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Mini-review

Natural product as a source of prodrug

Jagannathan Padmavathy[1] and Devarajan Saravanan[2]

[1]Department of Pharmaceutics, Jaya College of Paramedical Sciences, College of Pharmacy, CTH Road, Thiruninravur 602024, Chennai, Tamil Nadu, India; [2]Department of Pharmaceutical Chemistry, Ratnam Institute of Pharmacy, Pidathapolur, Nellore 524346, Andhra Pradesh, India.

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Abstract

The natural products are the chemical constituents that are generated from the living organism. The natural products are isolated from the plants, animals, and microorganisms which are used in drug design and drug discovery. Natural product is then modified by chemical synthesis as either total or semi-synthetic way. The natural products show various pharmacological activity which can be used for the treatment of a variety of diseases. Natural products could be regarded as a source of quantifiable and chemically pure known products and also natural products can be utilized as complex mixtures subjected to chemical variability. The present review article adds up the prodrugs from natural products as well as prodrugs developed from the natural products.

Introduction

Nature always stands first in the healing of various ailments. Many products are available from the various natural sources like the plant, animal, microbial and mineral sources, serving to treat many diseases in humans (Sheetal Verma and Singh, 2008; Katz and Baltz, 2016). Many newly discovered drug molecules serve as excellent medicine for the treatment of chronic illness like cancer, AIDS, tuberculosis etc. About 25% of the drugs prescribed come from the plants (Rates, 2001; Gurnani et al., 2014; Luo et al., 2014; Farnsworth and Morris, 1976; Raskin and Ripoll, 2004), 25% from the animals and 10% from the microbes (Qaralleh, 2016).

Many systems of medicine like Ayurveda, Unani, Kampo, Chinese medicine, and Siddha utilizes natural products as the source of the drug, for about 100 decades (Koehn and Carter, 2005; Atanasov et al., 2015).

The secondary metabolites from the natural products serve as a base for the development of a large number of drugs (Table I).

Drug discovery from natural products has reclaimed attention of the pharmaceutical industry and it is on the

Table I

Secondary metabolites from the natural product

Metabolite	Natural source
Artemisinin	*Artemisia annua*
Cephalosporin	Marine fungi
Colchicine	*Colchicum autumnale*
Daunomycin	*Streptomyces clavuligerus*
Eptifibatide	Venom of Southeastern pygmy rattlesnake
Ginsenosides	*Panax quinquefolius*
Heparin	Canine liver cells
Insulin	Bovine/porcine pancreatic extracts
Kainic acid	Red algae
Lepirudin	Saliva of leech
Magainin	Skin of the frog and toad
Paclitaxel	*Taxus brevifolia*
Penicillin	*Penicillium notatum*
Premarin	Pregnant mare's urine
Protamine	Salmon fish sperm
Triptolide	*Tripterygium wilfordii*

verge of a comeback due to new technological inputs that promise better returns on investment (Lahlou, 2013; van Herwerden and Sussmuth, 2016).

The study in the natural products is on the high score to exploit a variety of lead structures for the development of drugs for the treatment of various diseases (Lahlou, 2007; Siddiqui et al., 2014). As such natural products are important in medicinal sciences and biology for the development of new derivatives of natural drugs, called prodrugs.

Prodrugs could occur naturally like numerous botanical constituents or phytoconstituents also endogenous substances, or they could derive from semisynthetic processes or synthetic-designed intentionally during the rational drug design or unintentionally during the drug development. Examples of prodrugs which occur naturally or have been formed unintentionally during the drug development include psilocybin, aspirin, codeine, irinotecan, L-dopa, heroin, and several antiviral nucleosides (Wu, 2009).

Various natural products were successfully utilized as prodrugs such as taxol, doxorubicin, morphine, atropine, salicin, quinine, prontosil, lovastatin, salicylic acid, digoxin, caffeine etc. in the market (Ovadje et al., 2015). The essential factor related to the identification of natural product based bioactive compounds are currently known. A few natural products are prodrugs that have to be metabolized *in vivo* by a mammalian organism or intestinal microorganisms to yield the pharmacologically active compounds (Atanasov et al., 2015).

In the present scenario, developed and developing countries have started to use the herbal drugs and remedies due to increasing awareness about adverse effects of the modern medicine, which has resulted in the demand for natural products derived prodrugs. Now-a-days, there's been a renewed interest in studies of prodrugs from the natural product because of the failure of the pharmaceutical drugs in the therapeutic areas like anti-infective, immunosuppressant and metabolic diseases due to poor water solubility, severe side effects, and drug specificity. Natural products studies will continue to discover a number of lead structures that can be utilized for templates for the development of new prodrugs in the pharmaceutical industry (Chin et al., 2006). They serve as a source for the development of prodrugs with extended therapeutic activity. Hence, there has been major studies focused on decreasing the impact of the factors and various prodrugs have been developing from the natural products.

Prodrugs from Natural Sources

The compound which is inactive, but is converted by chemical or enzymatic means to the active drug is prodrug (Zhang et al., 2014; Han and Amidon, 2000). An example of the synthetic prodrugs includes tolmetin prodrug for glycine, bacampicillin prodrug for ampicillin. Prodrug strategy has been used for many years to solve unwanted drug properties (Jana et al., 2010). Prodrug development needs technical skill in handling.

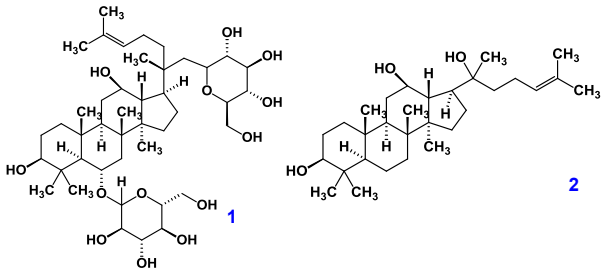
The prodrugs are activated enzymatically or chemically. Prodrugs can be used to increase polarity, lipophilicity, to improve bioavailability and to target specific site (Dahan et al., 2014; Dahan et al., 2012; Stella et al., 2007) and reduction of toxicity (Stella et al., 1985).

The prodrugs can also be obtained from the natural sources. Some of the prodrugs of natural origin include romidepsin, butyrin, psilocybin, salvestrols, spiruchostatin A, prontosil, melatonin, baicalin, matricin, sennosides, barbaloin, geniposide, lignans etc (Kumar et al., 2014).

In the present work, new research on the prodrugs of natural origin are presented, as they are of much value in the modern world, for the well-being of the humans (Table II).

Ginsenosides

Ginsenosides (**1**) are isolated from the *Panax quinquefolius*. This is a natural product triterpene saponins and steroid glycosides. Ginsenosides are the members of a dammarane family, which consists of a 4-ring and steroid-like structure. All ginsenosides have two or three hydroxyl groups in the carbon 3 and 20. Ginsenosides are converted into active metabolites like 20(S)-protopanaxadiol Rb_1-Rb_3, Rc, Rd, Rg_3, Rh_2, Rs_1 (**2**) with help of human gut bacteria β-glycosidase Eubacterium sp. A-44 (Kobashi, 2004). Ginsenosides produced a variety of pharmacological activities such as anti-inflammatory, anti-oxidant, anti-cancer and vasorelaxation (Lee and Kim, 2014; Leung and Wong, 2010).



Saikosaponin

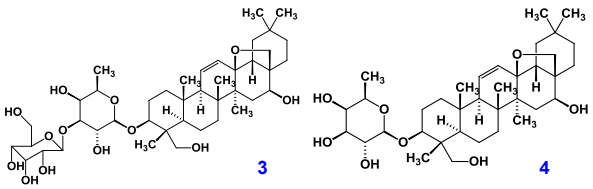
Saikosaponin is a triterpene saponin glycoside. It has been isolated from the *Bupleurum falcatum*. Saikosaponin (**3**) is converted into active metabolite prosaikogenin E1-E3 (**4**) by human gut bacteria fucosidase, Eubacterium sp. A-44 (Yu et al., 1997). Prosaikogenin E1

Table II

Prodrugs from natural product

Source	Prodrugs
Bupleurum falcatum	Saikosaponin
Citrus and grapefruits	Naringin
Blueberries, senna, mulberries, and raspberries	Resveratrol
Peppermint, rosemary, oregano, lavender, thyme, basil, apples, cranberries, hawthorn and elder	Ursolic acid
Aesculus californica, *Aesculus hippocastanum*, *Daphne mezereum*, *Bursaria spinosa* and dandelion coffee	Esculin
Muscle tissue	n-Acetylcarnosine
Citrus unshiu, *Citrus aurantium*, *Zanthoxylum gilletii*, lime, lemon, peppermint and *Agathosma serratifolia*	Hesperidin
Penicillium citinium	Mevastatin
Streptomyces	Duocarmycins
Streptomyces atroolivaceus	Leinamycin E1
Soybeans	Genistin and daidzin
Lemon fruit	Eriocitrin
Hypoxis hemerocallidea	Hypoxoside
Withania somnifera	2,3-dihydro-3β-O-sulfate withaferin A
Streptomyces hygroscopicus	Validamycin A
Unadulterated wines	γ-Butyro lactone
Bergenia crassifolia, wheat and bearberry	Arbutin
Horseradish, mustard and cabbage	Glucosinolates
Garlic	Alliin
Phaseolus lunatus	Linamarin
Sambucus Canadensis	Prunasin
Trifolium repens	Amygdalin
Zea mays	Dhurrin
Zamia pumila and *Cycas revolute*	Cycasin
Ceratocephalus testiculata	Ranunculin
Mitochondria	Aminolevulinic acid

-E3 possesses anti-inflammatory activity.



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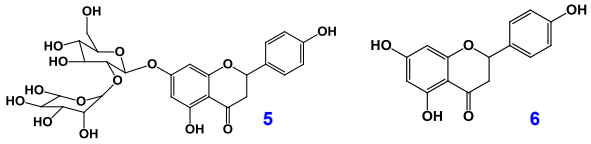
Naringin

Naringin (**5**) is a flavonoid found in the citrus and grapefruits, which produces bitter taste to grape and citrus fruits. Naringin is a prodrug form of naringenin (**6**). Naringin is metabolized into naringenin via prunin produced by human intestinal bacteria or YK-4 and JY-6. Naringin and naringenin are very powerful anti-oxidants, in comparison with naringin. Naringenin produces strong anti-oxidant activity due to the presence of sugar moiety in the naringin that causes steric hindrance of the scavenging group (Yu et al., 1997).



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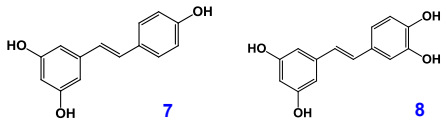
Resveratrol

Resveratrol (**7**) is natural phenol found in the blueberries, senna, mulberries, and raspberries and acts as an anti-cancer agent (Li et al., 2015). It is a prodrug form of picea-tannol. Piceatannol (**8**) is a natural phenol, produced naturally in various plants when the plant is attacked by pathogens such as bacteria or fungi. Resveratrol is metabolized in the body into piceatannol by the enzyme cytochrome P_{450} (Kukreja et al., 2014; Kim et al., 2009).



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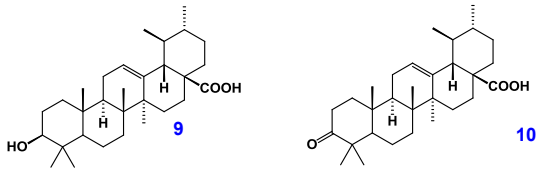
Ursolic acid

Ursolic acid (**9**) is a pentacyclic triterpenoid present in various plants such as peppermint, rosemary, oregano, lavender, thyme, basil, apples, cranberries, hawthorn and elder. Ursolic acid is a prodrug form of the ursonic acid (**10**). Ursolic acid is converted into ursonic acid by *Aspergillus flavus*. *In vitro*, ursolic acid prevents the expansion or growth of numerous cancer cells inhibiting the $STAT_3$ activation pathway as well as reduces the expansion or growth of cancer cells and stimulates apoptosis (Wang et al., 2011; Jia et al, 2015). Ursolic acid is also found to inhibit JNK expression and IL-2 activation of JURKAT leukemic T Cells, causing a decrease in proliferation, and T cells activation.



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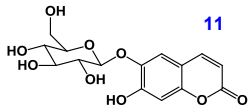
Esculin

Esculin (**11**) is a naturally occurring coumarin glycoside found in the *Aesculus californica*, *Aesculus hippocastanum*, *Daphne mezereum*, *Bursaria spinosa*, and dandelion coffee.

Esculin is used for the treatment of fungal infection on the skin. Esculin is a prodrug form of esculetin (12). Esculin is hydrolysed to esculetin in the body through β -glucosidases. β-glucosidases is produced by dermatophytes or dermal microbiota (Mercer et al., 2013). Esculitin is a natural lactone, which is a derivative of esculin. Esculetin possesses various pharmacological activities such as an anti-pathogenic, antitumor, anti-inflammatory, and neuroprotective activity (Wang et al., 2015; Tubaro et al., 1988).



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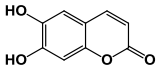

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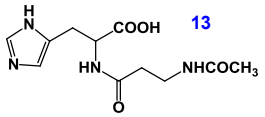
N-Acetylcarnosine

N-Acetylcarnosine is a naturally occurring compound in our body tissues, especially in muscle tissue. It is a free radical scavenger that is structurally related to dipeptide carnosine. N-acetylcarnosine (13) is used for the treatment of cataracts. It is prodrug form of carnosine. N-acetylcarnosine is converted into biologically active peptide carnosine by the enzyme carnosinase. Carnosine (14) is a dipeptide of the amino acids such as β-alanine and histidine. Carnosine scavenges the reactive oxygen species and α,β-unsaturated aldehyde formed from the peroxidation of fatty acids in cell membrane during the oxidative stress (Babizhayev, 2012).



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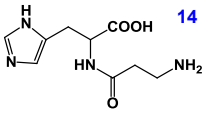

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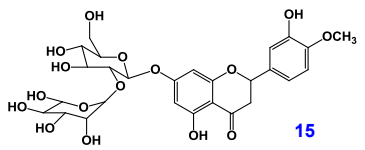
Hesperidin

Hesperidin (15) is a flavanone glycoside present in *Citrus unshiu*, *Citrus aurantium*, *Zanthoxylum gilletii*, lime, lemon, peppermint and leaves of *Agathosma serratifolia*. Hesperidin is prodrug form of hesperetin (16). Hesperidin is converted into hesperetin by human intestinal microflora hesperidin 6-O-alpha-L-rhamnosyl -beta-D-glucosidase. Hesperidin cannot prevent the histamine release from RBL-2H3 cells activated by IgE. Hesperetin prevents the histamine release from RBL-2H3 cells and inhibits cyclooxygenase 2 (Alam et al., 2014; Lee et al., 2004).



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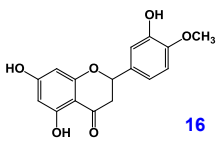

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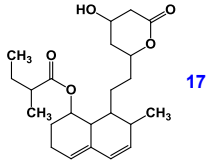
Mevastatin

Mevastatin (17) was isolated from *Penicillium citinium*. Mevastatin acts as a cholesterol lowering agent, which is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the rate-limiting step in the biosynthesis of cholesterol. Mevastatin acts as a prodrug and is converted into active form *in vivo* via the hydrolysis of the lactone ring and the hydrolyzed lactone ring resembles the tetrahedral intermediate produced by the enzyme HMG-CoA reductase. Mevastatin also acts as an antibacterial and antifungal agent (McFarland et al., 2014; Endo, 1992).



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Duocarmycins

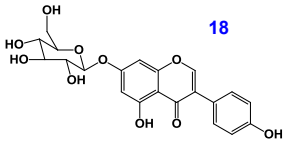
Duocarmycins such as A, B_1, B_2, C_1, C_2, D, SA and CC-1065 are natural prodrugs isolated from the *Streptomyces*. Duocarmycins are naturally occurring antitumor agents and are acting as a DNA minor groove binding alkylating agent. Duocarmycins attaches to the minor groove of DNA and alkylates the purine base adenine at N_3 position. The alkylation of DNA base disrupts the nucleic acid structure that leads to tumor cell death (Searcey, 2002).

Leinamycin E_1

Leinamycin E1 is natural prodrug isolated from the *Streptomyces atroolivaceus*. It is potent antitumor antibiotic. Leinamycin E_1 possesses antitumor activity by the episulfonium ion mediated DNA alkylation. Leinamycin E_1 is oxidatively converted into episulfonium ion intermediate by the reactive oxygen species. Episulfonium ion intermediate alkylates the purine base adenine at N_3 position. The alkylation of DNA base disrupts the nucleic acid structure that leads to tumor cell death (Huang et al., 2015).

Isoflavone glycosides

Isoflavone glycosides like genistin and daidzin are present in the soybeans and possess estrogenic activity. Genistin (18) and daidzin (19) are large hydrophilic structures that are not hydrolyzed easily by the intestinal absorptive bacteria. But, genistin and daidzin are hydrolyzed to unconjugated isoflavones such as genistein and daidzein respectively by hydrolytic enzymes produced by intestinal bacteria. Genistein (20) and daidzein (21) are readily absorbed and produce more estrogenic effects compared to genistin and daidzin. Genistein and daidzein enter into circulation after absorption through the intestine and transported



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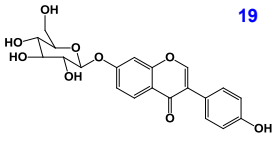

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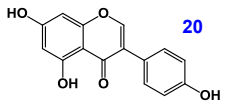
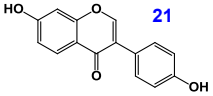
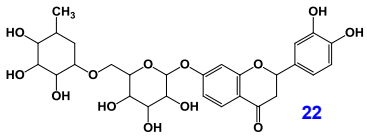
to the liver. In the liver, genistein, and daidzein are conjugated by liver metabolizing enzymes and are converted into more water soluble glucuronidated, glycosylated and sulfated isoflavones (Rafii, 2015).

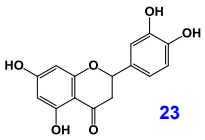


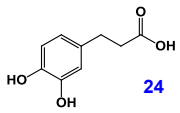


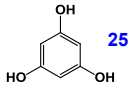
Eriocitrin

Eriocitrin (22) is an anti-oxidative flavonoid glycoside present in the lemon fruit. It prevents the oxidative damage by free radicals. Eriocitrin is metabolized to eriodictyol by the intestinal bacteria, *Bacteroides uniformis* or *Bacteroides distasonis* and then eriodictyol (23) is converted into 3,4-dihydroxyhydrocinnamic (24) and phloroglucinol (25) by *Clostridium butyricum*. The eriocitrin metabolites exhibited strong anti-oxidant activity (Miyake et al., 2000).



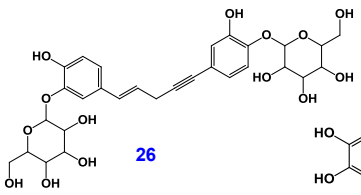


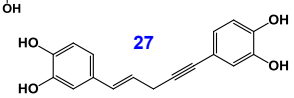




Hypoxoside

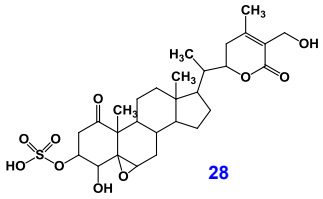
Hypoxoside (26) is a norlignane glycoside found in the *Hypoxis hemerocallidea*. Hypoxoside is not absorbed into the blood stream but is converted into biologically active compound agloycone rooperal (27) in the human gut by enzyme β-glucosidase, the enzyme which is present in the gastrointestinal tract. Rooperal exhibited various pharmacological activities such as anti-inflammatory, analgesic and anti-oxidant activities (Smit et al., 1995).

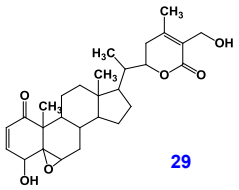




2,3-Dihydro-3β-O-sulfate withaferin A

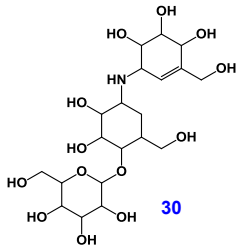
2,3-Dihydro-3β-O-sulfate withaferin A (28) is a natural product found in the roots of *Withania somnifera*. *Withania somnifera* generally called as ashwagandha, which has been used for so many years in Indian system of medicine to enhance the health conditions for elderly peoples and as a tonic to relieve stress. Ashwagandha also exhibited anti-cancer and antiangiogenic activities. 2,3-Dihydro-3β-O-sulfate withaferin A is pharmacologically inactive compound, which is converted into pharmacologically active compound withaferin A (29) in *in vivo*. Withaferin A acts as an anti-oxidant (Xu et al., 2009).

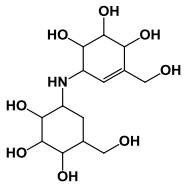




Validamycin A

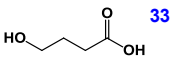
Validamycin A (30) is a fungicide and antibiotic produced by *Streptomyces hygroscopicus*, which is used as an inhibitor of trehalase. It is used for damping off of cucumbers and used for the control of sheath blight of rice. Validamycin A is a prodrug which is converted into pharmacologically more active compound validoxylamine A (31). Validoxylamine A is a strong inhibitor of trehalase (Sharma, 2014).





γ –Butyrolactone

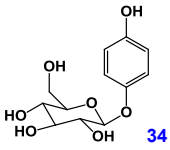
γ-Butyrolactone (32) is a naturally occurring substance present in the unadulterated wines and act as a recreational intoxicant. It is prodrug form of γ-hydroxy butyric acid (33). In human, γ-butyro lactone is converted into γ-hydroxy butyric acid by the enzyme lactonase present in the blood (Elliott and Burgess, 2005).



Arbutin

Arbutin (34) is a glycosylated hydroquinone present in the *Bergenia crassifolia*, wheat, and bearberry. It is a skin whitening cosmetic ingredient, which acts as a prodrug of the toxic active drug hydroquinone (35). Arbutin is hydrolysed to hydroquinone in the skin by skin bacteria

like *Staphylococcus aureus* and *Staphylococcus epidermidis* (Bang et al., 2008). Hydroquinone is more potent skin lightening agent compared to arbutin. Hydroquinone also exhibited other effects like genotoxicity, nephrotoxicity, and cytotoxicity (Rai and Carpinella, 2006).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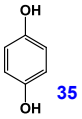
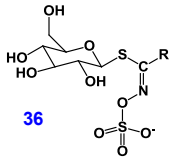

35

Glucosinolates

Glucosinolates (36) are natural phytocomponents present in the pungent plants like horseradish, mustard, and cabbage. Glucosinolates protect the animals against chemically induced cancer, boosting the anti-oxidant status and induces phase II detoxication enzymes. Glucosinolates are converted into active compound isothiocyanate (37) in the presence of water by the enzyme myrosinase, which is conjugated with conjugating agent glutathione after which it is consecutively metabolized into mercapturic acids. Such metabolites are known as dithiocarbamates (Shapiro et al., 2001).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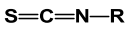
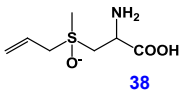

37

Alliin

Alliin **(38)** is a natural phytoconstituent present in the fresh garlic. It is prodrug form of allicin. Alliin is a cysteine derivative. When the garlic is crushed, the alliin is converted into active compound allicin **(39)** by alliinase enzyme. Allicin possesses various pharmacological activities like antiviral, antifungal and antibacterial activities. Allicin is unstable compound, which is immediately converted into diallyl disulfide (Wink, 2003).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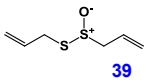
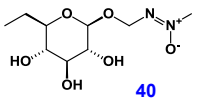

39

Cyanogenic glycosides

Cyanogenic glycosides such as linamarin, prunasin, amygdalin, and dhurrin are found in the so many food plants like *Phaseolus lunatus*, *Sambucus canadensis*, *Trifolium repens* and *Zea mays*. Cyanogenic glycosides are prodrug form of hydrogen cyanide. Cyanogenic glycosides are found in the vacuoles and the β-glucosidase enzyme is present in the cytosol of the plants. When the plants are damaged by trampling, mastication, drought and wilting, the cyanogenic glycosides are converted into hydrogen cyanide by the enzyme β-glucosidase (Wink, 2003).

Cycasin

Cycasin (40) is the phytotoxin present in *Zamia pumila* and *Cycas revolute*. Cycasin is converted into active compound methylazoxymenthanol (41) by intestinal enzyme β-glucosidase, which causes the midzonal coagulative hepatic necrosis, centrilobular and gastrointestinal irritation (Smith et al., 1967).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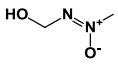
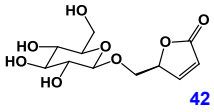

41

Ranunculin

Ranunculin (42) is an unstable glucoside present in the plant *Ceratocephalus testiculata*. When the plant is wounded, the ranunculin is enzymatically converted into glucose and active compound protoanemonin (43). Protoanemonin produces various adverse effects like paralysis, jaundice, acute hepatitis, vomiting, nausea, spasms and dizziness (Martin et al., 1990).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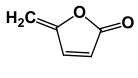
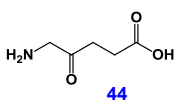

43

Aminolevulinic acid

It is a naturally occurring endogenous metabolite produced in the mitochondria by the condensation of succinyl CoA and glycine by the enzyme aminolevulinic acid. Aminolevulinic acid (44) is used for the treatment of cancer. Conjugation of eight molecules of aminolevulinic acid to produced protoporphyrin IX (45). Aminolevulinic acid is metabolized to active sensitizer protoporphyrin IX into all cells. Protoporphyrin IX converted into heme by the enzyme ferrochelatase. Protoporphyrin IX is not immediately conver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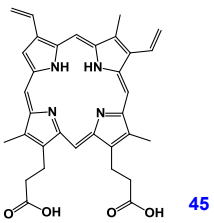

45

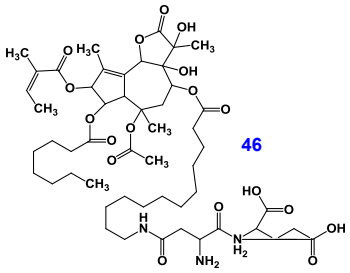
ted into heme which results in accumulation of protoporphyrin IX in the cells. The target cells exposed to

light that leads to excitation of photosensitizer and production of reactive oxygen species which produced the cytotoxic effects (Wachowska et al., 2011).

Prodrugs Developed from Natural Products

Mipsagargin (G-202)

Mipsagargin (**46**) is prodrug form of thapsigargin (**47**). Thapsigargin is the sesquiterpene lactone present in the plant *Thapsia garganica* and in the fruits and roots of *Mediterranean* species. Thapsigargin inhibits Ca^{2+}-ATPase leading to apoptosis and has also been utilized in the treatment of solid tumors, which is activated by PSMA mediated cleavage of an inert masking peptide.



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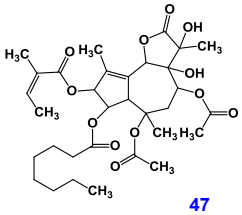
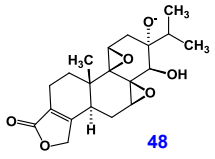


47

Thapsigargin is an inhibitor of sarcoplasmic and endoplasmic reticulum calcium adenosine triphosphate pump protein, which is necessary for cell viability (Andersen et al., 2015).

Triptolide prodrug

Triptolide (**48**) is a diterpene triepoxide, isolated from *Tripterygium wilfordii*. *In vitro*, triptolide inhibits proliferation and induces apoptosis of various cancer cell lines and *in vivo*, it prevents the tumor growth and metastases. Triptolide has poor aqueous solubility. To overcome this problem, the disodium phosphono-oxymethyl prodrug of triptolide (**49**) is designed to target various cancers like pancreatic, breast and prostate cancers (Patil et al., 2015).



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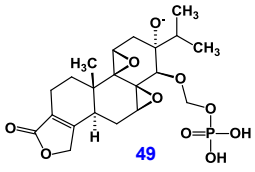
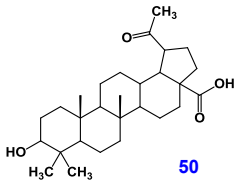


49

Betulinic acid

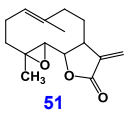
Betulinic acid (**50**) is a pentacyclic triterpenoid found in the bark of *Betula pubescens*. Betulinic acid is a cancer-fighting phytoconstituent, possessing various other pharmacological activities like anti-inflammatory, antiretroviral and antimalarial activities. Betulinic acid has a very low water solubility and shorter half-life. To overcome these problems, betulinic acid prodrug was formulated with help of multi-arm polyethylene glycol linkers. The betulinic acid prodrug showed more water solubility, high drug loading capacity and excellent *in vitro* anti-cancer activity (Dai et al., 2014).



50

Sesquiterpene lactones

The sesquiterpene lactones (**51**) are classes of terpenoids possessing various pharmacological activities such as antibacterial, antifungal, antiviral, insecticidal and anti-cancer activities because of the presence of α-methylene -γ-lactone. Sesquiterpene lactones are biologically active and have poor aqueous solubility. Sesquiterpene lactones act as Michael acceptor. To overcome the problems, sesquiterpene lactones prodrugs (**52**) were formulated with the addition of the amine to the α-methylene-γ-lactone to mask this group from nucleophilic attack as well as to increase solubility (Woods et al., 2013).



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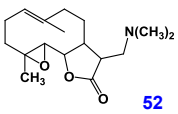
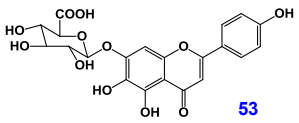


52

Scutellarin

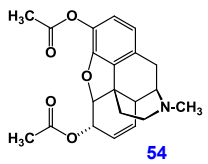
Scutellarin (**53**) is a flavone type of phenolic phyto-constituents present in *Scutellaria lateriflora* and *Scutellaria barbata* which is poor absorbed. To overcome this problem, ethyl ester, benzyl ester and glycolamide ester of scutellarin prodrugs were synthesized. Glycolamide ester of scutellarin prodrug showed good absorption and stability compared to ethyl ester and benzyl ester prodrugs of scutellarin (Cao et al., 2006).



53

Heroin

Heroin (**54**) is a prodrug form of morphine (**55**). Heroin acts as an opioid painkiller which is used as a recreational drug for its euphoric effects, anti-diarrhoeal and cough suppressant. Heroin is converted into morphine by deacetylation (Sawynok, 1986).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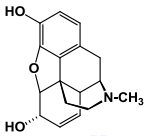
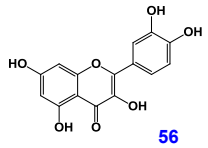

55

Quercetin-3-O-acyl esters

Quercitin (56) is a flavonol present in the leaves, vegetables, grains and fruits which are synthesized naturally in plants from phenylalanine. Quercetin acts as an anti-oxidant but is poorly absorbed. In order to enhance the absorption, quercetin-3-O-acyl esters such as quercetin propyl (57) and quercetin butyl esters (58) were prepared as prodrugs. Quercetin propyl and quercetin butyl esters had shown more water solubility and better permeability when compared to quercetin (Montenegro et al., 2007).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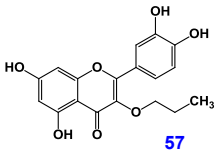
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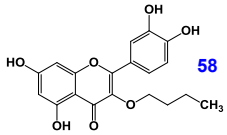
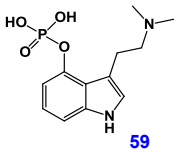

58

Psilocybin

Psilocybin (59) is a psychedelic substance naturally present in the *Psilocybe semilanceata*, *Psilocybe azurescens* and *Psilocybe cyanescens*. Psilocybin is a prodrug, which is converted into biologically active psilocin (60) by cleavage of phosphoric ester group by alkaline phosphatase in the brain. Psilocin is an agonist of many serotonergic receptors such as $5HT_{1A}$, $5HT_{1D}$, $5HT_{2A}$, and $5HT_{2C}$ in the brain. Psilocin regulates the motivation and mood (Rautio et al., 2008).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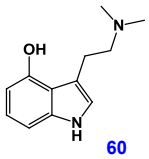
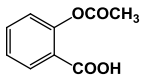

60

Aspirin

Aspirin (61) is prodrug form of salicylic acid (62). Salicylic acid is a phenolic acid found in the Willow tree. Aspirin reduces the pain, decreases the production of prostaglandins and thromboxanes, reduces the fever, and prevents blood clotting. Aspirin is converted into biologically active salicylic acid in the stomach (Kastrati et al., 2015).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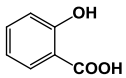
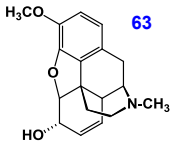

62

Codeine

Codeine (63) is a prodrug form of morphine (64). Morphine is isolated from *Papaver somniferum* and opium poppy, which acts as narcotic analgesic. Codeine is converted into morphine by CYP2D6 (Smith, 2009). Codeine is widely used for the treatment of mild to moderate pain, diarrhea, and as a cough suppressant.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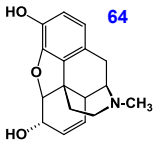
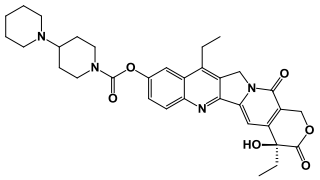

64

Irinotecan

Irinotecan (65) is derived from camptothecin. Camptothecin is isolated from *Camptotheca acuminata*. Irinotecan is used for the treatment of gastric tumors and colonic cancer, which is converted into active 7-ethyl-10 -hydroxycamptothecin (66) by the enzyme carboxylesterase (Marsh and Hoskins, 2010).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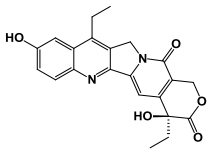
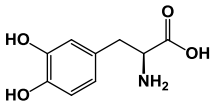

66

L-Dopa

L-Dopa (67) is found in *Vicia faba* and *Mucuna pruriens* which are used for the treatment of Parkinson's disease. L-Dopa is converted into active dopamine (68) by the enzyme amino acid decarboxylase (Di Stefano et al., 2011).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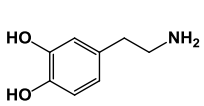
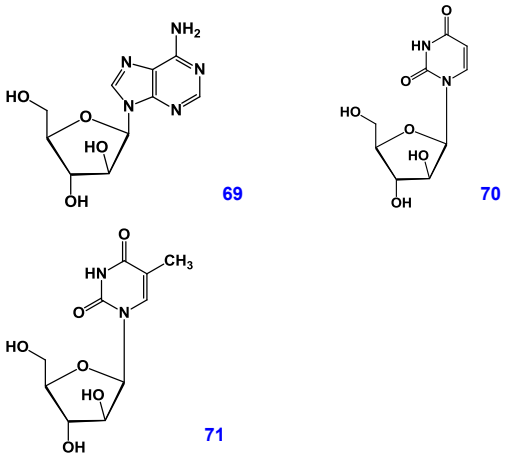

68

Vidarabine

Vidarabine (69), an antiviral drug that is active against the varicella zoster virus and herpes simplex virus. Spongouridine (70) and spongothymidine (71) were isolated from the *Tethya crypta* which contains D-ribose

and D-arabinose. Spongouridine and spongothymidine were used as a template for the synthesis of vidarabine (Kijjoa and Sawangwong, 2004).



Conclusion

Considering the importance of the drugs from the natural sources, a new era has developed in which the allopathic medicines are replaced to a great extent by the herbal medicines. A well-known reason for such a revolution occurring in the field of medicine being the awareness among the people worldwide about the serious side effects occurring due to the use of allopathic medicines. On contrary, our nature has blessed us with numerous types of medicines from plants, animals, marine sources and microbes. In the present scenario, prodrugs from natural sources have always been an area of research in the field of pharmacy and medicine. They are gaining more and more importance in the field of novel drug discovery.

In the present research work, we have extended the search for the prodrugs from natural sources which mean not only herbs but also from marine, animal, and microbes. This present area provides more scope for the research and development for the treatment of many chronic and fatal diseases like cancer, viral diseases, autoimmune diseases etc. and also for the development of the novel drug dosage forms. We have included around 24 new prodrugs from nature along with 13 prodrugs developed from natural products for improving its physical properties. Furthermore studies are yet to be carried out to develop the dosage forms out of the prodrug which can serve as a boon to the human society.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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Author Info
Devarajan Saravanan (Principal contact)
e-mail: saravananpidatha@gmail.com; Phone: +09030195077

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