Ancient Roots of Modern Medicines; their Prospects and Promises

Sandeep S. Shrivastava¹, Pankaj M. Kharabe²,*

ABSTRACT

Drug development from natural products precedes human history by thousands of years. Mankind has learned to take the advantages of such discovered principles by nature which they now used to treat human diseases. Since, owing to the close evolutionary history with plants and animals species, many metabolites that they produce, mimics the human biological activities such as the neurotransmitters, enzymes and hormones. Therefore, many metabolites that plants and animals produce are now used by human being to treat the diseases like diabetes, cancer, microbial infections and Alzheimer’s disease. The advent of combinatorial chemistry, organic chemistry and high throughput screening (HTS) has developed many lead molecules to treat human diseases. Unfortunately, these renewed techniques did not bring any expected returns in terms of new drug discoveries and therefore many researchers have shifted their research efforts back to the natural products to discover and develop the multidimensional and multibroad spectrum medicines using genomic engineering, combinatorial mucbiosynthesis and modern analytical techniques. In the present review, we have discussed comprehensively the journey of modern medicines with their prospects and promises.

Key words: Combinatorial chemistry, High throughput screening (HTS), Genomic engineering, Genomic mining, Combinatorial mucbiosynthesis.

INTRODUCTION

The medicinal importance of natural products those derived from plants and animals precedes human history by thousands of years. Over the several past centuries, owing to the widespread biological activities and medicinal importance of natural products, nearly every civilization in the orient and occident accumulated their own skills and knowledge of their use. Since, our earliest ancestors chewed off the leaves of certain wound healing plant species to get relief from pain or wrapped them around their skin to prevent from injuries,[1] and the scrapped skins of certain frog’s species that had been used by Indian tribes to heal wounds.[2]

Over the ensuing millennia, mankind have discovered and used an enormous range of folk herbal medicines, though they didn’t know the active phytochemicals and their efficacy; still they remain a ‘sole means’ to discover today’s produgs, synthetic and semisynthetic medicines. Quinine isolated from the cinchona bark of Cinchona officinalis is now used as an antimalarial drug that had long been used as an anti-pyretic by the tribal people in the Amazon region.[3] Same alkaloid derived from Cinchona succirubra, known for several centuries by South American Indians to treat malaria; now it is used to synthesise several series of quinolones and nalidixic acid.[4] Reserpine, from Rauvolvia serpentina had long been used as antipsychotic drug by Indian tribe—called it “pagle ki dava” (means a drug for psycho). However, the cost of its synthesis is three times than derived naturally.[5] Moreover, many other approved drugs; digoxin from Digitalis purpurea, ephedrine from Ephedra americana, aspirin from willow bark, ergometrine from Claviceps purpurea and atropine from Atropa belladonna are now judiciously used to treat diseases which had long been used by our primitives.

Over the same millennia, many animal species were also used to treat human diseases. As recorded, the men of South American tribes, after hunting attempts, scrape-off the juice from frog’s skin and smear it on their inflicted injuries. Indeed, not until 1970s it was known, the active compound was dermaseptin. It kills off germs probably by penetrating itself into the phospholipid bilayer.[5] Subsequently, more than 200 polypeptides including magainin, ranalexin, brevinins, exenatide, ziconotide and trabectedin were isolated and identified.[6-13] Similarly, another polypeptide; teprotide isolated from the venom of the Brazilian pit viper; Bothrops jararaca is used to develop ACE inhibitors— captopril and enalapril.[14] The discovery of antimicrobial properties from molds probably goes back to the earliest recorded human history. Since 5000 years ago, Chinese scribes have used moldy soya beans to treat wounds. A Greek farmer woman, by 3600 years ago, reported to cure an
inflicted soldier, using a mold that was scraped from cheese. The Ebers papyrus from Egypt (1550 BC) described the use of spoiled barley bread to treat the injuries. Subsequently, the importance of molds in drug discovery was continued to the nineteenth century even without much known how they could act on human being.

Thus, built on our earliest ancestors approaches, many physicians and pharmacist in era; circa—2600 BC-200 AD have added their own insight and knowledge of medicinal importance of natural products and did explain how to use them in combination or alone that have endowed many important clues for discoveries of modern medicines. They did understand—‘many plants and animal species contain numerous active principles which act differently on human body to produce desired therapeutics effects’ but their specific identity; chemical structures and related physico-chemical properties were remained unknown and continued until to the eighteenth century.

In the late 1990s, several pharmaceutical companies have attempted the renewed high throughput screening (HTS) and combinatorial chemistry to develop and modernise originally invented natural drugs to enhance their pharma-kinetic-dynamic properties. Nevertheless, these strategies did not bring any expected returns in terms of new drug discoveries and development; hence, they shifted their research efforts back to the natural tools, adopting the renewed techniques like modern analytical techniques, genomic mining and combinatorial mucobiosynthesis. Furthermore, the advent of modern analytical techniques has made possible to isolate and purify many active constituents from plants, animals and microorganisms that hold much potential to treat diseases.

Early history of natural products origin

The oldest medicinal manuscript, written in Mesopotamia, circa 2600 BC, had documented thousands of clay tablets in cuneiform, described numerous medicinal herbs including species like *Thymus vulgaris*, *Carum carvi*, *Cupressus sempervirens*, *Glycyrrhiza glabra*, *Commiphora myrrha*, and *Papaver somniferum* which are still used in treatment of illness; extending from minor cough to severe infections and inflammations. The ancient Egyptian, *Ebers Papryrus*, dated around 1550 BC, documented thousands of complex medicinal prescriptions, and the use of more than hundreds of natural products including *Aloe vera*, *Botswelia carteri*, and *Ricinus communis*.¹⁵

Over the same millennia, natural products derived medicines were already flourished in the Orient. Ayurveda—written on the holy papyri of *Betula utilis* presumed to be the oldest written medicinal manuscript which described thousands of medicinal herbs—précised in millions of poetic hymns.¹⁶ Simultaneously, Sushruta (circa 600 BC) renowned Indian physician and surgeon of those millennia, apart from using surgical practices, also reported the medicinal importance of plants and animal species.¹⁷ Comparatively, there is very little known about any written earliest manuscripts of ancient Chinese herbal medicine but the most eminent encyclopedia of ’Chinese Materia Medica’ listed around 6000 drugs, among them 4800 therapeutic agents are from plant origin. In Chinese medicine, the species like *Coptidis rhizoma* and *Evodia rutaecarpa*, known as *Zuo Jin Wan*, have long been used to treat gastric disorders but recently it has been envisaged that these activities could because of berberine, calystegine, limonene, rutecarpine and obacunone which are the potent inhibitors of enteric microflora—*Helicobacter pylori*.¹⁸ More importantly, these plant species are still used as a frontline antibiotics and anti-ulcer agents. Moreover, in ancient Chinese medicine; Qian Ceng Ta (*Huperzia serrata*) used for many centuries to treat fever and inflammation, though it has no any antipyretic or anti-inflammatory properties, but a potent inhibitor of acetyl cholinesterase enzyme and hence approved to treat the Alzheimer disease.¹⁹

In the well civilised ancient western world, many Greek physicians have given immense contribution in development and processing of herbal drugs. Among them the renowned physician, Hippocrates of Cos (circa 460–377 BC), accumulated more than 400 plant species and described their medicinal potentials in his ’Corpus Hippocraticum’. He documented the use of melon juice as a laxative, diuretic effect of *Ornithogalum caudatum* and the anesthetic effect from *Atropa belladonna*.²⁰ Galen (129–200 AD), another great Greek physician and pharmacist, reported around 540 medicinal plant species and emphasised— ‘the medicinal plants not only contain the active phytochemicals, but also consisting of harmful ingredients which act collectively to produce any biological effects on human being’.

During the same era, the drug discovery from natural resources had already flourished in roman civilisation. Pedanius Dioscorides (circa 40–90 AD) in his well-known De Materia Medica described the efficacy and dosage form of several combinations of plant extracts and became the first person who erected the foundations of pharmacology in Europe.²¹ Despite the comprehensive use of plants derived natural products as medicine, their effective components that have desired therapeutic effects was remained unknown until the eighteenth and nineteenth centuries.

Subsequently, modern chemistry dealing with separation sciences has been improved in a new era to isolate and purify the active ingredients from the crude plant extracts. In 1805, the German pharmacists—Friedrich Wilhelm Serturner, extracted and isolated, morphine from *Papaver somniferum* and was recorded the first naturally derived phytochemical that was commercialised by Merck in 1826.²² Later on, many western pharmaceutical companies began to isolate the active medicinal constituents from herbal plants which they used as a precursor for the development of synthetic and semi-synthetic compounds. Indeed until now, a large number of drug compounds have been analysed, purified and used as therapeutic agents by several pharmaceutical companies.

In twentieth century, the discovery of bactericidal effects of penicillin by Scottish microbiologist, Alexander Fleming (1928), derived from *Penicillium* mould, inspired further discoveries antimicrobial compounds including doxorubicin from *Sterptomyces peucetius*, avermectin from *Sterptomyces avermitilis*, streptomycin from *Actinomycine griseus*, cephalosporin from *Cephalosporium acremonium*, carabenem from *Sterptomyces cattleya*.

Furthermore, structural modulation was initiated to improve upon drug solubility, stability, bioavailability and efficacy.²³ In result, recently approved drugs by FDA or under the clinical trials; arteether (Artemotil) from *Artemisia annua*,[⁴] galantamine (Reminyl) from *Galanthus woronowii*,²⁵ nitisinone (Orfadin) from *Callistemon citrinus*,²⁶ tiotropium (Spiriva) from *Atropa belladonna*,²⁷ paclitaxel (taxol) from *Taxus brevifolia*, vinflunine (lavian) from *Catharanthus roseus*,²⁸ exatecan (DX-8951f), from *Camptotheca acuminata*,²⁹ calanolid from *Calophyllum lanigerum* and consolidation from *Tabernaemontana divaricata* (Table 1; Figure 1).

After knowing various aspects of natural products in drug discoveries, many scientists have tried to explain the mystery of ‘why so many natural products have biological effects on living species’? In justification of evolution theory—it is a long term coexistence within living organisms. Probably, while interacting with one another, they develop certain messengers in terms of chemicals which influenced the biological activities of other interacting species.³⁰ Therefore, owing to the close human physiology with other co-existing species, it is not surprising that those metabolites active on herbivorous could also exhibit the same effects on human body. Thus, many chemical messengers that plants
| Nat. Product (Precursor) | Species                        | Discovered | Company                  | FDA phases (trials) | Clinical indications; mechanisms                                                                 |
|-------------------------|--------------------------------|------------|--------------------------|---------------------|------------------------------------------------------------------------------------------------|
| Jatrophane              | *Euphorbia semiperfoliata*     | 2003       | Bristol-M. Squibb (USA)  | Preclinical trials  | Malaria, Carcinomas; inhibit P-glycoprotein                                                   |
| Eleutherobin            | *Erythrophodium cabaracorum*   | 1995       | Bristol-M. Squibb (USA)  | Preclinical trials  | Ovarian carcinoma; inhibit tubulin polymerization                                              |
| Platensimycin, Platencin| *Streptomyces platensis*       | 2006       | Merck (USA)              | Preclinical trials  | Dermatitis, colitis; Inhibits β-ketoacyl synthase                                               |
| Mannopeptimycin         | *Streptomyces hygroscopicus*   | 1970       | Wyeth (USA)              | Preclinical trials  | MRSA infection; blocks trans-glycosylation                                                    |
| bardoxolone methyl      | *Centella asiatica, Camellia sinensis* | ----   | Reata (USA)              | Clinical trial      | COVID-19                                                                                       |
| omaveloxolone           | *Centella asiatica, Camellia sinensis* | ----   | Reata (USA)              | Clinical trial      | COVID-19                                                                                       |
| (+)-Discodermolide      | *Discodermia dissolata*        | 1990       | Novartis (USA)           | Discontinued        | Breast carcinoma; suppresses IL-2 by PMA-ionomycin                                              |
| Dictyostatin            | *Spongia, Theonellidae*        | 2004       | Univ. Temp. Ariz. (USA) | Phase I             | Adenoma pancreas; binding on β-tubulin                                                        |
| Nocathiacins            | *Amycolatopsis fastidiosa*     | 1999       | Bristol M. Squibb (USA)  | Phase I             | Pneumonia, meningitis; binds to 50S ribosome                                                    |
| Salinosporamide A       | *Salinispora tropica Salinispora arenicola* | 1980 | Nereus (USA)            | Phase II             | Colon, Lung & breast carcinomas; inhibits 20S protease                                           |
| Safracin                | *Pseudomonas fluorescens*      | 1983       | Johnson & Johnson (USA)  | Phase II             | Microbial infections; inhibits DNA replication                                                 |
| Arylomycin              | *Streptomyces roseosporus*     | 2004       | Lily (USA)               | Phase II             | Pneumonia; blocks Signal-1 peptidase                                                           |
| Calanolide A            | *Calophyllum lanigerum*        | 1987       | Sarawak (Malaysia)       | Phase II             | HIV-AIDS; tuberculosis; RNA reverse transcriptase                                                |
| Aclacinomycin (Aclarubicin) | *Streptomyces galilaeus*      | 1975       | Micro. Chem. (Japan)     | Phase II             | Leukemia; inhibits chromatin unfolding & DNA fragmentations                                   |
| Betulinic acid (botulin) | *Ziziphus mauritiana; Betula pubescens; Inonotus obliquus* | 1995 | Adv. Life Sciences (USA) | Phase II             | Malaria, HIV-AIDS; inhibits topoisomerase-I                                                    |
| isothiocyanate (sulforaphane) | *Brassica oleracea*          | ----       | Evgen Pharma (UK)        | Phase II             | metastatic breast cancer, COVID-19                                                            |
| Forodesine              | *Crithidium fasciculata*       | 2008       | Vern Schramm's lab (New Zealand) | Phase II             | T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia                        |
| Razupenem (Thienamycin) | *Streptomyces cattleya*        | ----       | Merck (USA)              | Phase II             | Pneumonia, dermal & urinary tract infection; inhibit peptidoglycan biosynthesis               |
| Cethromycin             | *Saccharopolyspora erythraea*  | 1997       | Abbott (USA)             | Phase III            | Respiratory tract infection; blocks 50S ribosome                                                |
| Pexiganan (Magainin)    | *Xenopus laevis*              | 2012       | Magainin (USA)           | Phase III            | Diabetic foot ulcer; disrupt cellular electrostatic interaction                               |
| Huperzine A             | *Huperzia serrata*            | 1986       | Shand. Luye (JAP)        | Phase III            | Alzheimer’s disease; inhibit acetylcholinesterase                                              |
| Pagibaximab             | H. M. C. antibody (IgG1)      | ----       | Bio.nexus-GSK (UK)       | Phase III            | Neonatal staphylococcal sepsis; inhibit lipoteichoic acid                                      |

produced against herbivorous are now used as sedatives, laxatives, emetics, anesthetics, antidiabetics and muscle relaxants (Table 2). In addition, mankind has taken the advantages of secondary metabolites from unicellular species which they used to kill or suppress the growth of other interacting species. Humans have learned to take the advantages of such messengers to develop the antibiotics (Table 3), antifungal (Table 4) and anticancer agents (Table 5). Several natural products mimic the molecular structures of human endogenous neurotransmitters, ligands, hormones, enzymes, and some other elements which are actively involved in inter/intracellular transduction. For example, the spinosyns, a group of 50 macromolecules, derived from *Saccharopolyspora spinosa*, as pesticide and insecticide; though they do not have any antimicrobial properties but due to close similarities in structures of certain neurotransmitters in animals, they block their nerve signal transmission.
several marine species, including cone snails while interacting with other species produces toxic polypeptides which owing to the close similarities in molecular structures of neurotransmitters; block their Ca$^{2+}$ channels to interrupt nerve signal transmission.\cite{35} Another example is telomestatin that mimics the tetraguanine fragments of telomeres and inhibit the enzyme telomerase.\cite{36} Furthermore, a purine analogue pentostatin from *Streptomyces antibioticus* which resembles the adenosine nucleoside; and exenatide (*Byetta*\textsuperscript{®}), derived from the venom of *Heloderma suspectum* emulate the structure of incretin.\cite{37}

The theory of coexistence has been solely accepted by knowing the fact that several human genes are homologues with plants, animals and microorganisms; even in some extent, plants, humans and animals shares some similar gene sequences for development of neurotransmitters, hormones and secondary metabolites.\cite{38-40} For example, sitosterol, stigmasterol, lanosterol and brassinolides which are used to regulate cellular development in plant kingdom; they are structurally similar to human growth regulating steroids— testosterone and estrogen. Infact, different vertebrates and mammals also produce similar androgenic steroids for the same purpose (Figure 2). Considering these similarities, many bioidentical hormones, such as diosgenin from yams and soy have been used to develop the human steroids.

Adding to this fact, recently it was proved, the secondary metabolites derived from plants and insects use the same signaling pathway to induce the pain in humans and animals. For example, the venom of certain tarantula species shares the same signaling pathway of pain in

![Figure 1: Molecular structures of selected phytochemicals; under clinical trials.](image)

(A) Artemisinin from *Artemisia annua*, (B) Nitisinone from *Callistemon citrinus*, (C) Conolidine from *Tabernae montana divericata*, (D) Tiotropium from *Atropa belladonna*, (E) Exatecan from *Camptothecacum acuminata*, (F) Galamtamine from *Galanthus woronowii*, (G) Calanolide from *Calophyllum lanigerum*, (H) Bardoxolone methyl from *Centella asiatica*, *Camellia sinensis*, (I) Safracin A from *Pseudomonas fluorescens*, (J) Vinflunine from *Catharanthus roseus*

![Figure 2: Structural Correlation of Natural Steroids in Plants, Insects, Fungi, Animals and Humans:](image)

(A) Core Skeletal Structure of Natural Steroids: 1,2-Cyclopentanoperhydrophenanthrene (sterane); (B) Testosterone: extracted from Vertebrates; (C) Hellebrigenin: excreted from Toad skin; (D) Cucurbitacin: anticancer agent obtained from *Cucurbita andreana*; (E) Ecdysone: molting hormone obtained from arthropods; (F) Brassinolide: isolated from Bark and Pollens of *Brassica napus*; (G) Forskolin: derived from root of *Colesus forskohlii*; (H) Ergosteroid: extracted from fungi *Claviceps purpurea*; (I) Bile acid; excreted through liver in Mammals.
Table 2: Antidiabetic, antialzheimer’s, antimalarial and miscellaneous drugs from natural products.

| Nat. Products (Precursor) | Species | Discovered | Company | FDA approval | Clinical indications; mechanism |
|---------------------------|---------|------------|---------|--------------|---------------------------------|
| Lovastatin, Mevinolin     | Aspergillus terreus; Monascus ruber | 1979 | Merck (USA) | 1985 | Hypercholesterolemia; inhibits HMG-CoA reductase |
| Acarbose                  | Actinoplanes | 1970 | Bayer (Germany) | 1990 | Diabetes mellitus-I; inhibits α-Glucosidase |
| Voglibose                 | Inonotus obliquus, Streptomyces hygroscopicus | 1981 | Takeda (Japan) | 1994 | Diabetes mellitus-I; inhibits α-Glucosidase |
| Atorvastatin (Compactin)  | Actinoplanes teichomyceticus | 1985 | Pfizer (USA) | 1996 | Dyslipidemia; blocks HMG-CoA Reductase |
| Lipstatin                 | Streptomyces toxytrichini | 1983 | Hoff. Roche (Switzerland) | 1999 | Hyperlipidemia, atherosclerosis; inhibits pancreatic lipase |
| Mevastatin (Compactin)    | Penicillium brevicompactum; Penicillium citrinum | 1976 | Sankyo (Japan); Beecham (UK) | 2002 | Hypercholesterolemia; blocks HMG-CoA reductase |
| Pitavastin (Compactin)    | Aspergillus terreus | 1976 | Sankyo (Japan) | 2003 | Dyslipidemia; blocks HMG-CoA Reductase |
| Rosuvastin (Compactin)    | Penicillium brevicompactum | 1976 | Sankyo (Japan) | 2003 | Dyslipidemia; blocks HMG-CoA Reductase |
| Incretin (Exendin)        | Helodermia suspectum; Helodermia horridum | 1992 | Amylin (USA) | 2005 | Diabetes mellitus-II; suppresses glucagon |
| Exenatide (Incretin)      | Helodermia suspectum | 1992 | Astra-Zeneca (UK) | 2005 | Diabetes mellitus II; GLP-1 receptor agonist |
| Pravastatin               | Streptomyces carophilus | 1989 | Bristol-M. Squibb (USA) | 2006 | Hypercholesterolemia; inhibits HMG-CoA reductase |
| Natural products for treatment of Alzheimer's disease | | | | | |
| Bryostatin-1              | Bugula neritina-Endobugula sertula | 1980 | Rock. Biotech (USA) | 2001 | Inhibits serine/threonine kinases |
| Galantamine, Galanthamine | Galanthus woronowii; Galanthus nivalis | 1959 | Sopharma (Russia); Janssen (Belgium) | 2002 | Vascular dementia, inhibit acetylcholinesterase |
| Antimalarial drugs from natural products | | | | | |
| Artemisinin, Qinghaosu    | Artemisia annua | 1971 | Qinghaosu Res. (China) | 2000 | Inhibit sarco/endoplasmic reticulum Ca++ -ATPase (SERCA) in Plasmodium falciparum |
| Arteether (Artemisinin)   | Artemisia annua | 1977 | Artecel (Netherland) | 2000 | |
| Artemether (Artemisinin)  | Artemisia annua | 1977 | Qinghaosu Res. (China) | 2009 | |
| Miscellaneous compounds derived from natural products | | | | | |
| Teprotide (Captopril)     | Bothrops jararaca | 1975 | Bristol M. Squibb (USA) | 1981 | Hypertension; inhibits angiotensin converting enzyme |
| Plaunotol                 | Croton sublyratus | 1977 | Sankyo (Japan) | 1987 | Colic ulcer; suppress gastric bicarbonate secretion |
| Ivermectin (Avermectin B) | Stertomyces avermitillis | 1979 | Merck (Switzerland) | 1987 | Anthelmintic; inhibits GABA |
| Podophyllotoxin           | Podophyllum peltatum | 1936 | Burroughs Wellcome (UK) | 1990 | Genital warts; inhibits topoisomerase-II |
| Forskolin                 | Coleus forskohlii | 1977 | Hoechst (India) | 1999 | Stimulate cAMP & cGMP; inhibits intracellular Ca++ |
| Bivalirudin               | Haementeria officinalis | …… | MDCO-App (USA) | 2001 | Angina pectoris; inhibits thrombin |
| Diosgenin, Hecogenin      | Dioscorea althaeoides, | 1936 | Botanica-Mex (Mexico) | 2002 | Steroid synthesis precursor |
| Nitisinone (Leptospermone) | Callistemon citrinus | (1991); | Astra Zeneca (UK) | 2002 | Tyrosinaemia; inhibits 4-hydroxyphenylpyruvate oxidase |
| Milbemycin                | Stertomyces hygroscopicus | 1972 | Novartis (Switzerland) | 2002 | Anthelmintic; suppresses nerve hyperpolarisation |
| Miglustin (Nojirimycin)   | Stertomyces lavandulae | 1999 | Actelion (Switzerland) | 2003 | Gaucher’s-1; blocks glucosyl ceramide synthase |
| Ziconotide (β-conotoxin)  | Conus magus (Cone snail) | 1980 | Azur (USA) | 2004 | Analgesic; blocks Ca++ channels |
| Nat. Product (Precursor) | Species | Discovered | Company | FDA Approval | Clinical indications; mechanism |
|--------------------------|---------|------------|---------|--------------|----------------------------------|
| Fosfomycin | Streptomyces fradiae | 1969 | Merck (USA) | 1988 | Uterine infections; inhibits UDO-N-acetylglucosamine-3-enolpyruvyl transferase |
| Clarithromycin | Saccharopolyspora erythraea | 1970 | Taisho (Japan); Abbott (USA) | 1991 | Respiratory infection; binds 50S ribosome |
| Cefpirome | Cephalosporium acremonium | 1988 | Astellas (Japan) | 1992 | Meningitis, pneumonia; bind to PBPs and |
| Dirithromycin (Erythromycin) | Streptomyces erythreus | 1988 | Abbott (USA) | 1993 | Dermal & Respiratory infections; binds to 50S ribosome |
| Cefozopran (Cephalosporin) | Cephalosporium acremonium | ---- | Fujisawa (Japan) | 1995 | Urinary tract infections, bind to PBPs |
| Cefepime (Cephalosporin) | Cephalosporium acremonium | 1994 | Fujisawa (Japan) | 1997 | Meningitis, pneumonia, dermal & uterine infections |
| Cefdinir (Cephalosporin) | Cephalosporium acremonium | 1991 | Fujisawa (Japan) | 1997 | Otitis media, pharyngitis, dermal infection; bind to PBPs |
| Flurithromycin (Erythromycin) | Streptomyces erythreus | 1988 | Abbott (USA) | 1997 | Respiratory & dermal infections; binds to 50S ribosome |
| Cefoselis (Cephalosporin) | Cephalosporium acremonium | 1991 | Fujisawa (Japan) | 1998 | Respiratory tract infections; binds to PBPs |
| Rifapentine (Rifamycin) | Amycolatopsis mediterranei | 1965 | Sanafi-Aventis (France) | 1998 | Tuberculosis; inhibits RNA polymerase |
| Rifapentine (Rifamycin) | Amycolatopsis mediterranei | 1965 | Sanafi-Aventis (France) | 1998 | Tuberculosis; inhibits RNA polymerase |
| Magainin | Xenopus laevis | 1987 | Magainin; Glaxo (UK) | 1999 | Microbial infections; penetrates microbial phospholipid bilayer |
| Valnemulin (Pleuromutilin) | Clitopilus passeckerianus; Pleurotus mutilus | 1954 | Novartis (France) | 1999 | Swine dysentery; inhibits peptidyl transferase of 23S RNA |
| Mesotrione (Leptospermone) | Callistemon citrinus | 1988 | Syngenta (Switzerland) | 2000 | Insecticide; inhibits 4-hydroxyphenylpyruvate deoxygenase |
| Cefditoren, Fumagillin | Aspergillus fumigatus | ... | TAP (USA) | 2001 | Pneumonia, bronchitis, pharyngitis, tonsillitis; inactivates PBPs |
| Erythromycin | Streptomyces erythreus | 1952 | Abbott (USA) | 2001 | Pneumonia, vaginitis; blocks ribosomal methylase of 23S ribosome |
| Biapenem (Thienamycin) | Streptomyces cattleya | 1976 | Merck (USA) | 2002 | Respiratory & urinary tract infection; inhibits peptidoglycan biosynthesis |
| Thienamycin | Streptomyces cattleya | 1976 | Merck (USA) | 2002 | Pneumonia, dermal& urinary tract infection; Inhibits peptidoglycan biosynthesis |
| Leptospermone | Leptospermum scoparium; | 1977 | Stauffer (USA) | 2002 | Insecticide; inactivates p-hydroxyphenylpyruvate deoxygenase |
| Ertapenem | Erithromycin | 1976 | Merck (USA) | 2002 | Pneumonia, diabetic foot& dermal infection, inhibits peptidoglycan biosynthesis |
human that is used by capsaicin from plant species Capsicum annuum. In addition, certain triketones from Callistemon citrinus like nitisinone, mesotriene and leptosporenone act on the same 4-hydroxyphenylpyruvate dehydrogenase enzyme in plants and animals, in particular, acting on 4-HPDP enzyme in plants produce herbicidal effects due to blocking of plastoquinone and tocopherol biosynthesis. In humans, acting on the same 4-HDDP suppress the tyrosine catabolism. \[41,42\]

Beginning from the symbiotic relationship among all living species, mankind has improvised his metabolic and digestive system to transform certain phytochemicals into more active metabolites. Nevertheless, these metabolites are not inherent to humans, but transform into more active proto-drugs. \[43\] For instance, willow bark from Salix alba have been used to get relief from pain and fever but its effective compound is salicylic acid— willow bark only produces the salicin, a precursor of salicylic acid that is hydrolysed to salicylic alcohol and then oxidized to more effective salicylic acid— willow bark only produces the salicin, a precursor of salicylic acid that is hydrolysed to salicylic alcohol and then oxidized to more effective salicylic acid— willow bark only produces the salicin, a precursor of salicylic acid that is hydrolysed to salicylic alcohol and then oxidized to more effective salicylic acid— willow bark only produces the salicin, a precursor of salicylic acid that is hydrolysed to salicylic alcohol and then oxidized to more effective salicylic acid— willow bark only produces the salicin, a precursor of salicylic acid that is hydrolysed to salicylic alcohol 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Another example is a fidaxomicin, derived from Dactylosphorangium aurantiacum. It has no any antimicrobial properties but when it is hydrolysed to OP-1118, it becomes more effective to treat microbial infections. \[45\]

Arbutin, another secondary metabolite from Turnera diffusa used to treat gastric inflammations and urinary tract infections but it is only effective when it get metabolized into hydroquinone derivative. \[46\] Many phenolic compounds like sennosides from species Cassia angustifolia...
and *Cassia acutifolia* are only active when biotransformed into anthrone derivative by enteric microflora.

Including these, several species during interaction share some common metabolites, even without changing their molecular structures they used to counteract other species as well as to regulate their own biological activities. For example, saxitoxin is produced by dinoflagellates, but it was explored from shellfish that consumed the dinoflagellates, although it was not produced by selfish but it relies on dinoflagellates to get this saxitoxin. The same compound was also detected in Panamanian golden frog, but its original producer is microbes that are consumed by insects, which in turn consumed by frogs and selfish.\(^{[36]}\)

### Table 4: Antifungal agents from natural products.

| Nat. product (Precursor) | Species | Discovered | Company | FDA Approval | Clinical indications; mechanism |
|--------------------------|---------|------------|---------|--------------|----------------------------------|
| Validamycin              | *Streptomyces hygroscopicus* | 1970       | Takeda (Japan) | 1990 | Fungicide; Inhibit trehalase |
| Tacrolimus               | *Streptomyces tsukubaensis* | 1984       | Astellas, Fujisawa (Japan) | 1994 | Dermatitis, psoriasis; inhibit calcineurin |
| Spargualin               | *Bacillus laterosporus* | 1982       | Inst. microbial chem. (Japan) | 1994 | Fungal infections; inhibits interleukin-2 |
| Mizonarine               | *Eupenicilium brefeldianum* | 1974       | Toyo (Japan) | 1995 | Renal transplantation; Inhibits T-and B-cell proliferation |
| Mucidine, Strobiulin K   | *Oudemansiella mucida; Bolinia lutea* | 1969       | Syngenta (Switzerland) | 1996 | Fungal infection; inhibits mitochondrial respiration |
| Sirolimus (Rapamycin)    | *Streptomyces hygroscopicus* | 1974       | Pfizer (USA) | 1999 | Candidiasis; inactivates protein kinase complex |
| Echinocandin, Pneumocandin | *Papularia sphaeroasperma* | 1974       | Fujisawa (Japan) | 2000 | Fungal infections; blocks 1,3-β glucan synthase |
| Pneumocandin B           | *Papularia sphaeroasperma; Glarea lozoynensis* | 1970       | Eli Lilly (USA) | 2001 | Candidiasis, aspergillosis; inhibitsβ-(1,3)-glucan synthesis |
| Pyraclostrobin (Strobilurin) | *Bolinia lutea* | 2000       | BASF (Germany) | 2002 | Fungal infections; inhibits mitochondrial respiration |
| Caspofungin              | *Papularia sphaeroasperma* | 1989       | Merck (USA) | 2002 | Candidiasis, candidemia; inactivates β-1,3-D-glucan synthase |
| Ascomycin, Immunomycin   | *Streptomyces hygroscopicus* | ----       | Novartis (Switzerland) | 2002 | Dermatoses, dermatitis, psoriasis; inhibits Th1 cytokines |
| Picoxystrobin (Strobilurin) | *Bolinia lutea* | 2000       | Syngenta (Switzerland) | 2002 | Fungal infections; inhibits mitochondrial respiration |
| Mycophenolate mofetil    | *Penicillium brevicompactum* | 1893       | Novartis (France) | 2003 | Inactivates inosine monophosphate dehydrogenase |
| Dimoxystrobin (Strobilurin) | *Bolinia lutea* | 2001       | BASF (Germany) | 2003 | Fungicide; inhibit mitochondrial respiration |
| Mycophenolic acid        | *Penicillium stoloniferum; Penicillium echinulatum.* | 1896       | Novartis (Switzerland) | 2003 | Fungicide; inhibit inosine monophosphate dehydrogenase |
| Fluoxastrobin (Strobilurin) | *Bolinia lutea* | 1994       | Bayer (Germany) | 2004 | Fungicide; inhibit mitochondrial respiration |
| Anidulafungin            | *Papularia sphaeroasperma* | 1974       | Pfizer (USA) | 2006 | Aspergillosis & Candidiasis; Bind to β-1,3-D-glucan synthase |
| Orystasbofin (Strobilurin) | *Bolinia lutea* | 2006       | BASF (Germany) | 2006 | Fungicide; mitochondrial respiration |
| Pimecolimus (Ascomycin)  | *Streptomyces hygroscopicus* | 2001       | Novartis (Switzerland) | 2006 | Atopic dermatitis; calcineurin |
| Micafungin               | *Papularia sphaeroasperma* | 1990       | Fujisawa; Astellas (Japan) | 2005, 2008 | Esophageal candidiasis; β-1,3-D-glucan synthase |
| Zotalolimus (Rapamycin)  | *Streptomyces hygroscopicus* | 2005       | Abbott (USA) | 2008 | Cardiovascular surgery; suppress T-lymphocyte activation |
| Everolimus (Rapamycin)   | *Streptomyces hygroscopicus* | 2004       | Biocon (India) | 2009 | Renal infection; cyclophilin FKBP-12, T-lymphocyte activation |
| Myriocin                 | *Mycella sterilia; Isaria sinclarii; Myriococcum albomyces* | 1970       | Novartis (Switzerland) | 2010 | Renal transplantation; serine palmitoyl transferase |
| Nat. product (Precursor) | Species | Discovered | Company | FDA Approval | Clinical indications; mechanism |
|--------------------------|---------|------------|---------|--------------|---------------------------------|
| Bleomycin                | Streptomyces verticillus | 1962 | Nippon (Japan); B. M. Squibb (USA) | 1973 | Hodgkin's lymphoma; inactivates topoisomerase-II |
| Mitomycin (Mitosane)     | Streptomyces caespitosus | 1956 | Kyowa Kirin (Japan) | 1973 | Carcinomas bladder, pterygia; inhibits RNA synthesis |
| Aclarubicin              | Streptomyces galilaeus | 1975 | Umezawa (Japan) | 1981 | Acute myeloid leukemia |
| Streptozotocin, Streptozocin | Streptomyces achromogenes | 1952 | Pfizer (USA) | 1982 | Carcinomas pancreas; inhibits ADP ribosylation |
| Daunorubicin             | Streptomyces peucetius | 1966 | Nexstar (USA) | 1987 | Myelocytic leukemia; inhibit s topoisomerase-II |
| Bestatin (Ubenimex)      | Streptomyces olivoreticuli | 1976 | Inst. microbial chem. (Japan) | 1987 | Carcinoma cervical; inhibit aminopeptidase N (APN)/CD |
| Pentostatin (Coformycin) | Streptomyces antibioticus | 1974 | Inst. Microbial Chem (Japan) | 1992 | Lymphoid malignancies; inhibits adenosine deaminase |
| Arglabin-DMA             | Artemisia glabella | 1981 | Inst. Phytochemistry (USSR) | 1994 | Ras-related malignancies; inhibits farneyltransferase |
| Epirubicin               | Streptomyces peucetius | 1980 | Pharmacia-Upjohn (USA) | 1999 | Carcinomas Ovary & breast; inhibit topoisomerase-II |
| Calicheamicin γ          | Micromonospora echinospora | 1988 | Lederle (USA) | 2000 | Myeloid leukemia; split 5’-TCCT, 5’-ACCT of DNA |
| Gemtuzumab ozogamicin    | Micromonospora echinospora | 1980 | Wyeth-Ayerst (USA) | 2000 | Myelogenous leukaemia; DNA cleavage |
| Fulvestrant              | Estradiol estrogen Hormone | 1995 | Atossa Genetics (USA) | 2002 | (HR)-positive Metastatic Breast Cancer |
| Doxorubicin, Adriamycin  | Streptomyces peucetius | 1967 | Farmitalia (Italy) | 2002 | Leukaemia, lung & thyroid carcinoma, Hodgkin lymphomas; inhibits topoisomerase II |
| Amrubicin (Doxorubicin)  | Streptomyces peucetius | 1967 | Sumitomo (Japan) | 2002 | Lung carcinoma; inhibits topoisomerase-II |
| Camptothecin             | Camptotheca acuminata | 1996 | Chong Dang (S. Korea); Glaxo (UK) | 2004 | Cervical cancer; inhibits human topoisomerase-1 |
| Taxol (Paclitaxel)       | Taxus brevifolia | 1971 | B. M. Squibb (USA) | 2005 | Breast cancer; inhibits depolarization of microtubules |
| Squalamine               | Squalus acanthias | 1995 | Magainin (USA) | 2005 | Malignant glioma; alters electrostatic charges |
| Docetaxel                | Taxus brevifolia | 1995 | Sanofis-Aventis (France) | 2006 | Gastro-esophageal & breast carcinoma; binds to β-tubulin |
| Vorinostat (Trichostatin) | Streptomyces hygroscopicus | 1971 | Merck (USA) | 2006 | T-cell lymphoma; Inhibits histone deacetylase HDAC1 |
| Ixabepilone (Epothilone) | Sorangium cellulosum | 1995 | B. M. Squibb (USA) | 2007 | Non-Hodgkin's lymphoma, breast cancer; inhibits β-tubulin |
| Epothilone A-F           | Sorangium cellulosum | 1987 | Gesellschaft (Germany) | 2008 | Breast cancer; inhibits depolarisation of microtubules |
| Ecteinascidin (Trabectedin) | Ecteinascidia turbinata-Endoecteinascidia frumentenis | 1969 | PharmaMar (Spain) | 2007, 2009 | Tissues sarcoma, ovarian carcinoma; inhibits cellular proliferation |
| Valrubicin (Doxorubicin) | Streptomyces peucetius | 1998 | Endo (USA) | 2009 | Bladder & breast cancer; inhibits topoisomerase-II |
| Romidespin, Depsipeptide | Chromobacterium violaceum | 1994 | Fujisawa (Japan) | 2009 | Myeloma; inhibits histone deacetylase |
| Halichondrin B           | Halichondria okadai | 1985 | Eisai (Japan) | 2010 | Breast cancer; inhibits tubulin targeted mitosis |
| Eribulin                 | Halichondria okadai | 1998 | Eisai (Japan) | 2010 | Metastatic Breast Cancer |
| Ingenol Mebutate         | Euphorbia peplus | 1980 | Peplin Ltd. (Australia) | 2012 | Actinic keratosis, Myeloid leukemia |
Challenges in drug discoveries and development

It was reported that the process of new drug discovery takes more than ten years and cost more than one billion dollars. In addition, owing to the problems linked with their toxicities, stability and solubility, many lead molecules were discarded.\[^{46-48}\] In fact, as documented only one in 500 molecules would successfully precede a painstaking journey of clinical trials and getting the approval for further use. Thus, the discovery and development of better and effective medicines is enticing and for achieving these many modern techniques held immense challenges.\[^{49,50}\] Such as— first, owing to the involvement of bewildering numbers of biosynthetic pathways, many natural products inbuilt with various stereogenic centres and exist with complex molecular structures that could discourage any chemical modifications to enhance their therapeutic activities.\[^{34,36,51}\] Second, the yield of secondary metabolites after extraction process is very low. Moreover, although the plant and animal extracts available in large quantity, their subsequent purification from a mixture of several related compounds is difficult.\[^{50}\] Third, the therapeutic efficacy of herbal medicines most often depends on their synergistic or antagonistic activities with other molecules in a mixture—but after the isolation and purification process, there might be the possibilities of complete loss of any therapeutic effects. In addition, the inherent risk of adverse drug-drug interactions due to the possibilities of synergistic/antagonistic effects of multi-drug combinations is also challenging.\[^{52}\]

In the past few decades, the uncontrolled rapid development of resistance has ushered the use of renewed techniques to produce the multibroad spectrum antibiotics at regular intervals. For instance, between 1962 and 2002, except the discoveries of synthetic analogues; nalidixic acid and linezolid, there is no any new natural antibiotic has been approved and commercialised—though there are plenty of but many of them were the modifications of approved one.\[^{53}\] Above all, the drug discoveries from natural products have taken a primary role in modern drug development. Importantly, according to the statistics, between years 1983-2000, approximately 22,500, all new drugs were discovered. Many of them were approved by FDA or undergoing clinical trials. Among them, roughly around 13,500 molecules were antimicrobial, antifungal and anticancer agents; out of them nearly 425 were derived from plant species and around 675 were discovered from microbial species. Essentially, from microbial species, approximately 300 leads were discovered from actinomycetes, 256 from Fung and near about 115 were discovered from unicellular species.\[^{46,52,54}\]

Prospects in drug discovery from natural products

Current approaches like genetic engineering and genome mining have given immense contribution to develop the new drugs by decoding millions of gene sequences of unicellular species. Implementing these techniques, ziconotide is derived from tropical marine cone snail and commercialised by Neurex Pharmaceutical in 2004.\[^{55}\] Another example is trabectedin (ecteinascidin), isolated from sea-squirt and commercialised by PharmaMar in 2007.\[^{56}\] Like these many other drugs, purified after gene manipulations which are presently under various phases of clinical trials.

Modern drug discoveries using the combinatorial chemistry and high throughput screening (HTS) obliged to develop the new drugs on ‘one-drug—one-disease’ strategy. Nevertheless, the transmission of diseases in human involves various factors including, neurotransmitters, hormones, enzymes and polypeptides which act either alone or in combination. However, many drugs originated from combinatorial chemistry and HTS substituted with less number of functional units and hence often fail to produce any desired therapeutic effects.

Considering these facts, many pharmaceutical companies are now engaged in development of multidimensional and multibroadspectrum medicines that have some advantages in dealing with devastating disease and infections. Recently, such new strategy; mutasynthesis or chemoenzymatic synthesis developed the new promising antibacterial and anticancer drugs including mannopeptimycin, daptomycin, cryptophycin, vancomycin and rapamycin (Figure 1.1).\[^{11,56-59}\] Therefore, the recent improvement in modern chemistry has ushered how to develop the natural medicines to treat human diseases.

Subsequently, the advent of chromatographic techniques such as ultra-high performance liquid chromatography (UHPLC), super critical fluid liquid chromatography (SFC) and capillary zone electrophoresis (CZE) attached with mass spectroscopy (MS) or nuclear magnetic resonance (NMR) has taken a primary role in drug analysis and made possible to isolate and identify the new and effective drugs including steroids, tocopherols, flavonoids, polyphenols and alkaloids which has given a new insight to look their various mode of actions on human body. Therefore, the advancement in phytochemical analysis has inspired many developments in organic and analytical chemistry, leading to the evolution in synthetic methodologies to develop the analogues with improved biological efficacies—such as the development of ixabepilone and temsirolimus from precursors, epothilone and sirolimus respectively.\[^{60}\]

The modern tools of analytical techniques have now allowed to the analyst to interpret the exact molecular nature and structures of complex metabolites. For example, the selective stationary phases in HPLC-MS/MS such as the versatile C\(_{18}\) adsorbents with acidified aqueous phase have been used in screening of phytochemicals from plant species— for example, as displayed in Figure 3A, the order of selectivities of retained
chromatography used to isolate the phenols and phenolic acids (Figure 3C, 3D); and the cyano column in NP-HPLC used to isolate the phytosterols from other undesired products (Figure 3E).

Thus, throughout human evolution the medicinal importance of natural products is enormous and known to mankind from ancient ages. They have provided various important clues for the synthesis and development of non-natural medicines where in particular, the recent research work so far had been largely neglected. The advent of modern analytical techniques has given enormous contribution in isolation and purification of active constituents from natural products and the recent advances in mucobiotechnology has ushered the development of multibroadspectrum medicines. Moreover, recent advances in genetic engineering developed several medicines that mimic endogenous neurotransmitters, hormones and enzymes— which are now used to treat many devastating diseases like Alzheimer’s disease and dementia.

As discussed above, the techniques to improve and analyse the drug–drug interaction, drug-receptor interaction and their molecular modifications to improve any biological effects still poses challenges to new drug development. Despite these, today’s researchers, using the advanced tools of synthetic, analytical and certain –omics techniques could have learn from previous historical records to fight against critical diseases— since these records displayed thousands of year’s experience of medicinal use, written by our earliest physicians and pharmacists.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

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