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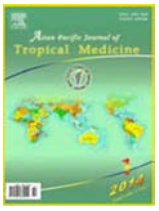

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An update on prodrugs from natural products

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ABSTRACT

A natural prodrug is a chemical compound or substance obtained from plants, microorganism, animal and marine sources. Natural products are small molecule source for Food and Drug Administration approved drugs and major sources for drug discovery. Most of the drugs for different ailment diseases undergo first pass metabolism, resulting in drug inactivation and the generation of toxic metabolites in body. Enormous numbers of prodrugs naturally present in plants, microorganism, animal and marine sources and those prodrugs undergoes chemical reaction to form non-toxic compounds. This review summarizes the list of prodrugs naturally present in the natural product.

1. Introduction

Pharmaceutical drugs are chemical or combination of chemicals designed to treat a variety of diseases. However, these drugs may also be dangerous to certain people. Pharmaceutical drugs are prescribed to alleviate symptoms as well as the root cause of diseases. These pharmaceutical drugs may weaken or damage the organs, sometimes cause other diseases, for example, nonsteroidal anti-inflammatory drugs prescribed for the treatment of rheumatoid arthritis. Even though nonsteroidal anti-inflammatory drugs alleviate the joint pain, they produce severe side effects such as gastrointestinal bleeding, ulcers, increasing risk of heart disease and fluid retention. Anti-diabetic drugs prescribed for the treatment of diabetes mellitus can end up causing liver damage. Chemotherapy and radiation used to treat cancer can weaken the other organs. Natural products are helping with the body to get back to its disease fighting form.

Natural products can be extracted from tissues of terrestrial plants and marine organisms fermentation broths. Natural products act as lead molecules for the synthesis of different potent drugs. Natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials, including terrestrial plants, terrestrial microorganisms, marine organisms, terrestrial vertebrates and invertebrates[1-6]. The value of natural products in this regard can be assessed using three criteria such as the rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semi-synthetic and total synthetic modification, the frequency of use in the treatment of disease and the number of diseases treated or prevented by these substances. The plant, animal, fungal and marine derived compounds have a long history of clinical use, better patient acceptance and tolerance[7]. This review covers prodrugs from natural sources.

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2. Prodrugs from plant, microbial, animal and marine sources

2.1. Romidepsin

Romidepsin (Figure 1a) is an example of natural anticancer agent obtained from the bacteria *Chromobacterium*

violaceum and used for the treatment of cutaneous and peripheral T-cell lymphoma and a variety of different cancers. It is a natural prodrug and works by blocking enzymes known as histone deacetylases (HDAC) and inducing apoptosis[8]. Romidepsin contains disulphide bond, the disulfide bond undergoing reduction in the cell to release a thiol group[9]. The thiol group interacts reversibly with a zinc atom in the binding pocket of HDAC enzyme. This enzyme is zinc dependent.

2.2. Butyrin

Butyrin (Figure 1b) is a triglyceride naturally occurring in butter. It's also known as tributyrin, which is a prodrug of butyric acid (Figure 1c). Butyrin is a liquid fat with acrid taste and composed of an ester of butyric acid and glycerol. Tributyrin is also used to identify the bacterium *Moraxella catarrhalis* in microbiological laboratories and it is a stable and rapidly absorbed prodrug of butyric acid that enhances antiproliferative effects of dihydroxycholecalciferol in human colon cancer cells[10].

2.3. Psilocybin

Psilocybin (Figure 1d) is a prodrug of psilocin (Figure 1e), isolated from *Psilocybe mexicana* and *Stropharia cubensis*. It produces psycho action because they structurally similar to neurotransmitter such as serotonin and norepinephrine, and transmits the nerve impulses from one neuron to another, especially in the brain. The psilocybin binds into the same neurotransmitter receptors and stimulate them, leading to false signals being created[11].

2.4. Salvestrols

Salvestrols are prodrugs of resveratrol (Figure 1f). Salvestrols are a group of naturally-occurring anticancer plant compounds, discovered in 1998 as a result of the combined research of Professor Dan Burke. It is non-toxic to normal body's cells, which is activated to resveratrol from the inside of human cancer cells by the enzyme, CYP_1B_1 (pronounced "sip one bee one"). The activated resveratrol stops growing cancer cell, because it is toxic to cancer cell but not to normal body cells[12].

2.5. Spiruchostatin A

Spiruchostatins are a group of chemical compounds isolated from *Pseudomonas* sp. It is a gene expression-enhancing substance and exists in two main forms such as spiruchostatin A (Figure 7) and spiruchostatin B. Spiruchostatin A is a depsipeptide natural product with close structural similarities to FK228, a HDAC inhibitor (HDI). Spiruchostatin A is a potent inhibitor of the growth of various cancer cell lines and potent inhibitor of class I HDAC activity *in vitro* and acted as a prodrug[13].

2.6. Prontosil

Prontosil (Figure 1h) is a prodrug of sulphonamide (Figure 1i). Prontosil, also called sulfamidochrysoidine, is used in the treatment of general bacterial infections in humans. Prontosil was introduced into medicine in the 1930s. Prontosil was resulted from a research, directed by German chemist and pathologist Gerhard Domagk on the antibacterial action of azo dyes. A red azo dye is of low toxicity. Prontosil is shown by Domagk to prevent mortality in mice infected with *Streptococcus* bacteria. The dye is also effective in controlling *Staphylococcus* infections in rabbits. Within a relatively short period, it is demonstrated that prontosil is effective not only in combating experimental infections in animals, but also in againsting streptococcal diseases in humans, including meningitis and puerperal sepsis. Later it is found that prontosil is disrupted in the tissues to form *para*-aminobenzenesulfonamide (sulfanilamide). Prontosil has been replaced in clinical use by newer sulfonamide drugs, including sulfanilamide, sulfathiazole, sulfamethoxazole and others[14].

2.7. γ-Hydroxybutyric acid (GHB)

GHB is a naturally occurring substance in beef, wine, small citrus fruits, central nervous system and small amount of all animals. It's also known as 4-hydroxybutanoic acid and sodium oxybate. GHB (Figure 1j) is naturally produced in human body's cells, which is used to treat conditions such as clinical depression, alcoholism, insomnia and narcolepsy. It has been used as a general anesthetic in a medical setting. GHB is used to improve athletic performance. It is also used as an intoxicant (illegally in many jurisdictions) or as a date rape drug. GHB is structurally related to the ketone body β-hydroxybutyrate. GHB has at least two distinct binding sites in the central nervous system. GHB is an agonist at the newly characterized GHB receptor, which is excitatory, and it is a weak agonist at the GABAB receptor, which is inhibitory. GHB is producing a pharmacological action similar to some neurotransmitters. GHB is synthesized from GABA in neurons and released by the neurons fire. GABA does not cross the blood-brain-barrier by taken orally.

GHB induces the accumulation of either a tryptophan derivative, or tryptophan in the extracellular space of the cell and by increasing the tryptophan transport across the blood-brain barrier. GHB induces stimulation of tissue serotonin turnover by increasing the tryptophan transport across the blood-brain barrier. The stimulated serotonin is uptaken by serotonergic cells. The serotonergic system is involved in the regulation of mood, sleep and anxiety[15].

2.8. Melatonin

Melatonin (Figure 1k), as a prodrug of N^1-acetyl-5-methoxykynuramine (AMK) (Figure 1l) is also known chemically as *N*-acetyl-5-methoxytryptamine and it is a naturally occurring compound found in animals, plants,

and microbes. In animals, circulating levels of the hormone melatonin vary in a daily cycle, thereby allowing the entrainment of the circadian rhythms of several biological functions. Many biological effects of melatonin are produced through activation of melatonin receptors, while others are due to its role as a pervasive and powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA. Melatonin oxidation by free radicals to form biologically active metabolites such as N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and AMK. AMK interacts with reactive oxygen and nitrogen species, conveys protection to mitochondria, inhibits and down regulates cyclooxygenase 2[16].

2.9. Phytoestrogens

Phytoestrogens are adaptogens and estrogen hormone-like chemicals found in plants. They are a group of chemicals which include isoflavones, flavones, coumestans and lignans. The main sources of phytoestrogen are soybean and flaxseed and their derivatives. Other food types such as nuts, oil seeds and herbs are also sources of phytoestrogens, eventhough in relatively low concentrations. Phytoestrogens can be beneficial when the estrogen levels are either increased or decreased. Phytoestrogens are prodrug of estrogen. When phytoestrogens are metabolized, they can bind with the same cellular sites of the estrogen and produce estrogenic activity. Phytoestrogens are weak estrogenic compounds compared to estrogen. When estrogen levels are high, phytoestrogens produces a much less estrogenic activity in estrogen binding site and when the estrogen levels are low and estrogen binding sites are empty, phytoestrogens bind in estrogen binding site, produce the estrogen activity. Phytoestrogens reduce risks of incidence of cardiovascular disease, breast cancer and prostate cancer[17].

2.10. Baicalin

Baicalin (Figure 1m), as a prodrug of baicalein (Figure 1n), is metabolized to baicalein through metabolism of intestinal bacteria and enterohepatic circulation. Baicalein, the aglycone moiety of baicalin, is a new prodrug able to inhibit prolyloligopeptidase. It is a natural compound with a long history of safe administration to humans and a highly attractive base from which to develop new treatments for schizophrenia, bipolar affective disorder and related neuropsychiatric diseases[18].

2.11. Matricin

Matricin (Figure 1o), as a prodrug of chamazulene (Figure 2a), is a colourless, crystalline substance from the individual flowers of chamomile right which contain up to 0.15%. It was first isolated in 1957. Matricin acts as chamazulene and it is a blue violet essential oil with anti-inflammatory action, to which the group of polycyclic aromatic hydrocarbons and

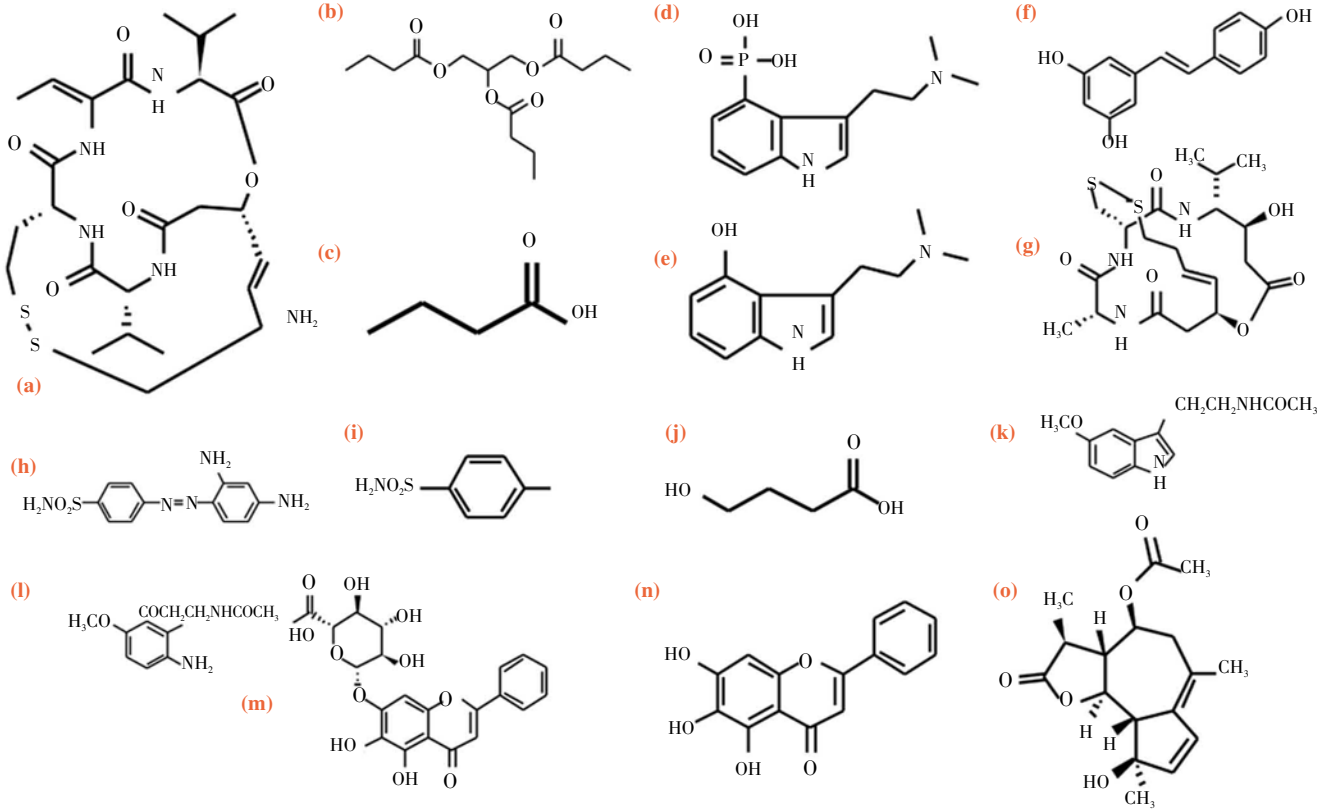

Figure 1. Structure of different compounds.

a: Romidepsin; b: Butyrin; c: Butyric acid; d: Psilocybin; e: Psilocin; f: Resveratrol; g: Spiruchostatin A; h: Prontosil; i: Sulphonamide; j: γ-Hydroxybutyric acidpsilocin; k: Melatonin; l: Amk; m: Baicalin; n: Baicalein; o: Matricin.

the terpene derivative belong. Matricin can be converted to chamazulene in gastric fluid[19].

2.12. Sennoside A

Sennoside A (Figure 2b) is a prodrug of rhein anthrone (Figure 2c). Sennosides are a number of anthrax quinone derivatives used as laxatives. They are dimeric glycosides named after their abundant occurrence in plants of the genus *Senna*. Sennoside A is in active which is converted into rheinanthrone in colon by β-glucosides *Bifidobacterium* sp. SEN C-C reductase *Pepotostreptococcus intermedius*[20].

2.13. Glycyrrhizin

Glycyrrhizin (Figure 2d), as a prodrug of glycyrrhetinic acid (or glycyrrhizic acid or glycyrrhizinic acid) (Figure 2e), is the main sweet-tasting compound from liquorice root. It is a triterpenoid saponin glycoside and an inactive compound which is converted into active compound aglycone glycyrrhetinic acid plus two molecules of glucuronic acid by β-glucuronides *Eubacterium* sp. GLH. It is effective in the treatment of peptic ulcer and also has expectorant (antitussive) properties. It has some additional pharmacological properties including antiviral, antifungal, antiprotozoal and antibacterial activities[21].

2.14. Barbaloin

Barbaloin (Figure 2f) is C-glucoside of aloe emodin anthrone (Figure 2g), which is found in *Aloe vera*. It is a mixture of two diastereomers, termed barbaloin (or aloin A) and isobarbaloin (or aloin B), both having similar chemical properties. Barbaloin is an anthraquinone glycoside and has different pharmacological activities such as anti-inflammatory, antiviral, strong inhibitory effect on histamine release, antimicrobial, cathartic, antioxidant and anticancer. Barbaloin is also a prodrug of aloe emodin anthrone,

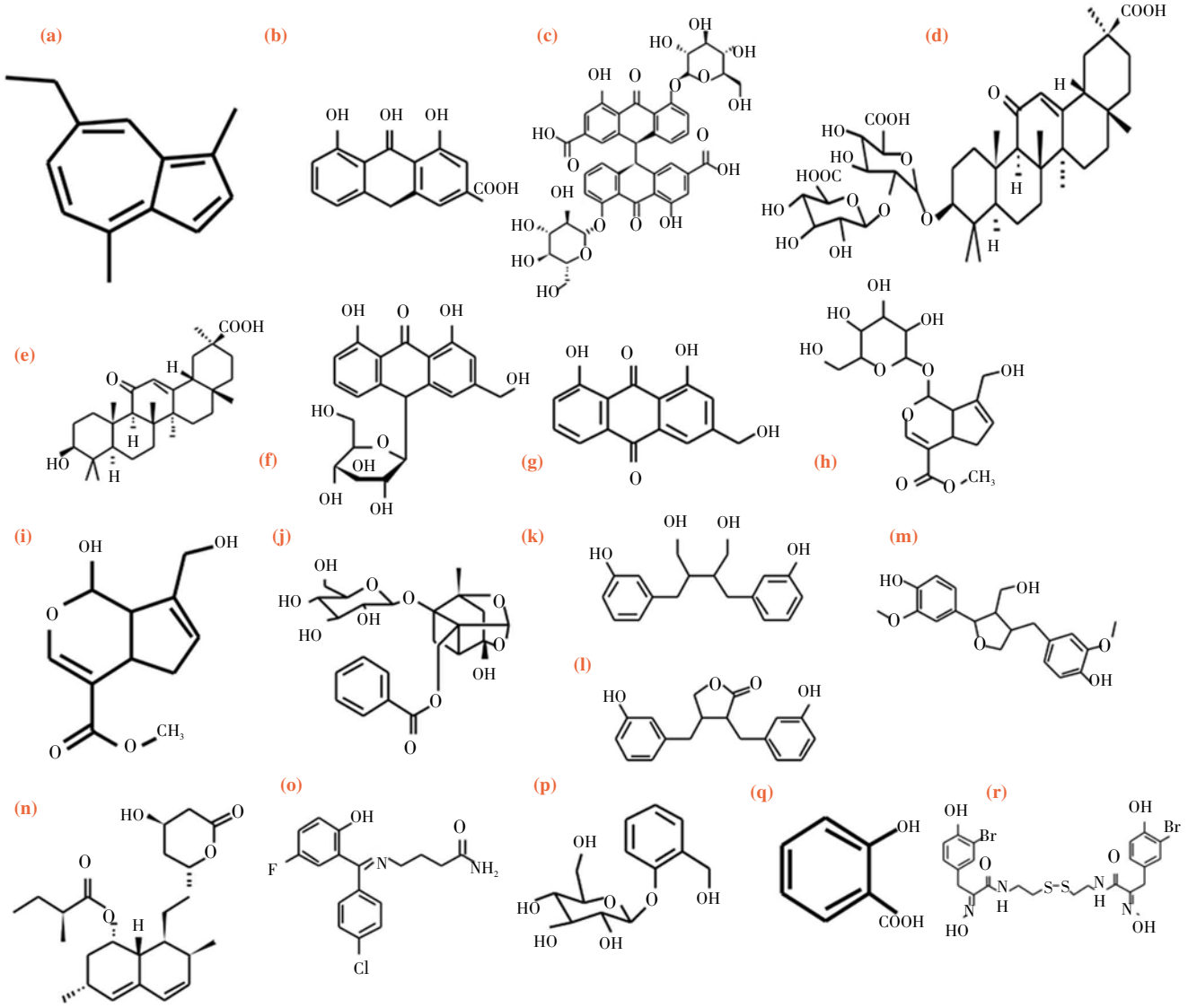

Figure 2. Structures of different compounds.

a: Chamazulene; b: Sennoside A; c: Rhein anthron; d: Glycyrrhi; e: Glycyrrhetinic acid; f: Barbaloin; g: Aloe emodin anthrone; h: Geniposide; i: Genipin; j: Paeoniflorin; k: Enterodiol; l: Enterolactone; m: Lariciresinol; n: Lovastatin; o: Progabide; p: Salicin; q: Salicylic Acid; r: Psammaplin A;

which is converted into active aloe emodin anthrone in the alimentary tract by β-glucuronides *Eubacterium* sp.[22].

2.15. Geniposide

Geniposide (Figure 2h) iridoid glycosides are isolated from dried ripe fruit of red, blue and purple gardenia. Geniposide has a variety of pharmacological activities such as pain, laxatives, anti-inflammatory treatment of soft tissue injury, gallbladder, hepatoprotective and inhibition of gastric secretion and reduce the role of pancreatic amylase. It is a prodrug of genipin (Figure 2i) and converted by human intestinal microflora enzymes such as β-glucosidase to the active drug genipin in the alimentary tract. Genipin has many other medicinal effects, such as anti-inflammatory, anticancer, antithrombotic, antibacterial, gastritis curative, diabetes curative, neurotoxicity inhibition and antidepressant like effects. In addition, genipin is a natural cross-linking agent in biological applications and is also used to prepare a series of blue pigments used in the food industry[23].

2.16. Paeoniflorin

Paeoniflorin (Figure 2j) is a chemical compound. It is one of the major constituents of an herbal medicine derived from *Paeonia lactiflora*. It can also be isolated from the fresh water fern *Salvinia molesta*. In *Paeonia*, it can form new compounds with addition of phenolic substituents. Paeoniflorin have variety of pharmacological activities such as neuro protective, liver protective anticonvulsant, anti-proliferative, anti-hyperglycaemic, anti-hypertension and anti-inflammatory.

Paeoniflorin is a prodrug of paeonimetabolin. It is converted by human intestinal microflora enzymes such as β-glucosidase esterase to the active drug paeonimetabolin in the alimentary tract[24].

2.17. Lignans

The lignans are a group of chemical compounds found in certain plants of the Asteraceae, Convolvulaceae including the greater burdock (*Arctium lappa*), *Saussurea heteromalla* and *Ipomoea cairica*. It has shown antiviral, antioxidant and anticancer effects and been used in the treatment of HIV. They are prodrugs when in part of the human diet, some lignans are metabolized to form mammalian lignans known as enterodiol (Figure 2k) and enterolactone (Figure 2l) by intestinal bacteria. Lignans can also be metabolized to form mammalian lignans including pinoresinol, lariciresinol (Figure 2m), secoisolariciresinol, matairesinol, hydroxymatairesinol, syringaresinol and sesamin[25].

2.18. Lavastatin

Lovastatin (Figure 2n) is a fungal derived product obtained from *Aspergillus* terreus, *Monascus rubber*, *Pleurotus ostreatus* and *Pleurotus* spp. It is a potent inhibitor of the enzyme, 3-hydro-3methylglutaryl-coenzyme A reductase. This enzyme is rate determining catalyst for the irreversible conversion of HMG-CoA to mevalonic acid in the synthesis of cholesterol[26]. Lovastatin contains lactone ring which is hydrolysed to the active heptanoic acid. The active heptanoic acids reversibly bind with HMG-CoA reductase and inhibit the conversion of HMG-CoA to mevalonic acid and prevent the cholesterol biosynthesis. Lovastatin is used for the treatment of dyslipidemia and the prevention of cardiovascular disease.

2.19. Progabide

Progabide (Figure 2o) is a prodrug of GABA. It is converted in to GABA upon entering the central nervous system and used for the treatment of convulsion[27].

2.20. Salicin

Salicin (Figure 2p) is an alcoholic β-glucoside obtained from willow bark. It is closely related to aspirin and used for the treatment of inflammation. Salicin is a prodrug of salicylic acid and it can be converted in to salicylic acid (Figure 2q) by esterases enzyme[28].

2.21. Psammaplin A (Psam A)

Psammaplin A (Figure 2r) is a natural prodrug isolated from the psammaplinaplysilla sponge. It is an DNA methyltransferase inhibitor, antibiotic and antitumor. It inhibits the activities of several key enzymes in prokaryotic and eukaryotic systems including those involved in epigenetic control of gene expression, DNA replication, angiogensis and microbial detoxification[29].

3. Conclusion

Natural products can come from everywhere. People most commonly think of plants first when talking about natural products, but trees and shrubs can also provide excellent sources of material that could provide the basis of a new therapeutic agent. Animals too, whether highly developed or poorly developed, whether they live on land, sea, or in the air can be excellent sources of natural products. Bacteria, smuts, rusts, yeasts, molds, fungi and many other forms of what we consider to be primitive life can provide compounds or lead to compounds that can potentially be very useful

therapeutic agents. Naturally derived prodrugs have played an important role in the development of new synthetic prodrugs for different ailment. In this review article, 21 prodrugs present in the natural product were discussed. A number of synthetic prodrugs are likely to be launched in the market to treat different ailment but prodrugs from natural product have lesser side effects, easy accessibility and low cost. In the future, further study claims an open area of research for sound consideration for development of new prodrugs.

Conflict of interest statement

We declare that we have no conflict of interest.

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