase speeds up to 100 folds of the rate of urea hydrolysis and converts to ammonia and carbon dioxide [10–13]. Meanwhile, this finding in medicinal plants including *Canavalia ensiformis* which belongs to Fabaceae, the urease has been fully explored and converted the innovative in the field of biochemistry learning as the principal enzyme to be crystallized [14, 15] and likewise confirmed to be firmly needy on nickel ions [6]. The requirement on Ni^{2+} ions for catalytic action is a sole piece of urease between hydrolytic enzymes [10, 12].

In 1995, Jabri and coworkers succeeded to fully report the three-dimensional structure of urease enzyme from crystallography studies done with urease enzyme derived from *Klebsiella aerogenes* [16]. Later on, additional structures were revealed for ureases identified in *Bacillus pasteurii*, *Helicobacter pylori*, and maximum newly *C. ensiformis* [17–19]. Certainly, the characterization of the urease enzyme structure from a legume was central to improve and comprehend the supplies for ureolytic properties of this type of enzymes in diverse animals [20].

The countless resemblance of amino acid order among ureases since multiple origins recommends a mutual family for this enzyme [21]. Urease enzyme part an elementary trimeric collection with one, two, or three subunits that can combine creating dodecameric or hexameric. Each active position comprises two Ni^{2+} ions separately after all additional between 3.5 and 3.7 Å, linked by oxygen particles of a lysine carbamate rest and a hydroxide ion [22].

Medicinal plants and fungus ureases showed a solitary polypeptide chain though bacteria which must be 2/3 of dissimilar subunits (A, B, and C) [23]. The combination of Ni^{2+} ions in protein structure is supported by additional proteins, supposed to be specific urease chaperones [23].

Urease enzyme in the background of *H. pylori*, which raise the medium pH by the accretion of NH_3, is a urease trait of great medical position [13]. Gastrointestinal infections or urine by ureolytic bacteria can be a basis of health problems in humans and many other animals including pyelonephritis, kidney stone formation, ultimately hepatic coma, and hepatic encephalopathy [24]. Consequently, the main public health subjects are connected by *H. pylori*, Gram-negative bacteria that are bright to live in an environment as acidic as that of the stomach (pH 2–4). By way of significance, *H. pylori* poison can bring gastric irritation and raise the risk for the growth of duodenal, gastric adenocarcinoma, gastric ulcers, and gastric lymphoma [24].

Fifty percent of the universal population is dedicated by *H. pylori*. *H. pylori* can persevere in the stomach for the entire life of diseased persons without producing illness signs. The high occurrence of *H. pylori* in human population designates that such microorganism has established mechanisms for confrontation against host fortifications [25]. The urease enzyme present in cytoplasm or bound to *H. pylori* superficial is the chief virulence factor of such human pathogen [25]. It is suggested that the lyses of some pathogen cells tip to the issue of cytosolic ureases which connect to the superficial of intact bacterial cells and basis the hydrolysis of urea existing in human guts at an absorption of 3 mM. The NH_3 fashioned raises the medium pH, which produces an outgoing location for *H. pylori* survival [26]. Throughout the past 20 years, the endorsed first-line therapy for *H. pylori* abolition contained the mixture of the antibiotics amoxicillin and clarithromycin with omeprazole, a proton pump cell inhibitor. The upsurge of *H. pylori* resistance to these antibiotics (chiefly to clarithromycin) completes this therapy which is a non-attractive choice in new ages [27]. Additional action plans have arose to competition *H. pylori* infections, which comprise the usage of bismuth salts joint with a proton pump cell inhibitor [28]. Furthermore, urease inhibitors might be active therapies for the cure of diseases produced by urease-dependent pathogenic microorganisms. However, the commercially accessible urease inhibitors, including hydroxamic acid derivatives, phosphorodiamidates, and imidazoles, are toxic and have low stability, feature that stop their clinical usage [29]. The main search for new, known, novel, and bioactive urease inhibitors which enhanced stability and low toxicity is necessary to improve life excellence of human beings and animals.

4.2. Xanthine oxidase

Gout is a public illness with a universal spreading. Hyperuricemia, related with gout, is current in 5–30% of the overall people [30]. It appears to be growing universally and is measured as an important risk issue in thoughtful complaints similar to tophaceous gout, gouty nephropathy, and nephrolithiasis [31, 32]. Hyperuricemia consequences from the overproduction or under-excretion of uric acid and is importantly unfair by the high dietary consumption of foods ironic in nucleic acids, such as meats, leguminous seeds, and certain kinds of sea food. Throughout the previous step of purine metabolism, xanthine oxidase catalyzes the oxidation of xanthine and hypoxanthine into uric acid uricosuric drugs which development the urinary removal of uric acid, and xanthine oxidase inhibitors which block the mortal step in uric acid bio-synthesis, can minor the plasma uric acid concentration, and are usually working for the conduct of gout [33]. Furthermore, xanthine oxidase helps as a significant organic source of oxygen resulting to free radicals that pay to oxidative damage of existing materials producing several extreme positions like inflammation, carcinogenesis, hepatitis, ischemia reperfusion,

as well as elderly [34, 35]. Allopurinol is the individual clinically used xanthine oxidase inhibitor in the cure of gout [36]. This drug bases countless side effects including nephropathy, hepatitis, and allergic responses [37]. Thus, the exploration for new xanthine oxidase inhibitors with advanced therapeutic potential and less side effects wanted not only to treat gout but also fight numerous additional diseases connected with xanthine oxidase action.

4.3. Angiotensin-converting enzyme

Angiotensin I-converting enzyme action (ACE, peptidyldipeptide hydrolase, kininase II, EC 3.4.15.1) plays a significant part in ruling of blood pressure [38]. Angiotensin I-converting enzyme is a significant blood pressure controller that catalyzes the release of His-Leu from the carboxyl irredeemable angiotensin I, which, in go, produces a strong vasopressor octapeptide, angiotensin II. Angiotensin I-converting enzyme is also complicated in the poverty of vasodilator bradykinin [39]. The greatest if not all commercialized angiotensin I-converting enzyme inhibitors have developed peptides from the venom of the Brazilian viper *Bothrops jararaca* as classical materials [40]. Also, this animal basis, microorganisms, and plants deliver chemical substances with angiotensin I-converting enzyme inhibitory activity which might help as perfect materials in the growth of new angiotensin I-converting enzyme inhibitors. Angiotensin I-converting enzyme inhibitors prevent the formation of angiotensin II by ACE and thus decrease outlying vascular confrontation and blood pressure. These synthetic drugs are supposed to have sure side effects such as cough, taste conflicts, and skin rashes [41]. Consequently, for safe and cost-effective use, curiosity in finding food sources as angiotensin I-converting enzyme inhibitor has improved. Further compelling angiotensin I-converting enzyme inhibitors have been intended and synthesized to indulgence of hypertension excellently. Oral management of these drugs regularly results in unsolicited side effects; nutritional method strength be a healthier medium by which blood pressure in skillful. Besides, some trainings obligate been made on single plant species where several classes of angiotensin I-converting enzyme inhibitory molecules must be recognized, such as flavonoids, xanthones, proanthocyanidins, secoiridoids, and peptides for a complete evaluation of natural compounds [42–48].

4.4. α-Amylase

α-Amylase is a protein enzyme (EC 3.2.1.1) which hydrolyses α bonds of big, α-bonded polysaccharides, including starch and glycogen, elastic glucose, and maltose [49]. That is the main form of the amylase existing in humans and other mammals [50, 51]. It is also existing in seeds covering starch as a food reserve, which is secreted by many fungi.

Though it originates in numerous tissues, amylase is greatest projecting in saliva and pancreatic juice, and all of them have its individual isoform of human α-amylase. They act inversely on isoelectric focusing, and also be detached in testing by consuming precise monoclonal antibodies. Amylase is created in saliva and disruption starch into maltose and dextrin. This form of amylase is also called ptyalin. It will break down bulky, insoluble starch molecules into soluble starches making consecutively minor starches and finally maltose. Ptyalin performances on linear α(1–4) glycosidic linkages, but parts hydrolysis wants an enzyme that

presentations on cleft products. Gastric acid deactivates the salivary amylase in the stomach. In gastric juice agreed to pH near to 3.3–4, where ptyalin was deactivated completely at 37°C in 20 min. In difference, 50% of amylase activity is sustained after 150 min of introduction to gastric juice at pH 4.3 [52, 53]. Together, starch and substrate for ptyalin and then product (glucose of short chains) are capable to partly defend it touching in-activation by gastric acid. Ptyalin additional to buffer at pH 3.0 underwent whole inactivation in 120 min; adding of the starch at a 0.1% level caused 10% of the activity residual, and similar addition of starch to a 1.0% level produced about 40% of the activity residual at 120 min [54].

4.5. α-Glucosidase enzymes

Alpha-glucosidase; α-glucopyranoside; glucoinvertase; including glucoamylase, maltase, glucosidosucrase, maltase, glucosidoinvertase, alpha-D-glucosidase, hydrolase, α-1,4-glucosidase, and α-D-glucoside glucohydrolase are glucosidases positioned in the brush end of the small intestine which acts upon α(1–4) bonds [55–61]. In dissimilarity to β-glucosidase, the α-glucosidase decomposes starch and disaccharides in to glucose. In the meanwhile maltase enzyme decompose maltose is nearly functionally equal.

The key role of α-glucosidase is to hydrolyze incurable nonreducing (1–4) attached α-glucose which remains to release a lonely α-glucose molecule [62]. α-Glucosidase is mainly a carbohydrate which hydrolyzes the releases of α-glucose which is different to β-glucose. β-Glucose remains unconfined through glucoamylase, a similar enzyme. The substrate molecule discrimination of α-glucosidase is outstanding to subsite attractions of the active site of enzymes [62]. The main proposed mechanism comprises a nucleophilic shift of intermediate (oxocarbenium ion) [62].

Blood-sucking insect (*Rhodnius prolixus*) produces hemozoin when it digests hemoglobin of the host. The synthesis of hemozoin is reliant on the substrate connected to the site of α-glucosidase [63].

It has been documented in literature that α-glucosidases were extracted and then characterized from trout liver which exhibited maximum activity of the enzyme with increase rate that is 80% throughout workout in contrast to a latent trout.

This alteration was shown in correlation to the effects rise for liver glycogen phosphorylase.

From this it was offered that α-glucosidases in the glucosidic track play a significant portion in adding the phosphorolytic path in the livers' metabolic action to energy pressures of exercise.

The slight intestine of rat and yeast has α-glucosidases which exhibited to be reserved by numerous groups of flavonoid moiety [63].

Our research group has also reported phosphodiesterase-1 inhibitory, urease inhibition, and β-secretase enzyme effect of many natural products [64–67]. Novel glycine and phenylalanine sulfonamide derivatives have been reported for carbonic anhydrase inhibition activity [68]. It has recently documented that bovine liver tissue on glutathione reductase (GR) enzyme resolves the effects of adrenaline, thiamine, tyrosine, and dopamine. The bovine liver GR also effects on some natural amine [69]. Furthermore, the effects of particular catecholamines of the properties of carbonic anhydrase enzyme purified from bovine kidney tissue are also

documented. Some synthetic sulfonamides which contain molecules have also documented in literature for urease inhibition potential [70].

5. Conclusion

In conclusion medicinal plants and derived natural products from plants have potential enzyme inhibitor. This book chapter directed researcher to isolate bioactive compounds from plants which have excellent enzymatic action. Thus, the exploration for new, known, and novel enzyme inhibitors with progressive therapeutic potential and fewer side effects are required to treat diseases in mankind as well as in animals.

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