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Chapter 3

MEDICINAL BIOME: FROM TRADITION TO MODERNIZED PHARMACY

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ABSTRACT

Nature is undeniably an ethnomedicinal laboratory for ethnic people in their healthcare needs due to possessing living chemical constituents' library (secondary metabolites). The pharmacotherapeutic properties of floral and faunal natural products had reputed in different remedial traditions since primeval time and being uninterruptedly exploited in modern clinical pharmacy to cure complex disorders. Further, the ethnomedicines motivated the researchers to innovate new natural drugs along with synthetic derivatives designed on a technology basis, which simplifies and hastens the drug synthesis and discovery procedure against the multifarious problem of less successful drug discovery rate. Furthermore, people should aware and embolden for afforestation to resolve the perils such as biodiversity loss and environmental destruction to revive the natural dispensary as a raw material. The present chapter aims to set a correlation among natural products, ethnomedicines and clinical medicaments with advanced instrumental-computational technologies for synthesizing and designing novel drug compounds in a purified way for expanding the world's natural pharmacopoeia.

Keywords: Chemicotechnology, clinical drugs, ethnomedicines, nanomedicines, natural products.

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3.1. INTRODUCTION

The term ‘natural product’ signifies any living molecular substance (secondary metabolite) having precise chiral configuration (weighing < 3,000 Da) that generates as an offshoot or derivative during metabolic pathways. Overall 300,000 of secondary metabolites are prevailing to enhance the organisms’ survival on Earth (Kinghorn et al. 2009; McMurry 2010). Comparatively, secondary metabolites are widely synthesized from intermediates or shunt metabolites (acetyl-CoA, 1-deoxyxylulose-5-phosphate, mevalonic acid, and shikimic acid) than primary metabolites (during glycolysis, Kreb’s cycle or photosynthesis) and exhibit adoption of alternative pathways, which again strengthen the survival of organisms in nature along with being the core of potential medicaments (Dewick 2002; Sarker et al. 2006). Natural products (from microbes, plants, animals, marine organisms, etc.) have been uninterruptedly exploited as remedies by human since primeval time to cure ailments for which, they had to tackle extreme life risks in the beginning. Further, human established several conventional medicinal systems such as in India (Indian System of Medicine; ISM like Ayurveda, Unani, Siddha, Yoga, Homeopathy and Naturopathy), China (Traditional Chinese Medicine; TCM), Korea (Traditional Korean Medicine; TKM), Japan (Kampo), Australia (Traditional Aboriginal medicine), Russia (Russian herbal medicine), Africa (traditional medicine in Africa), America (Aztec medicine), Europe (European herbalism), etc. Conclusively, he mastered the technique of manufacturing alcohol and other novel drugs in a modernized way (Fabricant and Farnsworth 2001; Alves and Rosa 2007; Gao et al. 2007; Gurib-Fakim 2006; Shi et al. 2010).

3.2. ANCIENT MEDICINAL WISDOM

Earlier medicinal narration is the sorcery of experimentations, surgeons and resourcefulness. The immense success of human in the medicinal field is the outcome of several experimental failures. Humans since prehistoric period have shown devotion towards nature for his vital necessities (food, cloth and shelter) by developing flavors, fragrances, fertilizers, transportation, etc. and then, medicines afterwards. Every time, nature (flora and fauna) has been the foundation constituent of various traditional medicinal systems arose during different civilizations. The first medicinal record about natural products has been inscribed as cuneiform on several hundred clay tablets in Mesopotamia (2600 B.C.) explaining the curative uses of oils from *Commiphora* sp. (myrrh) and

Cupressus sempervirens (cypress), *Glycyrrhiza glabra* (licorice), *Papaver somniferum* (poppy), etc. The Egyptian manuscript '*Ebers Papyrus*' (1550 B.C.) compiles 700 drug formulae *viz.*, poultice, gargles, ointments, pills, etc. The '*Chinese Materia Medica*' of Wu-Shi-Er-Bing-Fang (1100 B.C.) comprises about 52 prescriptions. The ancient Indian medicinal record has diverged in two periods: *Vedic* (800 B.C.), where four holy books (Vedas) portrayed in Sanskrit were pillars of basic medicinal evidence; and the *Golden Era of Indian medicine* (800 B.C. to 1000 A.D.), when Ayurveda bloomed documenting the usage of *Aconitum*, *Datura*, *Sarcostemma* and *Cannabis*. Theophrastus (~300 B.C.) published medicinal and cultivation aspects of herbs in his '*History of Plants*' (Ahluwalia and Chopra 2007; Kelly et al. 2009). Avicenna (980 to 1037 A.D.) formulated about 1,400 drug plants by summarizing Greaco-Roman medicine in his '*Canon Medicine*' (Wink 1998; Cragg and Newman 2001). About 24 pieces of literature comprising more than 600 herbs with recipes were assembled by Pedanius Dioscorides in his '*De Materia Medica*' (78 A.D.). A Chinese encyclopedia entitled '*Pen-ts' asking mu*' compiled by Li Shish-Chen during Ming clan (1596 A.D.) elucidating 1,898 drug plants with 8,160 prescriptions. In 1757, Carolus Linnaeus documented a detailed systematic record of nearly 5,900 herbal plants in '*Species Plantarum*'. These revolutionary publications are constantly consulted by several herbalists, botanists, taxonomists and horticulturalists (Mann 1992; Nakanishi 1999; Halberstein 2005).

In Egyptian and Chinese civilizations, lichens remained a constantly reliable crude source of spices, perfumes, medicines and cosmetics. *Usnea dillenius*, a conventional anti-dandruff material, is still used in Ireland during sore eye treatment. *Parmelia omphalodes*, classic brown dye source in the British Isles, prevents feet inflammation and in Ireland is used as chin bad sores, cuts and burns remedy (Cameron 1900; MacFarlane 1929; Purvis 2000; Allen and Hatfield 2004). In Aran Islands, *Porphyra umbilicalis* (Rhodophyta) valued as a digestive cure. Steamed charcoal of *Piptoporus betulinus* (epiphytic birch fungus) serves as a traditional antiseptic and to prevent bleeding. Milk boiled *Agaricus campestris* (field mushroom) in ancient time valued as a remedy to soothe throat cancer (Swanton 1915; Swanton 1932; Martin 1934; Ó hEithir 1983; Hatfield 2005).

Earthworms as medicaments (hypotensive, diuretic, antispasmodic, antiasthmatic, antiallergic, spermatocide and antipyretic) are valued from about 4,000 years in China and mentioned in Li Schizhen's '*Compendium of Materia Medica*' (1578 A.D.). Rhino horn possesses historical medicinal uses (against typhoid, snakebite, hallucinations, fever, food poisoning, boils, devil possession and vomiting) in TCM according to Li Shish Chen (16th century) (Costa-Neto 2005).

3.3. ETHNOMEDICINE INSPIRED CLINICAL DRUGS

3.3.1. Plant Source

Approximately 80% share in herbal medicines used to arise from plants (bark, leaf and root) during the 1990s. Nearly ~400,000 plant species contribute to formulating pharmaceutical compounds. Worldwide, 10,000–1,500 plant species have recorded for remedial uses. In India, about 65 plant species have been commercially approved in pharmaceutical industries at the global level (Birari and Bhutani 2007; McChesney et al. 2007; Beutler 2009; Lahlou 2013; Saxena and Rao 2018).

WHO appraised that about 65% world populace (mainly developing nations) utilizes plant-derived folkloric medicines immensely in their disease treatment. Tradition Medicine Centers of WHO surveyed that for curing similar or associated ailments in developing nations, about 80% ethnomedicinal components out of 122 are collected from only 94 plant species (Farnsworth et al. 1985).

The impact of ethnomedicinal system in inventing novel drugs can be best exemplified by 'Quinine' (antimalarial formulation), extracted from *Cinchona officinalis* bark (cocaine plant) by Caventou and Pelletier (1820), that was long ago exploited by Amazonian native inhabitants in malarial fever and anaesthetic drug for eye surgery. During the 1600s in Europe, quinine bark was introduced as an antimalarial drug; and in mid 20th century, quinine got substituted by its two derivatives: 'Mefloquine' and 'Chloroquine' for malarial treatment. Another eminent antipyretic medicine formulated by Chinese scientists (1971) is 'Artemisinin', procured from *Artemisia annua* (wormwood plant), which possesses a renowned past in TCM (Traditional Chinese Medicine) for fever therapy. Nowadays, synthetic analogues of artemisinin (artesunate, artemisone, arterolane tosylate) are traded as antimalarial drugs. These analogues are magnificent in treating resistant malaria (Klayman 1985; Buss and Waigh 1995; Balick and Cox 1996; Wongsrichanalai et al. 2002; O'Neill and Posner 2004; Vennerstrom et al. 2004; Nagelschmitz et al. 2008; Posner et al. 2008).

The other principal drugs are 'Curcumin' (hypolipidemic) procured from *Curcuma longa* (conventional antimicrobial plant); 'Reserpine' (antihypertensive) from *Rauwolfia serpentina* (Ayurvedic snakebite formula); sympathomimetic amine 'Ephedrine' (antiasthma drug) along with 'Salmeterol' and 'Salbutamol' (β-agonists) from *Ephedra sinica*; 'Tubocurarin' (muscle-relaxant) from *Curarea* and *Chondrodendron* bark (source of arrow poison, curare, by Amazonian people); two anticholinergic alkaloids: 'Anisodine' and 'Anisodamine' from *Scopalia tanguitica* treat migraine and bacillary dysentery; and isoquinoline alkaloid 'Racemic tetrahydropalmatine' (tranquillizer and analgesic) from *Corydalis ambigua* (Kapoor 1990; Buss and Waigh 1995; Maridass and Britto 2008; Fu and Lin 2015).

F.W. Sertürner (1803-04) crystallized 'Morphine' from *Papaver somniferum* (opium poppy) to which E. Merck (1826) marketed commercially. By boiling crude morphine in acetic anhydride yielded 'Heroin' (diacetylmorphine), which quickly converted into 'Codeine' (analgesic). 'Aspirin' is the first pure semi-synthetic pain-killer procured from 'Salicin' (a natural substance) of *Salix alba* bark (birch or willow tree) by Bayer (1899) that further encouraged to yield other successful drugs (digitoxin, cocaine, pilocarpine, quinine and codeine) of today (Newman et al. 2000; Kinghorn 2001; Der Marderosian and Beutler 2002; Klockgether-Radke 2002; Brahmachari 2012). In the 1700s, 'Digitoxin' (cardiotonic glycoside) extracted from *Digitalis purpurea* (foxglove) was traced to be curing heart disorders (cardiac conduction enhancer). Long used 'Pilocarpine' (L-histidine-derived alkaloid) from *Pilocarpus jaborandi* for treating glaucoma was approved by FDA (1994) and to cure xerostomia (dry mouth) caused by radiation therapy of cancer, and Sjogren's syndrome (an autoimmune disorder) in 1998 (Aniszewski 2007). 'Ajmalicine' (indole alkaloid), first isolated by Siddiqi (1931), derived from *Rauwolfia serpentina* treats circulatory disorders. While, 'Aescin' (saponin mixture) from *Aesculus hippocastanum* (horse chestnut) is venotonic, anti-edematous and anti-inflammatory drug. The 'Metformin' (dimethylbiguanide, guanidine-derivative) procured from *Galega officinalis* cures diabetes type II (Farag et al. 2015) (Figure 3.1).

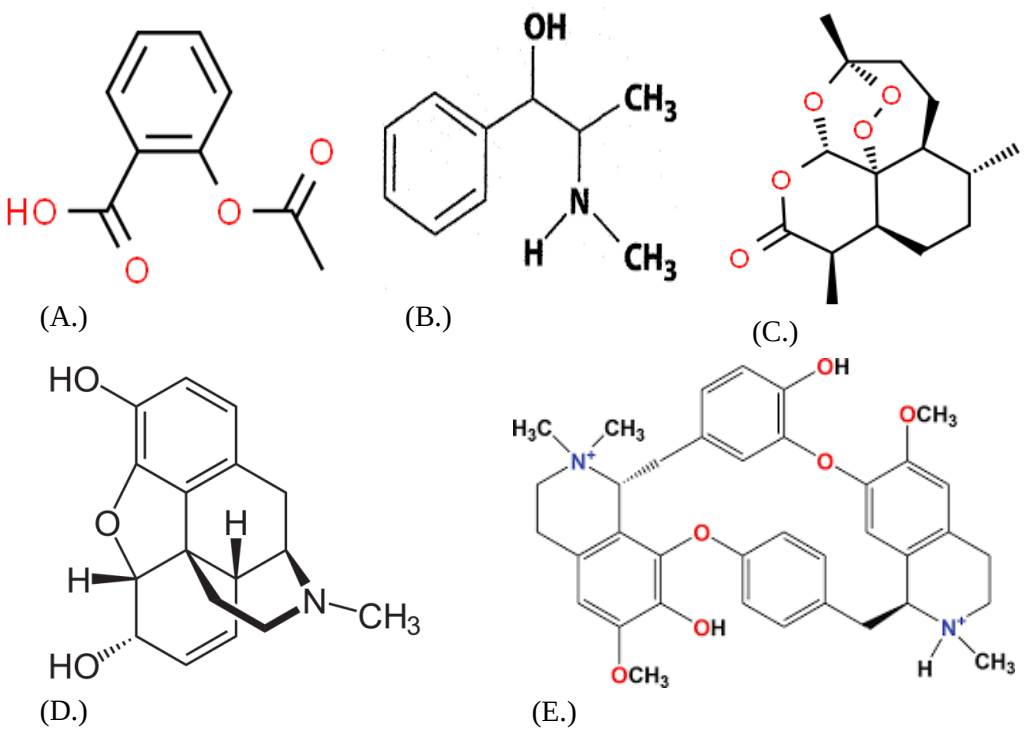


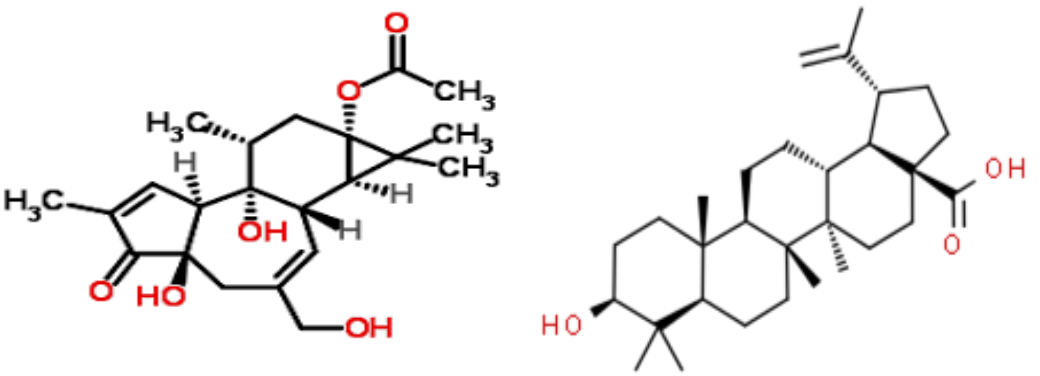
Figure 3.1. Natural drug products of plant origin: (A.) Aspirin, (B.) Ephedrine, (C.) Artemisinin, (D.) Morphine, and (E.) Tubocurarin.

Some other crucial commercial compounds are 'Syntocalmy®' (for insomnia and anxiety) isolated from *Passiflora incarnata* leaves, 'Acheflan®' (anti-inflammatory and analgesic) from *Codia verbenacea* essential oil, and 'Melagrião®' (for asthma and cough) from *Mikania glomerata* (Calixto 2019).

3.3.2. Antiviral Drugs

In 1992, 'Prostratin' (phorbol ester) yielded from *Homalanthus nutans* (traditional antiviral hepatitis tree of Western Samoa) wood has anti-HIV potential (Gustafson et al. 1992; Dias et al. 2012). Effective compounds against HIV include a monoterpenoid '4-Methyl-dl-tryptophan' yielded from *Catharanthus pusillus*; '3,4-odicaffeoylquinic acid, 3,5,7,8,4'- pentahydroxyflavanone and aromadendrin-7-β-D-glucopyranoside' from *Cuscuta reflexa*; coumarin 'Wedelolactone' (for HIV-1 IN) and 'Ecliptal' (HIV-1 PR) from *Eclipta prostrata*; alkaloids 'Benzophenanthridine and (+/-)-6-acetonyldihydrochelerythrine' from *Argemone mexicana* (Saxena and Rao 2018). Two antiviral coumarins 'Calanolide A' (from *Calophyllum lanigerum*) and 'Calanolide B' (diastereomer from *C. teysmannii*) show non-nucleoside reverse transcriptase inhibiting potential together with anti-tubercular activity (Kashman et al. 1992; Xu et al. 2004). An anti-influenza drug 'Oseltamivir phosphate (Tamiflu)' yielded from shikimic acid comprised in *Illicium verum* pods cures influenza virus A and B (Farag et al. 2015) (Figure 3.2).

Other anti-HIV trial medications include 'Suksdorfin' (pyranocoumarin) from *Lomantum suksdorfii* fruit, 'Betulinic acid' (lupine triterpene) from *Syzigium claviflorum* (Fujioka et al. 1994; Huang et al. 1994; Singh et al. 2005).



(A.) (B.)

Figure 3.2. Natural antiviral drug products of plant origin: (A.) Prostratin, and (B.) Betulinic Acid.

3.3.3. Anticancer Drugs

The term 'cancer' probably proposed by Hippocrates is the 2nd largest death threat globally. The first evidence of herbal anticancer drug was achieved by inventing 'Podophyllotoxin' from *Podophyllum peltatum* (1947) that hampers tubulin polymerization in oncocytes' microtubules. The 'Teniposide' and 'Etoposide' (podophyllotoxin derivatives) hinder DNA topoisomerase-II (repairs DNA strands) in cancer cells (Dewick 1997; Nirmala et al. 2011; Prakash 2013). 'Paclitaxel' (Taxol®) obtained from *Taxus brevifolia* leaves was first anti-carcinogenic formulation to trigger microtubule stabilization against Kaposi's sarcoma, ovarian, lung and breast cancers (Wani et al. 1971; Shu 1998). Taxol in natural sources remains in limited amount and requires expensive synthesis in the laboratory. But its analogue 'Baccatin III' (obtainable with ease from *T. brevifolia* needles) gets quickly converted into taxol in sufficient quantity (Nicolaou et al. 1994; Dewick 2002).

Several principal substances obtained from *Euphorbia hirta* (Euphorbin-A, B, C, D, E, quercitol, camphol, quercetin, myricitrin, gallic acid, leucocyanidol, etc.) arrest different carcinomas (melanoma and squamous cell cancer). The 'THC (Δ^9-tetrahydrocannabinol)' procured from *Cannabis sativa* stimulates auto-apoptosis in cancer cells (glioma, melanoma, hepatic, pancreatic, etc.). 'Parthenin' (sesquiterpene lactone) extracted from *Parthenium hysterophorus* inhibits tumorigenesis by synthesizing NO (nitric oxide) *via* iNOS (inducible NO synthase) overexpression (Saxena and Rao 2018). Wall and Wani (1966) isolated 'Camptothecin' (quinoline alkaloid) from *Camptotheca acuminata* stem-bark that shows cytotoxicity by inhibiting topoisomerase along with its analogues 'Irinotecan' and 'Topotecan' during chemotherapy (Wall and Wani 1996). The two vinca alkaloids 'Vincristine' and 'Vinblastine' yielded from *Catharanthus roseus* (Madagascar rosy periwinkle) are anti-tumour agents for curing leukaemia. A nitrogen-metabolite 'Indirubrin' isolated from *Indigofera tinctoria* treats chronic myelocytic leukaemia (Maridass and Britto 2008; Cragg and Newman 2009). An anti-angiogenic compound 'Combretastatin A-4 phosphate' (stilbene derivative) from *Combretum caffrum* (bush willow of S. Africa) ceases vascular supply in necrotic tumours (Holwell et al. 2002; Newman and Cragg 2005) (Figure 3.3).

Other cancer chemoprotective agents include '8-triptolide' (diterpene triepoxide) isolated from *Tripterygium wilfordii*, 'Pervilleine-A' from *Erythroxylum pervillei* roots, 'Silvestrol' from *Aglai foveolata* fruits, and 'Ingenol 3-o-angelate' from *Euphorbia peplus* (Farag et al. 2015).

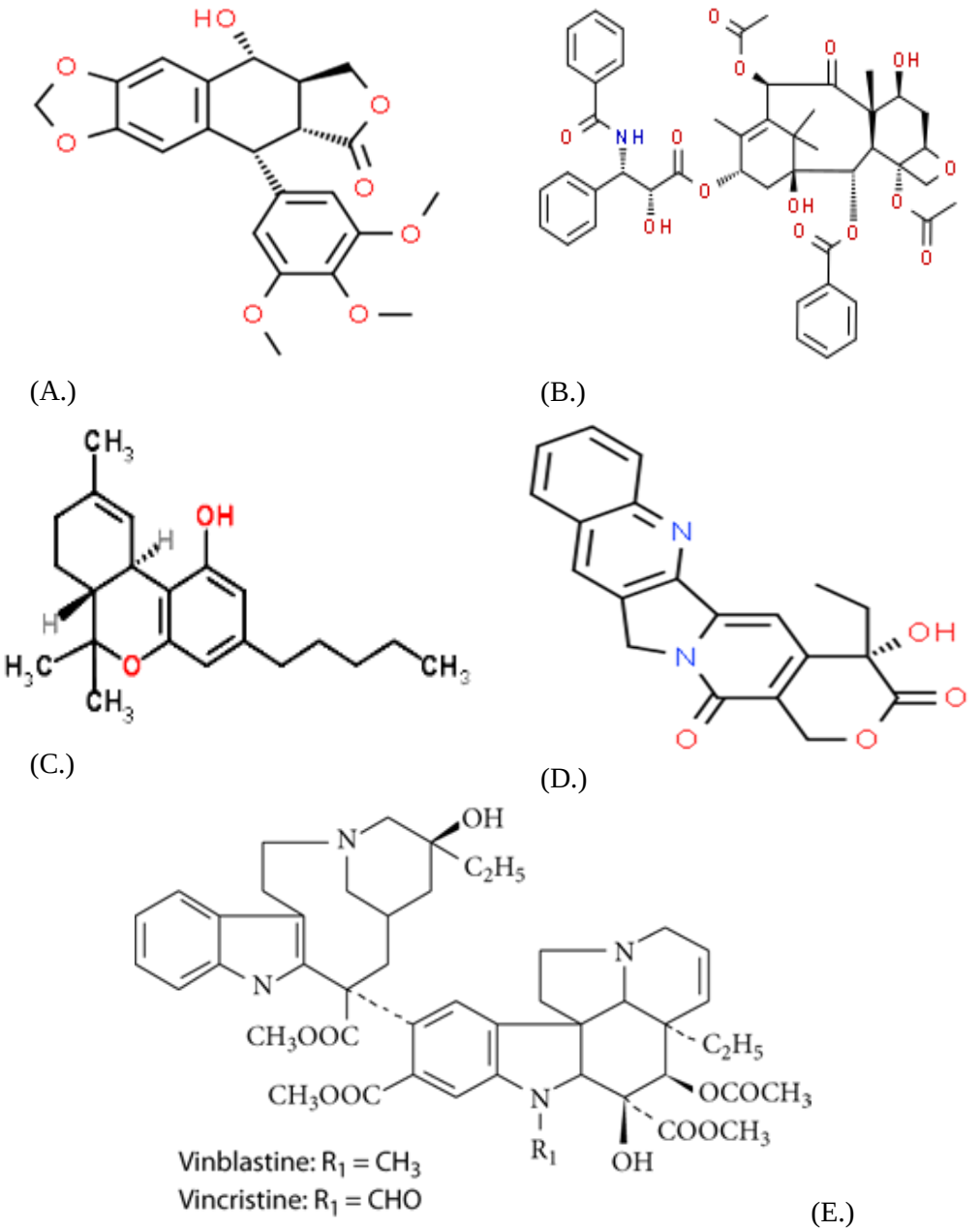


Figure 3.3. Natural anticancer drug products of plant origin: (A.) Podophyllotoxin, (B.) Paclitaxel, (C.) Δ^9-tetrahydrocannabinol, (D.) Camptothecin, and (E.) Vinca alkaloids.

3.3.4. Fungal and Microbial Source

Undoubtedly, microbes (mainly fungi and bacteria) had a significant contribution to natural drug designing through antibiotics. The credit for pioneer evidence of microbial

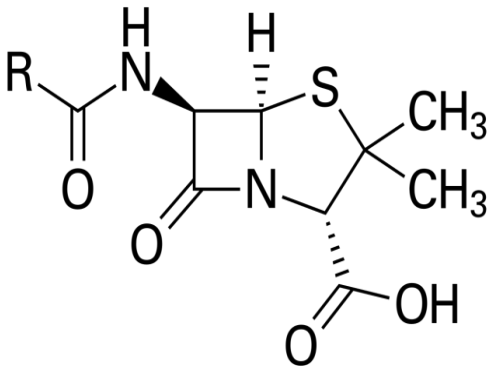
drug discovery goes to Alexander Flemming (1928), who isolated 'Penicillin' from *Penicillium rubens*, for which, in 1945, he shared Nobel prize with Florey and Chain of Physiology and Medicine (Abraham et al. 1941; Houbraken et al. 2011). This discovery inspired researchers for further innovations of antibiotics. A glycopeptide 'Vancomycin' (antimicrobial), discovered by Edmund Kornfeld (1953), from *Amycolatopsis orientalis* acts against many fungi, Gram-positive (*Streptococci* and *Staphylococci*) and Gram-negative bacteria and mycobacteria. FDA, in 1958, approved vancomycin for treating penicillin hypersensitive patients. A macrolide 'Erythromycin' along with trial derivatives 'BAL-19403', 'EP-420' and 'Cethromycin' (Restanza™, ABT-773) from *Saccharopolyspora erythraea* treats respiratory infections by counteracting Gram(+) bacilli and cocci. Anticancer drug 'Doxorubicin (Adriamycin®)' (amrubicin hydrochloride) yielded from *Streptomyces peucetius* treats thyroid cancer, sarcoma (bone and soft tissue), acute leukaemia, lung cancer, Hodgkin's and non-Hodgkin lymphomas. 'Torreyanic acid' extracted from *Pestalotiopsis microspora* (endophyte) of *Torreya taxifolia* (endangered tree) shows cytotoxicity (10x) against apoptosis causing protein kinase C (PKC) in cancer cells (Lee et al. 1996; Dewick 2002; Li et al. 2003; Butler 2004).

Some anti-HIV inhibitors include: 'Betulinic acid' (triterpenoid) procured from *Betula pubescens* bark has chemoprotective activity against topoisomerase-I, 'Ganoderic acid β' from *Ganoderma lucidum* spores and fruiting bodies acts against anti-HIV-1 protease (20 μM IC_{50} value), 'Bevirimat (PA-457)' from *Syzygium claviflorum* (Chinese herb) ceases HIV Gag protein processing (Kashiwada et al. 1996; Min et al. 1998; Yogeeswari and Sriram 2005; Martin et al. 2007; Heider et al. 2010).

Antibiotic 'Augmentin', a blend of 'Clavulanic acid' (β-lactamase inhibitor) from *Streptomyces clavuligerus* and 'Amoxicillin' (penicillin) from *Penicillium* sp., treats bacterial infections (pneumonia, sinusitis, bronchitis, skin and urinary problems) (Van der Sar 2006). Antifungal peptide 'Cryptocandin' from *Cryptosporiopsis quercina*, a fungal endophyte of *Tripterigeum wilfordii*, acts against fungal pathogens *Trycophyton mentagrophyte* and *Candida albicans*. Anti-tumour agents 'Sequoiatones-A & B' from *Aspergillus parasiticus*, endophyte on *Sequoia sempervirens* (redwood tree) cure breast cancer (Stierle et al. 1999; Guo et al. 2000; Chinworrungsee 2006). Two hCMV (human cytomegalovirus) protease inhibitors 'Cytonic acid A & B' were yielded from *Cytonaema* sp. (endophytic fungus). The CCK (cholecystokinin) antagonist 'Asperlicin' and its derivative 'Benzodiazepine' from *Aspergillus alliaceus* cure insomnia. A lovastatin 'Mevinolin' from *Aspergillus terreus* and *Pleurotus ostreatus* (oyster mushroom) helps in diminishing cholesterol (hypolipidemic) (Alberts et al. 1980; Liesch et al. 1985; Finlay et al. 2003; Herranz 2003). A macrolide 'Boromycin' (a natural antibacterial agent) isolated from *Streptomyces antibioticus* by Zahner et al. (1967) and Kohno et al. (1996) exhibits anti-HIV activity (Newman and Cragg 2016) (Figure 3.4).

Other antibiotics are 'Ivermectin or Avermectin' (anti-inflammatory and anti-anthelmintic) from *Streptomyces avermitilis*, 'Streptomycin' (antibacterial) from

Streptomyces griseus, and 'Rapamycin' (immunosuppressive) from *Streptomyces hygroscopicus* (Wangchuk 2018).



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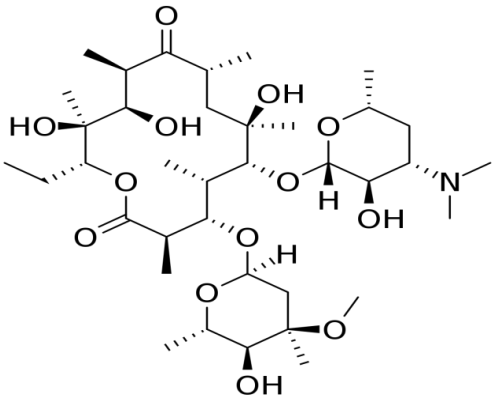

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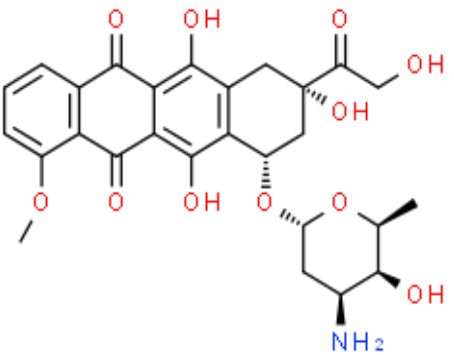

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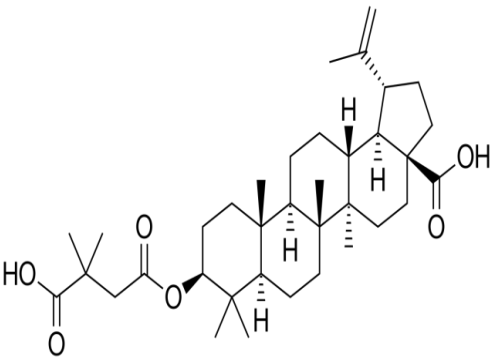

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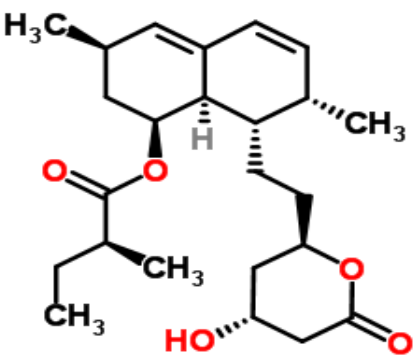

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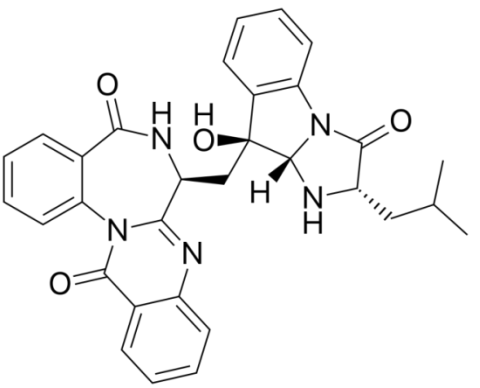

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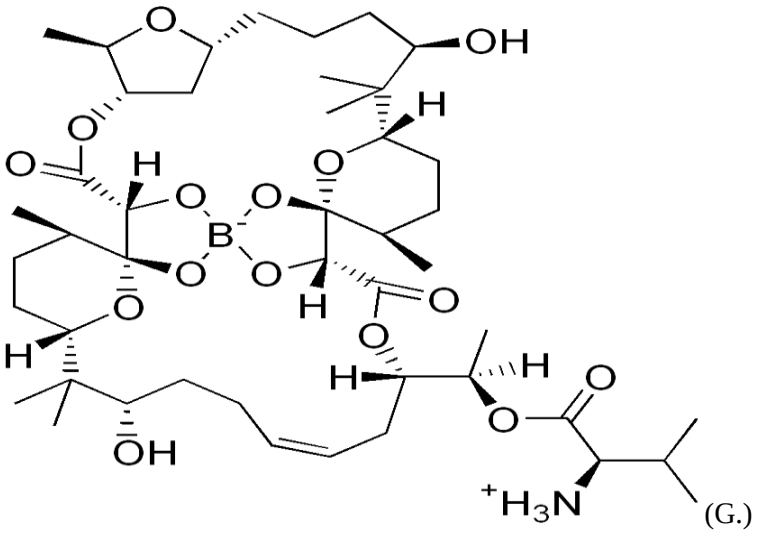


Figure 3.4. Natural drug products of fungal and microbial origin: (A.) Penicillin, (B.) Erythromycin, (C.) Doxorubicin, (D.) Bevirimat, (E.) Mevinolin, (F.) Asperlicin, and (G.) Boromycin.

3.3.5. Lichen Source

Lichens got their remedial fame *via* 'Doctrine of Signature', which follows 'like affects like' concept. For instance, *Peltigera aphthosa* (with warty thallus) cures thrush (fungal infection) in children and *Peltigera canina* (canine-like thallus) treats rabies (Upreti 1994). Since then, numerous bioactive medicaments have been characterized from lichens including a polysaccharide 'GE-3-S' (anti-HIV) from *Umblicaria esculenta*; 'Orsellinic acid' (nematicidal) from *Evernia prunastri*; 'Atranorin' (trypsin inhibitor) from *Pseudoevernia furfuracea*; '(-)-Usnic acid' (antitumour) from *Cladonia leptoclada*; '(+)-Usnic acid' (antimycobacterial) from *Cladonia arbuscula*; a pentacyclic hybocarpone 'Naphthazarin dimer' (cytotoxic against murine mastocytoma with 0.27 µM IC_{50}) from *Lecanora hybocarpa*; 'Hypericin derivative' (anti-HSV-1) from *Nephroma arcticum*; two depsidones 'Pannarin and 1-chloropannarin' (antioxidant) from *Erioderma chilense*; 'Fumaroprotocetraric acid' (HIV-1 reverse transcriptase inhibitor) from *Cetraria islandica*; 'Vulpinic acid' (antifungal) from *Alectoria ochroleuca*; '8-methylmenegazziaic acid' (radical scavenger) from *Hypotrachyna revoluta*; 'Rhamnopyranosyl galactofuranan' (immunity enhancer) from *Thamnolia subuliformis*; 'Lobaric acid' (porcine leucocyte 5-lipoxygenase inhibitor with 7 µM IC_{50}) from *Stereocaulon alpinum*; 'Methyl haematommate' (antifungal) from *Stereocaulon ramulosum*; 'Lichesterinic acid' (Epstein-Barr virus inhibitor) from *Usnic longissima*, etc. (Shukla et al. 2010) (Figure 3.5).

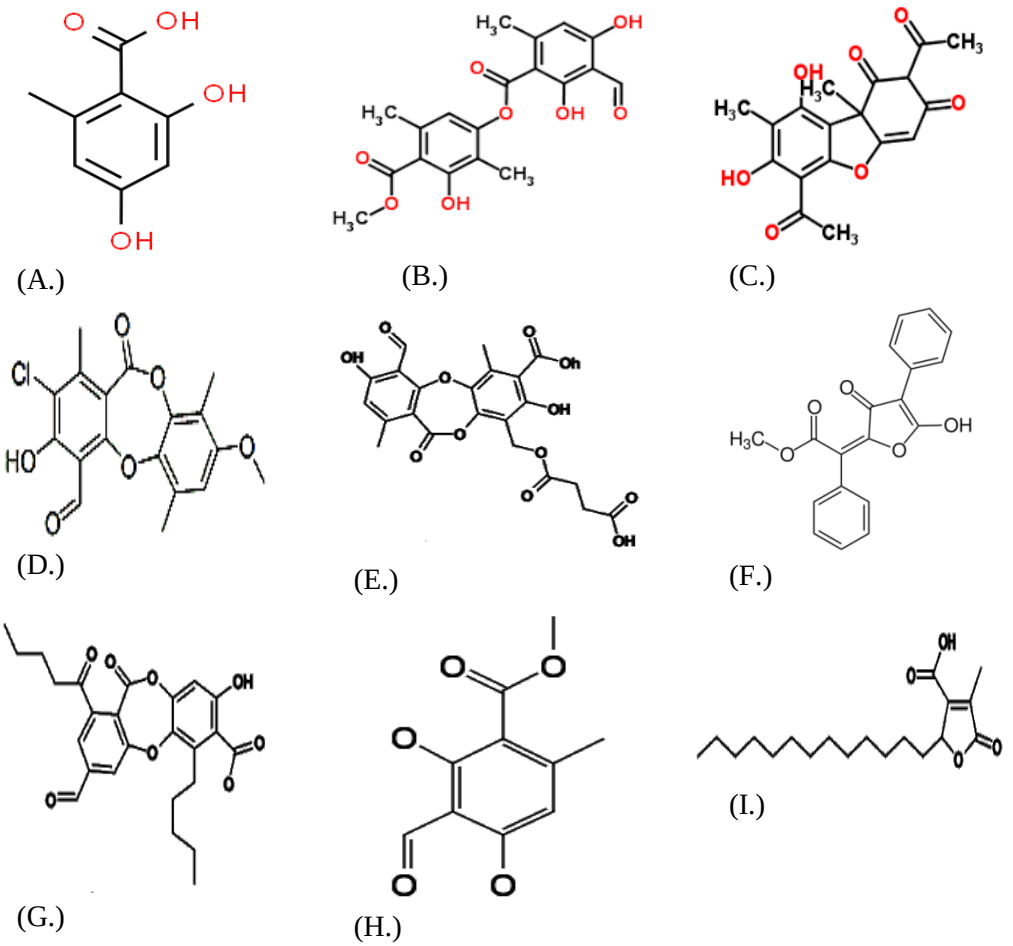


Figure 3.5. Natural drug products of lichen origin: (A.) Orsellinic acid, (B.) Atranorin, (C.) Usnic acid, (D.) Pannarin, (E.) Fumaroprotocetraric acid, (F.) Vulpinic acid, (G.) Lobaric acid, (H.) Methyl haematommate, and (I.) Lichesterinic acid.

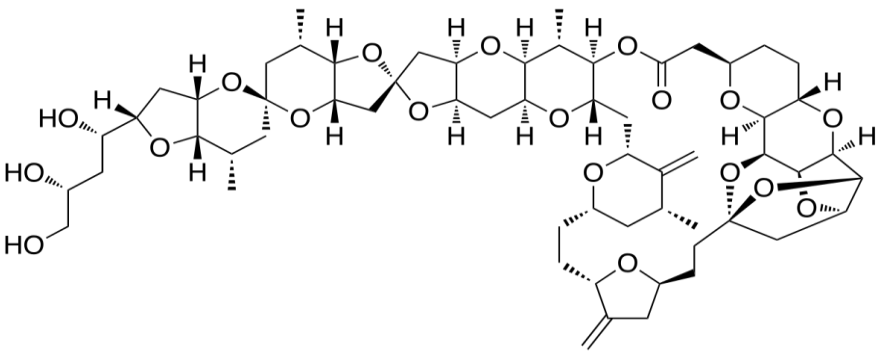
3.3.6. Marine Source

Oceans, wrapping up to 70% of Earth's surface, harbour enormous biota than terrestrial life-forms. Mostly, ocean-inhabiting organisms choose the sedentary way of life and synthesize extremely complex defense chemicals for avoiding predators. These defense chemicals get directly released into water, diluted and impart immediate remedial influences (Haefner 2003). The zeal of marine organisms-derived unique chemical compounds flourished in the 1950s. Since then, about 30,000 different bioactive products invented from marine lives (invertebrates, microorganisms and algae) (Salomon et al. 2004; Radjasa et al. 2011). Approximately, 10,000 natural products are alone synthesized

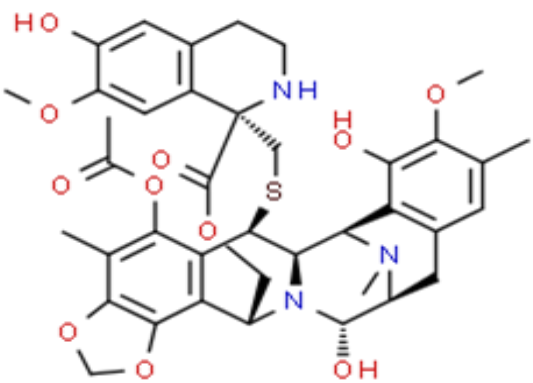
by invertebrates and per annum, the count increases about 1,000 (Montaser and Luesch 2011).

Sponges

The first-ever marine-derived bioactive constituents date back in the 1950s when 'Spongouridine' and 'Spongothymidine' (C-nucleosides) isolated from *Cryptotheca crypta* (Caribbean sponge) leading to synthesize two cytosine arabinosides 'Ara-A' and 'Ara-C' as antiviral and antileukemic agents, respectively (McConnel et al. 1994). European Union (2007) ratified 'Trabectedin' (ecteinascidin 743 or ET743 or Yondelis™) isolated from *Ecteinascidia turbinata* (an ascidian) as a first marine anticancer formulation (Rinehart et al. 1990; McConnel et al. 1994). Another extracted anticancer (breast carcinoma) compound is 'Halichondrin B' from *Halichondria okadai* (a Japanese sponge), *Phakellia carteri* (from Eastern Indian ocean), *Lissodendoryx* sp. (from New Zealand east coast ocean) and *Axinella* sp. (from Western Pacific ocean) along with structural analogue 'Halichondrin E-7389' (Uemura et al. 1985; Pettit et al. 1991; Pettit et al. 1993; Litaudon et al. 1994; Chin et al. 2006) (Figure 3.6).



(A.)



(B.)

Figure 3.6. Natural drug products of sponge origin: (A.) Halichondrin B, and (B.) Trabectedin.

Tunicates, Bryozoans and Seaweeds

In 1978, about 9 'Didemins' (depsipeptides), mainly Didemin-B, obtained from *Tridemnum* (tunicate) displays anticancer effects. An efficacious anticancer (melanoma, leukaemia and lymphoma) compound namely 'Plitidepsin' (a depsipeptide) extracted from *Aplidium albicans* (Mediterranean tunicate) (Henríquez et al. 2005; Mayer et al. 2010; Hussain et al. 2012; Muñoz-Alonso et al. 2013). An antineoplastic chemical 'Bryostatin 1' (polyether) with its cytotoxic effects on multiple-carcinoma has isolated from *Bulgula neritina* (a bryozoan) that is yet in trial phase to assess anti-Alzheimer effects (Butler, 2004; Alejandro et al. 2010). A compound 'Crenuladial' isolated from *Dilophus ligulatus* (brown alga) exhibits antibacterial activities against *Micrococcus luteus, Aeromonas hydrophyla* and *Staphylococcus aureus*. Diterpenes namely 'nor-dictyolide, 4-acetoxydictyololactone and dictyolodes A & B' were extracted from *Dictyota dichotoma* (brown alga) have anti-tumour effects (Ishitsuka and Kusumi 1988; Tringali et al. 1988). Some natural insecticides include 'Laurepinnacin' (acetylenic cyclic ether) from *Laurencia pinnata* (red alga) acts against *Culex pipiens* (mosquito larva); 1*β*-(2-*E*-chlorovinyl)-2*β*,4*α*, 5*α*-trichloro-1*α*,5*β*-dimethylcyclohexane and 1*α*-(2-*E*-chlorovinyl)-2*α*,4*β*,5*α*-trichloro-1*β*,5*β*-dimethylcyclohexane (cyclic polyhalogenated monoterpenes) from *Plocamium cartilagineum* (Chilean red alga) hinder *Macrosteles fascifrons* (Aster leafhopper) activity (Fukuzawa and Masamune 1981; Watanabe et al. 1989; San-Martin et al. 1991) (Figure 3.7).

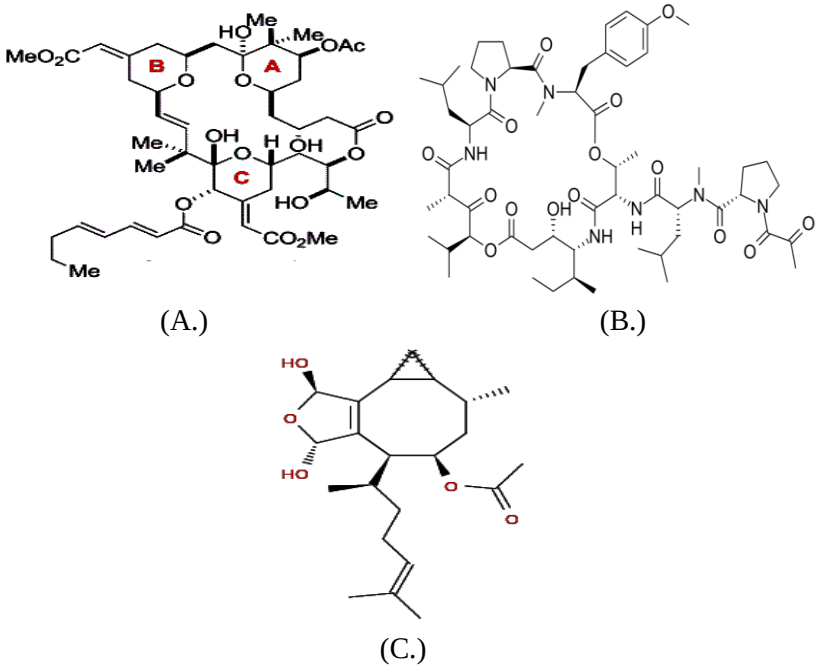
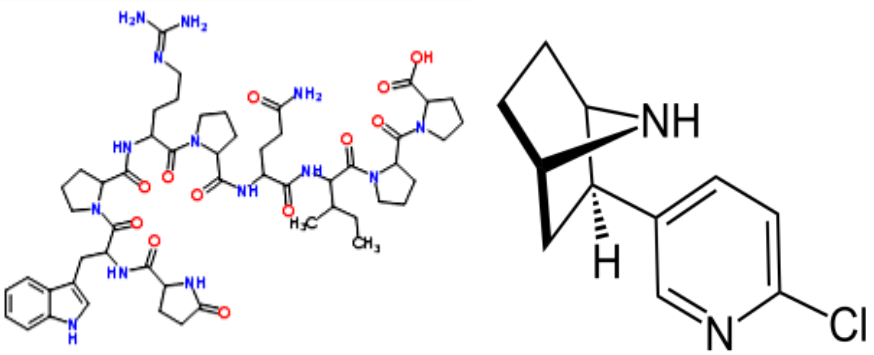


Figure 3.7. Natural drug products of tunicates, bryozoans and seaweeds origin: (A.) Bryostatin 1, (B.) Plitidepsin, and (C.) Crenuladial.



(A.) (B.)

Figure 3.8. Natural drug products of reptiles and frog origin: (A.) Teprotide, and (B.) Epibatidine.

Other important drugs are 'Ziconotide (Prialt®)', a peptide, extracted from *Conus magus* (sea cone snail), approved by FDA (2004) relieves neuropathic pain; and 'Spisulosine' from *Spisula polynyma* (sea clam) exhibits anti-tumour property (Alvarez-Miranda et al. 2003; Calixto 2019).

3.3.7. Reptiles and Frogs

A compound 'Teprotide' yielded from *Bothrops jararaca* (Brazilian pit viper) venom soothes cardiovascular problems by synthesizing ACE (angiotensin-converting enzyme) inhibitors (enalapril and captopril). Another hypotensive compound 'Bradykinin' (peptide) from *Bothrops jararaca* was discovered by Rocha e Silva and Wilson Teixeira Beraldo (1949). An anti-analgesic drug 'epibatidine' (excellent over morphine) had procured from *Epipedobates tricolor* (poisonous frog) skin. Another crucial drug isolated from *Heloderma suspectum* (Gila monster) venom is 'Exendin-4' along with its polypeptide 'Exenatide' for curing type-2 diabetes mellitus traded by Byetta and approved by Food and Drug Administration (2005) (Eng et al. 1992; Buss and Waigh 1995; Daly et al. 2005; Calixto 2019) (Figure 3.8).

3.4. Chemicotechnological Aspect of Natural Products

Natural wild pharmacy holds various biochemically activated constituents in itself that are difficult to extract. Since crude extraction techniques ('chemical' including purified compounds and 'biological' comprising bioassays) are monotonous and laborious, the dereplication of natural compounds from advanced technical methodologies becomes requisition (Figure 3.9). Further, the newly adopted and hyphened analytical techniques

include GC-MS (gas chromatography-mass spectrometry), FTIR (Fourier-transform infrared spectroscopy), NMR (nuclear magnetic resonance spectroscopy), HPLC (high-performance liquid chromatography), UV (ultraviolet absorption spectroscopy), AAS (atomic absorption spectroscopy), X-ray crystallography, CE (capillary electrophoresis), CC (column chromatography), TLC (thin layer chromatography) (Urban and Separovic 2005; Roessner and Beckles 2009), which help in constructing unknown bio-molecules *via* structural quantification of very slight extract amount along with retardation factor (Rf). Thus, these advanced spectroscopic techniques with detection specificity, resolution and sensitivity are considered as '*gold standard*' of pharmacokinetics for natural product-derived drug discovery by equipping all molecular fingerprint profiles of the given sample simultaneously. Also these techniques require less laborious and easier sample preparation as compared to older methodologies. Moreover, by unifying advanced computational software with above-mentioned techniques for modelling the novel drugs along with their analogues, less drug development related multidimensional complications increase in pharmacotherapeutics, pharmacokinetics and pharmacodynamics areas.

3.5. NANOTECHNOLOGY OF NATURAL PRODUCTS

Recently, the researchers have commenced focusing on nanotechnology-based medicines (nanomedicines) from natural products. The major contribution of nanotechnology signed for developing anticancer compounds as natural drugs doesn't get easily available and soluble in the human body leading to difficulties in clinical trials. Thus, medicines designed and hyphenated with nanotechnology may ease better bioavailability and bio-solubility during clinical trials and treatments due to their immediate synthesis and trouble-free incorporation with support of nano-vehicles. The elite nanoparticles incorporated into the body for drug delivery include SLNs (solid lipid nanoparticles), liposomes, polymer nanoparticles, micelles, dendrimers and crystal nanoparticles, of which liposomes have great contribution due to their liposomal aqueous compartment of hydrophilic phospholipids that enable easy bioavailability of hydrophilic drugs (Androutsopoulos et al. 2010; Muqbil et al. 2011; Khushnud and Mousa 2013).

Several nano-encapsulated medicines (nanoformulations) delivered into the human body cure inflammations caused by cancer, CNS (central nervous system) problems, cardiovascular disorders, Alzheimer's disease, diabetes, pathogenic bacteria, etc. Natural remedies bear eminence to suppress pro-inflammatory enzymes and pathways *viz.*, inflammatory transcription factors (NF-kB, cyclooxygenase-2 and AP-1). Thus, remedial natural constituents are integrated with nanoparticle vehicles to treat severe ailments (Nair et al. 2010; Prasad et al. 2010).

Some antimicrobial nanoformulations carried by nanoparticle vehicles are 'Eugenol' (from *Syzygium aromaticum, Cinnamomum verum, Origanum vulgare, Laurus nobilis* and

Ocimum basilicum), 'Curcumin' (from *Curcuma longa*), 'Carvacrol' (from *Origanum vulgare*) and 'Cinnamaldehyde' (from *Cinnamomum verum*) (Ouattara et al. 1997; Sharma et al. 2014). The nanocarrier loaded anti-Alzheimer's disease natural compounds include 'Artemisinin' (*Artemisia annua*), 'α-tocopherol' (*Castanea* and *Fagus*), 'Berberine' (*Coptis chinensis* and *Hydrastis canadensis*), 'Curcumin' (*Curcuma longa*), 'Genistein' (*Glycine max*), 'Ginsenoside Rb1 and Rg1' (*Panax ginseng*), 'Glaucocalyxin B' (*Rabdosia japonica*), 'Oridonin' (*Rabdosia rubescens*), 'Salidroside' (*Rhodiola rosea*), 'Tanshinone IIA' (*Slavia miltiorrhiza*), 'Xanthoceraside' (*Xanthoceras sorbifolia*), 'Tetrandrine' (*Stephania tetrandra*), 'Macranthoin G' (*Eucommia ulmoides*), 'Obovatol' (*Magnolia obovata*), etc. (Enrico 2019).

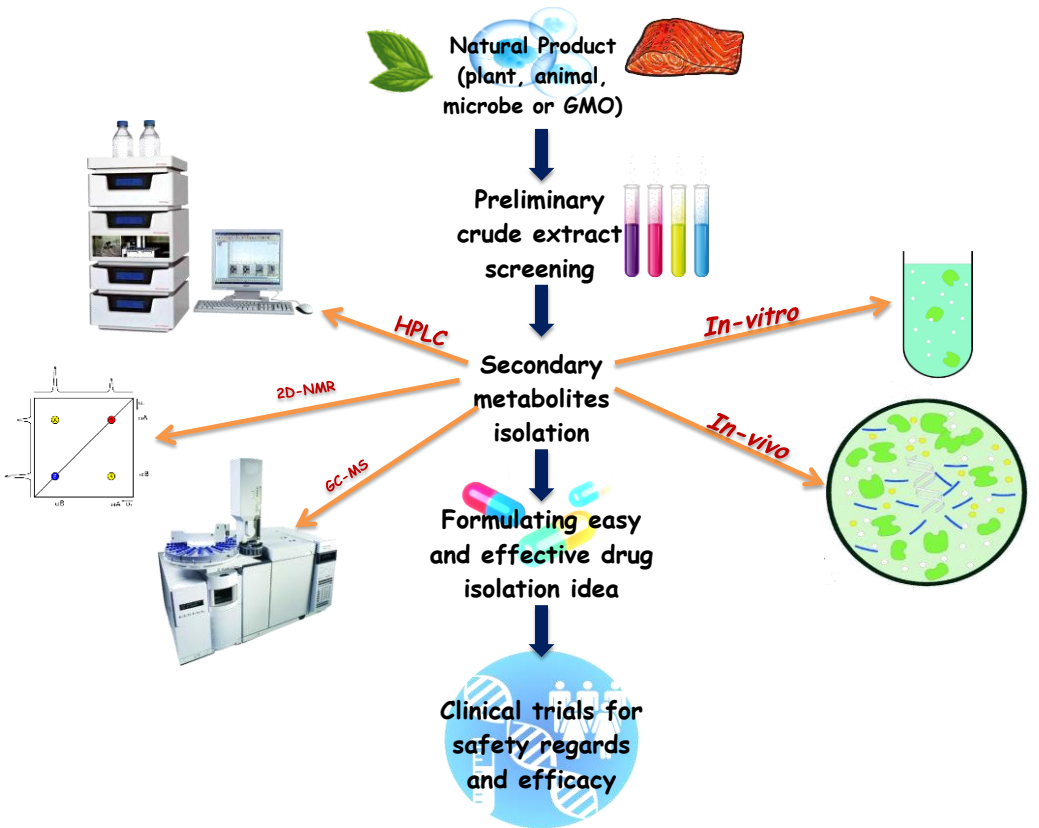


Figure 3.9. Drug extraction procedure.

3.6. CHALLENGES

Being indispensable, natural products are the treasure of medicines gifted by nature. The Ayurveda relies upon 70% herbs and 20 to 30% animals for its remedial preparations. But due to landmass extinction, biodiversity threat and other environmental hurdles,

precious natural pharmacy supplies are being diminishing day-by-day (Bhutani and Gohil 2010). Further, non-stop extraction of raw ingredients emerged from endangered species (either plant or animal) may create a catastrophe in the ecosystem (habitat destruction and extinction of endemic species) because of stock crisis. Higher water-salt level in the body generates obstacles in removing marine organisms' tissues with ease and for isolating essential compounds present in lesser quantity. Poor culturing of several invertebrates (mainly sponges) renders troubles in extracting compounds of interest (Molinski et al. 2009). Sometimes, extraction of extremely minute quantity (milligrams or micrograms) of promising compounds requires lots of raw material that constrains to formulate synthetic drugs, which is further a challenging chore to reap a plentiful amount of drug (Piel 2006).

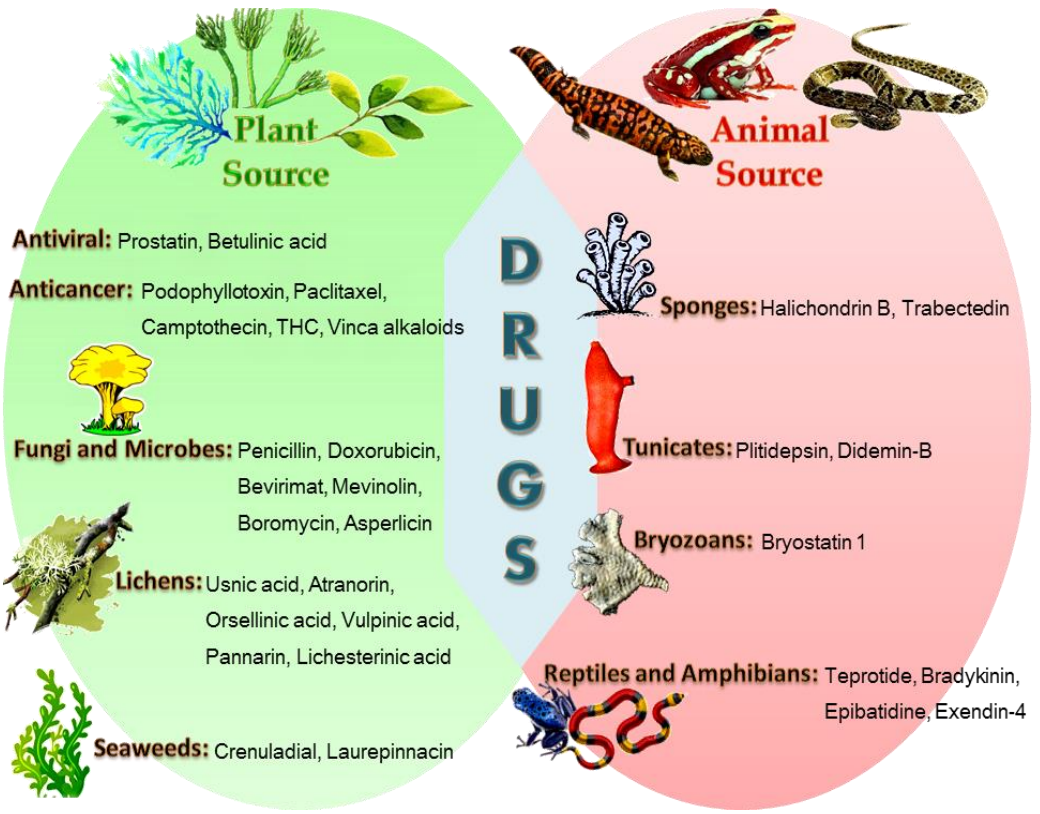


Figure 3.10. Diagrammatic representation of clinical natural drugs obtained from the floral and faunal source.

CONCLUSION

Since antiquity, natural products (floral and faunal) have been the foundation stuff of bioactive constituents employed in conventional therapies and remedies of today (Figure 3.10). They also inspire researchers to manufacture their synthetic substitutes in a desirable amount. Synthetically designed analogues of natural products on technology basis may

further aid in enrolling *de novo* structured drug candidates and to get possible biological responses when the action mechanism of the natural drug is lacking. Sometimes, the compound from natural resources fails to do its actual effects upon isolation process. Hence, the appendage of the latest technology (hyphenated instruments and nanotechnology) becomes prerequisite for improving the drug discovery procedure to dodge multidimensional obstruction during drug synthesis. Advanced technologies will help to fetch pure and authentic drug compounds leading to display their remedial effects in diminutive quantity (micromolar to nanomolar). In future, the computational softwares in fabricating novel drugs and analogues will lower these multidimensional problems of drug development in the fields of pharmacodynamics, pharmacotherapeutics and pharmacokinetics. The drug companies should share their marketed profit rewards (obtained from hauling out raw genetic resource) with the indigenous community as they pass on ethnomedicinal wisdom with companies. Further research is on demand to assess the gigantic pool of natural products because only a little fraction of them has validated scientifically to date that will also repress the doubt of safety and efficacy. Afforestation and replenishment of biodiversity are urgently necessitated to rescue the priceless natural drugstore.

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