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Review Article

Ancient Roots of Modern Medicines; their Prospects and Promises

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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 multibroadspectrum medicines using genomic engineering, combinatorial mucobiosynthesis 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 mucobiosynthesis.

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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 civilisation 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 prodrugs, synthetic and semisynthetic medicines. Quinine isolated from the cinchona bark of *Cinchona officinallis* 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 *Rauwolfia surpentina* 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,[5,6] 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.[7,8] Subsequently, more than 200 polypeptides including magainin, ranalexin, brevinins, exenatide, ziconotide and trabectedin were isolated and identified.[9-13] 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

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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 pharmaco-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 inflammation and infections. The ancient Egyptian, *Ebers Papyrus*, dated around 1550 BC, documented thousands of complex medicinal prescriptions, and the use of more than hundreds of natural products including *Aloe vera, Boswellia carteri*, and *Ricinus communis.*[15]

Over the same millennia, natural products derived medicines were already flourished in the Orient. Ayurveda— written on the holy pulp 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, calystigine, 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 serrate*) 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 pharmacist—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 griseous*, cephalosporin from *Cephalosporium acremonium*, carbapenem from *Streptomyces 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,*[24] galantamine (Reminyl®) from *Galanthus woronowii,*[25] nitisinone (Orfadin®) from *Callistemon citrinus,*[26] tiotropium (Spiriva®) from *Atropa belladonna,*[27] paclitaxel (taxol) from *Taxus brevifolia*, vinflunine (Javrol®) from *Catharanthus roseus,*[28] exatecan (DX-8951f), from *Camptotheca acuminate,*[29] calanolide from *Calophyllum lanigerum* and conolidine 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

Table 1: Natural products under clinical trials.

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	*Erythropodium caribaeorum*	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 dissoluta*	1990	Novartis (USA)	Discontinued	Breast carcinoma; suppresses IL-2 by PMA-ionomycin
Dictyostatin	*Spongia, Theonellidae*	2004	Univ. Temp. Ariz. (USA)	Phase 1	Adenoma pancreas; binding on β-tubulin
Nocathiacins	*Amycolatopsis fastidiosa*	1999	Bristol M. Squibb (USA)	Phase I	Pneumonia, meningitis; binds to 50S ribosome
Salinosporamide A	*Salinospora tropica Salinispora arenicola*	1980	Nereus (USA)	Phase II	Colon, lung & breast carcinomas; inhibits 20S proteasome
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	*Crithidia fasciculata*	2008	Vern Schramm's lab (New Zealand)	Phase II	T-cell acute lymphoblastic leukemia, B-cell acute lymphocytic 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).[31-33]

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.[34] 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.[4] In addition,

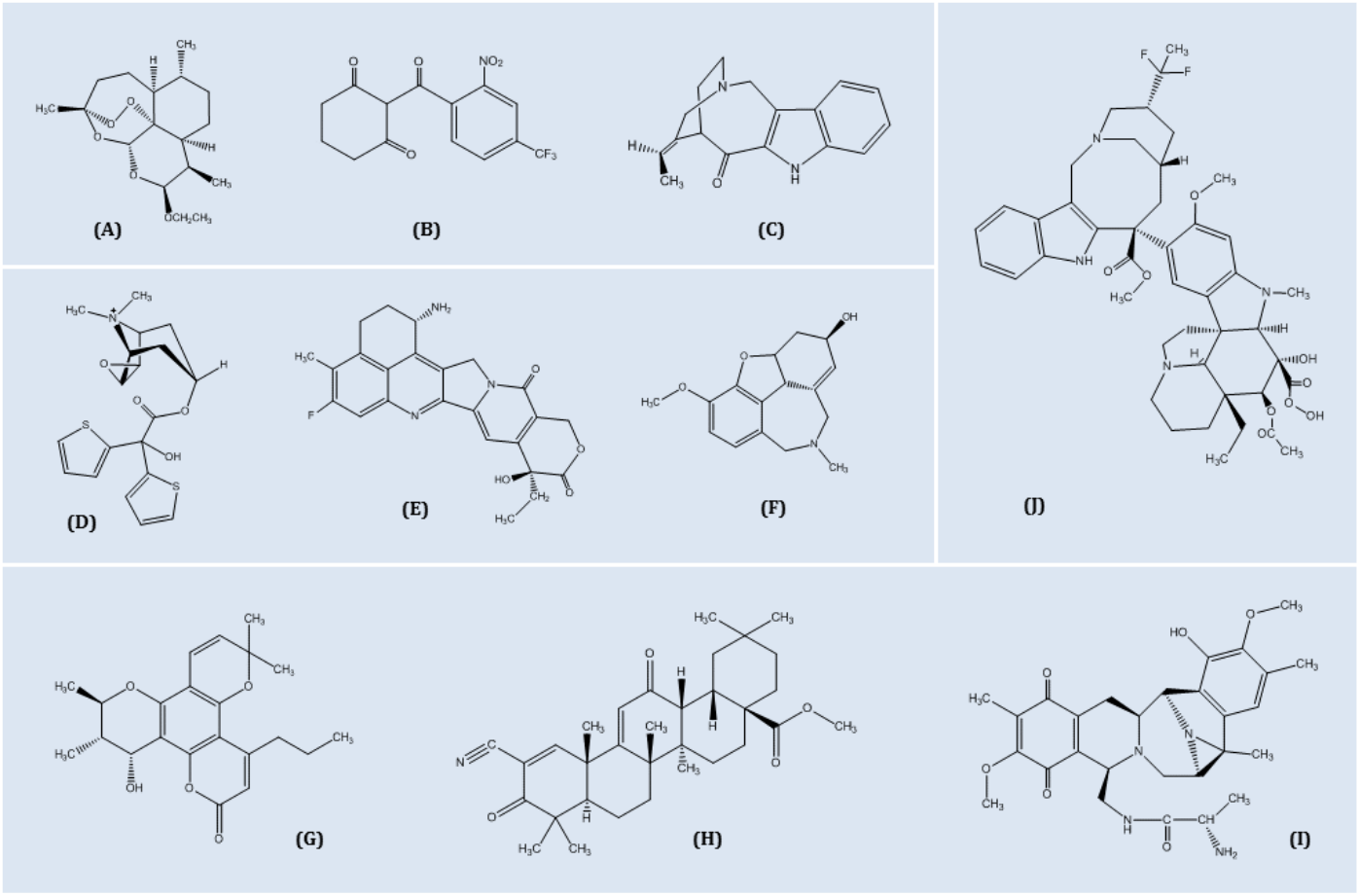

Figure1: Molecular structures of selected phytochemicals; under clinical trials.
(A) Artemisinin from *Artemisia annua*, (B) Nitisinone from *Callistemon citrinus*, (C) Conolidine from *Tabernaemontana divericata*, (D) Tiotropium from *Atropa belladonna*, (E) Exatecan from *Camptotheca acuminata*, (F) Galantamine 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*

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^{++} channels to interrupt nerve signal transmission.[35] Another example is telomestatin that mimics the tetraguanine fragments of telomeres and inhibit the enzyme telomerase.[36] Furthermore, a purine analogue pentostatin from *Streptomyces antibioticus* which resembles the adenosine nucleoside; and extenatide (Byetta®), derived from the venom of *Heloderma suspectum* emulate the structure of incretin.[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.[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

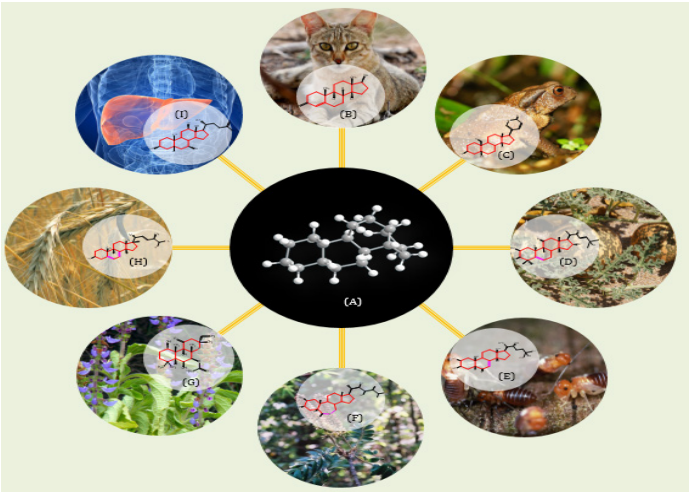

Figure 2: Structural Correlation of Natural Steroids in Plants, Insects, Fungi, Animals and Humans: (A) Core Skeletal Structure of Natural Steroids: 1,2-Cyclopentanoperhydrophenanthrene (sterane); (B) Testosterone: extracted from Vertebrates; (C) Hellebrigenin: excreted from Toad skin; (D) Cucurbitacin: 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 *Coleus 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 hygroscopicies*	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 toxytricini*	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
Pitavastatin (Compactin)	*Aspergillus terreus*	1976	Sankyo (Japan)	2003	Dyslipidemia; blocks HMG-CoA Reductase
Rosuvastatin (Compactin)	*Penicillium brevicompactum*	1976	Sankyo (Japan)	2003	Dyslipidemia; blocks HMG-CoA Reductase
Incretin (Exendin)	*Heloderma suspectum; Heloderma horridum*	1992	Amylin (USA)	2005	Diabetes mellitus-II; suppresses glucagon
Exenatide (Incretin)	*Heloderma suspectum*	1992	Astra-Zeneca (UK)	2005	Diabetes mellitus II; GLP-1 receptor agonist
Pravastatin	*Streptomyces carbophilus*	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*[31]	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	Artecef (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)	*Sterptomyces 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 officinallis*	…..	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	*Streptomyces hygroscopicus*	1972	Novartis (Switzerland)	2002	Antihelmintic; suppresses nerve hyperpolarisation
Miglustat (Nojirimycin)	*Streptomyces lavendulae*	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

Tiotropium	*Atropa belladonna*	2002	Boehringer (Germany); Pfizer (USA)	2004	Bronchodilator; blocks muscarinic receptors
Apomorphine (Morphine)	*Papaver somniferum*	1970	Mylan-Bertek (USA)	2004	Parkinson's disease, schizophrenia; dopamine receptors agonist
Dronabinol	*Cannabis sativa*	1964	GW Pharma (UK)	2005	Cachexia, emesis, pain; interacts with brain CB1 receptors
Capsaicin	*Capsicum annum*	1816	Astellas (Japan)	2009	Rheumatoid arthritis; blocks vanilloid receptor
Dimethyl fumarate (DMF)	*Fumaria officinalis*	1959	Fumapharm (Switzerland)	2013; 2017	Multiple sclerosis, Psoriasis, Biocides
Moxidectin	*Streptomyces cyanogriseus*	1980	American Cyanamid (USA)	2018	Onchocerciasis, Anthelmintic

Table 3: Antibacterial agents from natural products.

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*	…..	Astellas (Japan)	1992	Meningitis, pneumonia; bind to PBPs c
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; inhibitsRNA polymerase
Rifapentine (Rifamycin)	*Amycolatopsis mediterranei*	1965	Sanafi-Aventis (France)	1998	Tuberculosis; inhibitsRNA 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; inhibits4-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 (Thienamycin)	*Streptomyces cattleya*	1976	Merck (USA)	2002	Pneumonia, diabetic foot& dermal infection, inhibits peptidoglycan biosynthesis

Daptomycin	*Streptomyces roseosporus*	1986	Eli Lilly & Cubist (USA)	2003	Dermal infection; inhibits nucleic acid biosynthesis
Ramoplanin	*Actinoplanes strain 33076*	1984	Oscient (USA)	2004	Diarrhea; inhibits peptidoglycan biosynthesis
Tetracycline	*Streptomyces aureofaciens*	1948	Lederle (USA)	2005	Acne, dermal infection; binds to 30S ribosome
Carbapenem	*Streptomyces clavuligerus*	1976	Roche (Switzerland); Sankyo (Japan)	2001-2005	Pneumonia, urinary & dermal infection; inhibits peptide deformylase
Tigecycline (Tetracycline)	*Streptomyces aureofaciens*	1991	Wyeth-Lederle (USA)	2005	*C. difficile* infections; inhibit Tet efflux pumps
Cefquinome	*Cephalosporium acremonium*	…..	Astellas (Japan)	1994, 1999, 2005	Coliform mastitis; animal use
Telithromycin (Erythromycin)	*Saccharopolyspora erythraea*	2001	Sanofi-Aventis (France)	2004, 2006*	Respiratory infections; binds to 50S ribosome
Doripenem (Thienamycin)	*Streptomyces cattleya*	1976	Shionogi (Japan); Johnson & Johnson (USA)	2005,2007	Pneumonia, urinary tract infections; inhibits peptidoglycan biosynthesis
Retapamulin (Pleuromutilin)	*Pleurotus mutiliz*	1950	Glaxo (USA)	2007	Dermal infections; binds to 50S ribosome
Spinetoram (spinosyn)	*Saccharopolyspora spinosa*	1997	Sumitomo (Japan)	2007	Insecticide; disrupts Nicotinic receptors γ-aminobutyric acid
Telavancin (Vancomycin)	*Amycolatopsis orientalis*	1953	Astellas (Japan)	2009	Endocarditis, meningitis, pneumonia; inhibits peptidoglycan biosynthesis
Glufosinate	*Streptomyces viridochromogenes*	1977	Bayer (Germany)	2009	Insecticide; inhibits glutamine synthetase
Ceftaroline (Cephalosporin)	*Cephalosporium acremonium*	1945	Forest Labs. (USA)	2010	Dermal infection; binds to PBPs
Fidaxomicin, Tiacumicin	*Dactylosporangium aurantiacum;*	1970	Cubist (USA)	2011	Colitis; blocks RNA polymerase of *C. difficile*
Ceftobiprole (Cephalosporin)	*Cephalosporium acremonium*	1945	Johnson & Johnson (USA)	2014	Dermal infections, MRSA infection; bind to PBPs
Anthrasil	Human Immune globulin	2011	Cangene (USA)	2015	Antibacterial
bezlotoxumab	Human IgG1 monoclonal antibody	2006	Merck (Germany)	2016	Recurrence of Clostridium Difficile Infection
actoxumab	Human IgG1 monoclonal antibody	2006	Merck, Medarex (USA)	2016	Recurrence of Clostridium Difficile Infection
Meropenem/ vaborbactam	*Streptomyces cattleya*	1976	Sumitomo Dainippon (Japan)	2017	Meningitis, intra-abdominal infection, pneumonia, sepsis,
Plazomicin	*Micromonospora aurantiaca*	2012	Achaogen (USA)	2018	Urinary tract infections; pyelonephritis,
Omadacycline	*Streptomycetaceae*	2011	Tufts University; Paratek (USA)	2018	Community-acquired bacterial pneumonia, skin infections.
Eravacycline	*Streptomycetaceae*	----	Tetraphase (USA)	2018	Intra-abdominal infections
Sarecycline	*Streptomycetaceae*	----	Paratek Pharmaceuticals (USA)	2018	Severe Acne vulgaris
Lefamulin	*Clitopilus passeckerianus*	2018	Nabriva Therapeutics (USA)	2019	Community-acquired bacterial Pneumonia, Skin infections

human that is used by capsaicin from plant species *Capsicum anuum*. In addition, certain triketones from *Callistemon citrinus* like nitisinone, mesotrione and leptospermone act on the same 4-hydroxyphenylpyruvate dehydrogenase enzyme in plants and animals, in particular, acting on 4-HPPD 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 by gut microflora—*Pseudomonas testosterone*. Another example is a fidaxomicin, derived from *Dactylosporangium aurantiacum*. It has no any antimicrobial properties but when it is hydrolysed to OP-1118, it becomes more effective to treat microbial infections.[44] 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.[45] Many phenolic compounds like sennosides from species *Cassia angustifolia*

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
Spergualin	*Bacillus laterosporus*	1982	Inst. microbial chem. (Japan)	1994	Fungal infections; inhibits interleukin-2
Mizoribine	*Eupencilium brefeldianum*	1974	Toyo (Japan)	1995	Renal transplantation; Inhibits T-and B-cell proliferation
Mucidine, Strobilurin K	*Oudemansiella mucide; 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 sphaerosperma Aspergillusrugulovalvus*	1974	Fujisawa (Japan)	2000	Fungal infections; blocks1,3-β glucan synthase
Pneumocandin B	*Zelerion arboricola; Papularia sphaerosperma; Glarea lozoyensis*	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 sphaerosperma*	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 sphaerosperma Aspergillusrugulovalvus*	1974	Pfizer (USA)	2006	Aspergillosis & Candidiasis; Bind to β-1,3-D-glucan synthase
Orysastrobin (Strobilurin)	*Bolinia lutea*	2006	BASF (Germany)	2006	Fungicide; mitochondrial respiration
Pimecrolimus (Ascomycin)	*Streptomyces hygroscopicus*	2001	Novartis (Switzerland)	2006	Atopic dermatitis; calcineurin
Micafungin	*Papularia sphaerosperma*	1990	Fujisawa; Astellas (Japan)	2005, 2008	Esophageal candidiasis; β-1,3-D-glucan synthase
Zotarolimus (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 sterillia; Isaria sinclarii; Myriococcum albomyces*	1970	Novartis (Switzerland)	2010	Renal transplantation; serine palmitoyl transferase

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 5: Anticancer agents from natural products.

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 farnesyltransferase
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*	…..	Wyeth-Ayerst (USA)	2000	Myelogenous leukaemia; DNA cleavage
Fulvestrant	*Estradiol estrogen Hormone*	-----	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-I
Taxol (Paclitaxel)	*Taxus brevifolia*	1971	B. M. Squibb (USA)	2005	Breast cancer; inhibits depolarization of microtubules
Squalamine	*Squalus acanthias*	1995	Magainin (USA)	2005	Malignant gliomas; 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
Romidepsin, 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

Homoharringtonine/ Omacetaxine	*Cephalotaxus fortunei.*	1970	OncoPharm (USA)	2012	Chronic myeloid leukemia
Carfilzomib	*Actinomycetes strain*	1990	Onyx (USA);	2012	Multiple myeloma
Trastuzumab emtansine	*Monoclonal Antibody*	1992	Genentech (USA)	2013	Breast Cancer and Stomach Cancer
Atezolizumab	*humanized monoclonal antibody*	2015	Genentech/Roche (USA)	2016; 2019	Breast cancer, lung cancer and hepatocellular carcinoma
Midostaurin	*Streptomyces staurosporeus.*	1996	Novartis (Switzerland)	2017	Acute myeloid leukemia, Myelodysplastic syndrome, Advanced systemic mastocytosis
Inotuzumab ozogamicin	*humanized monoclonal antibody*	1991	Celltech (UK) and Wyeth (USA)	2017	acute lymphoblastic leukemia
Aplidine/Plitidepsin	*Aplidium albicans*	----	PharmaMar (Spain)	2018	Acute lymphoblastic leukemia
Polatuzumab vedotin	Antibody Drug Conjugate	-----	Genentech, Roche (USA)	2019	Large B-cell lymphoma

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.[52] 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.[53]

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.[51] 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.[4,36,54]

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.[52] 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).[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

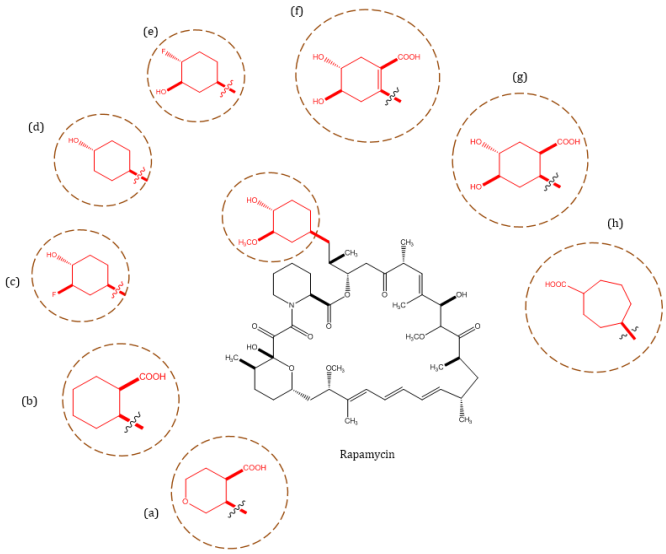

Figure 1.1: Replacement of 2-methoxycyclohexanol with a) tetrahydro-2H-pyran-4-carboxylic acid; b) cyclohexane carboxylic acid; c) 2-fluorocyclohexanol; d) cyclohexanol; e) (1R,2R)-2-fluorocyclohexanol; f) dihydroxycyclohex-1-enecarboxylic acid; e) 4,5-dihydroxycyclohex-1-enecarboxylic acid; f) 3,4-dihydroxycyclohexane carboxylic acid using mutasynthesis

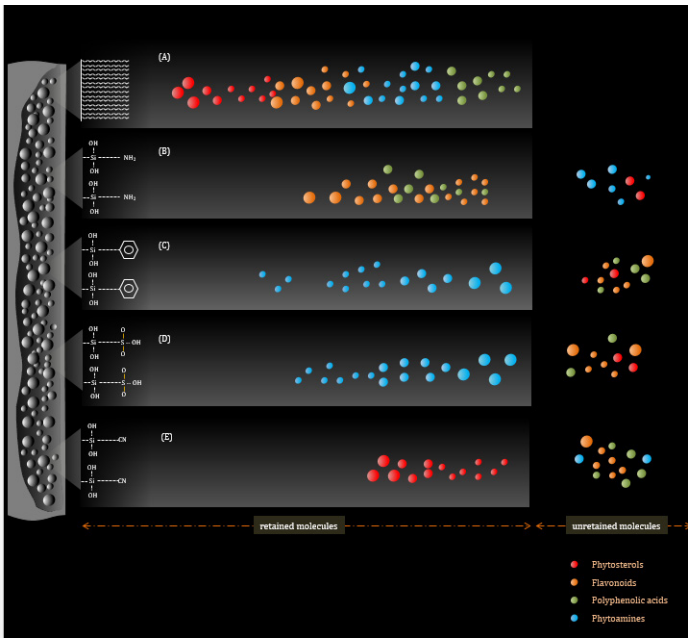

Figure 3: Sequence Pictogram of Natural Products: (A) RP-HPLC, selective towards all polar and non-polar phytochemicals; (B) Anion exchange Chromatography, selective towards separation of polyphenols and polyphenolic acids; (C) HILIC Analysis, Selective for very polar phytochemicals; (D) Cation exchange Chromatography, selective towards phytoamines; (E) NP-HPLC, selective towards phytosterols.

components as followed; phytosterols retained first, it is then followed by conjugated steroids, flavonoids, phytoamines and phenolic acids. Importantly, the objectives of this screening technology are to understand the physico-chemical properties of unknown drugs from plant species. In addition, ion exchange chromatography (IEC) used to segregate, one particular class of chemicals. For instance, amino column in liquid chromatography used to isolate the phenols and phenolic acids (Figure 3B). Strong cation exchangers (SCE) and hydrophilic interaction liquid chromatography (HILIC) used to isolate the phytoamines (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 mucobiosynthesis/mucosynthesis 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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