CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1479238

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON NATURAL PRODUCTS IN DRUG DISCOVERY

Nishad V M*, Anu S, A S William Arputha Sundar
Sree Krishna College of Pharmacy, Parasala, Trivandram Kerala, India 695502

Abstract:
Drug discovery from medicinal plants has evolved to include numerous fields of inquiry and various methods of analysis. The process typically begins with a botanist, ethnobotanist, ethnopharmacologist, or plant ecologist who collects and identifies the plant(s) of interest. Collection may involve species with known biological activity for which active compound(s) have not been isolated (e.g., traditionally used herbal remedies) or may involve taxa collected randomly for a large screening program. It is necessary to respect the intellectual property rights of a given country where plant(s) of interest are collected (14). Phytochemists (natural product chemists) prepare extracts from the plant materials, subject these extracts to biological screening in pharmacologically relevant assays, and commence the process of isolation and characterization of the active compound(s) through bioassay-guided fractionation. Molecular biology has become essential to medicinal plant drug discovery through the determination and implementation of appropriate screening assays directed towards physiologically relevant molecular targets. Pharmacognosy encapsulates all of these fields into a distinct interdisciplinary science. Pharmacognosy includes both the study of botanical dietary supplements, including herbal remedies (15; 16), as well as the search for single compound drug leads that may proceed through further development into Food and Drug Administration (FDA)- approved medicines.

Key Words: *Pharmacognosy, phytochemicals, extraction, structural elucidation, biological screening*

Cooresponding author:
Nishad VM,
Sreekrishna College of pharmacy
Parassala
Mob: 9995037215
nishadvm13@gmail.com,

QR code

Please cite this article in press Nishad V M et al., ***A Review on Natural Products in Drug Discovery.,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION:

Healing with medicinal plants is as old as mankind itself. The connection between man and his search for drugs in nature dates from the far past, of which there is ample evidence from various sources: written documents, preserved monuments, and even original plant medicines. Awareness of medicinal plants usage is a result of the many years of struggles against illnesses due to which man learned to pursue drugs in barks, seeds, fruit bodies, and other parts of the plants. While the old peoples used medicinal plants primarily as simple pharmaceutical forms—infusions, decoctions and macerations—in the Middle Ages, and in particular between 16th and 18th centuries, the demand for compound drugs was increasing. The compound drugs comprised medicinal plants along with drugs of animal and plant origin. If the drug the theriac was produced from a number of medicinal plants, rare animals, and minerals, it was highly valued and sold expensively. In more recent history, the use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century (1,2). Drug discovery from medicinal plants led to the isolation of early drugs such as cocaine, codeine, digitoxin, and quinine, in addition to morphine, of which some are still in use (3,4,2). Isolation and characterization of pharmacologically active compounds from medicinal plants continue today. The following provides a brief review of the importance of medicinal plants in drug discovery including noteworthy compounds isolated from this source, our research involving anticancer and antidiabetic drug discovery using medicinal plants, and finally current challenges in regard to natural product drug discovery.

The idea that effect of drug in human body are mediated by specific interactions of the drug molecule with biological macromolecules (proteins or nucleic acids in most cases) led scientist to the conclusion that individual chemical compounds in extracts, rather than some mystical "power of life" are the factors required for the biological activity of the drug. This lead to the beginning of a totally new era in pharmacology, as pure, isolated chemicals, instead of extracts, became the standard treatments for diseases. Indeed, many bioactive compounds, responsible for the effects of crude extract drugs, and their chemical structure was elucidated.

Process in Natural Product Drug

Most of the recently approved natural-product-based drugs are compounds from plants (including elliptinium, galantamine and huperzine), microbes (daptomycin) and animals (exenatide and ziconotide), as well as synthetic or semi-synthetic compounds based on natural products (e.g. tigecycline, everolimus, telithromycin, micafungin and caspofungin (6-8). They cover a range of therapeutic indications: anti-cancer, anti-infective, anti-diabetic, among others, and they show a great diversity of chemical structures. The chemical properties of the small-molecule natural products that have recently been developed into drugs have been analysed [9]. Half of them were found to be closely compliant with Lipinski's Rule of Five for orally available compounds, but the remainder had higher molecular weights, more rotable bonds and more stereogenic centres, although they retained relatively low log P values. It is clear that, on average, natural products are more readily absorbed than synthetic drugs. Despite these advantages and the past successes, many large pharmaceutical companies have decreased the use of natural products in drug discovery screening. This has been because of the perceived disadvantages of natural products (difficulties in access and supply, complexities of natural product chemistry and inherent slowness of working with natural products, and concerns about intellectual property rights), and the hopes associated with the use of collections of compounds prepared by combinatorial chemistry methods (for further discussion, see Refs.(8,10-13).

The process in natural product drug discovery usually required several separation circles and structure elucidation and was thus time consuming. New approaches to improve and accelerate the joint drug discovery and development process are expected to take place mainly from innovation in drug target elucidation and lead structure discovery. Powerful new technologies such as automated separation techniques, high throughput screening and combinatorial chemistry are revolutionizing drug discovery [2]. The present paper discusses and examines how natural products have produced successful results for the pharmaceutical industry for drug discovery and development, and why nature still remains as important source of new drug compounds until today.

Importance of medicinal plants in drug discovery

Numerous methods have been utilized to acquire compounds for drug discovery including isolation from plants and other natural sources, synthetic chemistry, combinatorial. Chemistry and molecular modeling (17-19). Despite the recent interest in molecular modeling, combinatorial chemistry, and other synthetic chemistry techniques by

pharmaceutical companies and funding organizations, natural products, and particularly medicinal plants, remain an important source of new drugs, new drug leads, and new chemical entities (NCEs) (4,7). Natural products have played an important role as new chemical entities (NCEs)—approximately 28% of NCEs between 1981 and 2002 were natural products or natural product-derived (20). Another 20% of NCEs during this time period were considered natural product mimics, meaning that the synthetic compound was derived from the study of natural products (20). Combining these categories, research on natural products accounts for approximately 48% of the NCEs reported from 1981–2002. Natural products provide a starting point for new synthetic compounds, with diverse structures and often with multiple stereocenters that can be challenging synthetically(21-24).Many structural features common to natural products (e.g.,chiral centers, aromatic rings, complex ring systems, degree of molecule saturation, and number and ratio of heteroatoms). have been shown to be highly relevant to drug discovery efforts (21, 24-27). Furthermore, since the escalation of interest in combinatorial chemistry and the subsequent realization that these compound libraries may not always be very diverse, many synthetic and medicinal chemists are exploring the creation of natural product and natural-product like libraries that combine the structural features of natural products with the compound-generating potential of combinatorial chemistry (28-32). Drugs derived from medicinal plants can serve not only as new drugs themselves but also as drug leads suitable for optimization by medicinal and synthetic chemists.

Even when new chemical structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads. Since the sequencing of the human genome, thousands of new molecular targets have been identified as important in various diseases (33). With the advent of high throughput screening assays directed towards these targets, known compounds from medicinal plants may show promising and possibly selective activity. Several known compounds isolated from traditionally used medicinal plants have already been shown to act on newly validated molecular targets, as exemplified by indirubin, which selectively inhibits cyclin dependent kinases (34, 35) and kamebakaurin, which has been shown to inhibit NFnB (36,37).

Other known compounds have also been shown to act on novel molecular targets, thus reviving interest in members of these frequently isolated plant compound classes. Three examples are cucurbitacin I, obtained from the National Cancer Institute (NCIDiversity Set of known compounds and found to be highly selective in inhibiting the JAK/STAT3 pathway in tumors with activated STAT3 (38), h-lapachone, which selectively kills cancer cells over normal cells through direct checkpoint activation during the cell cycle (39), and betulinic acid, with selective melanoma cytotoxicity through the activation of p38 (40-42).

Access To Natural Products

One analysis of newly introduced drugs states that only sorafenib has reached the market from an origin in high-throughput screening of combinatorial chemistry libraries [2]. With the growing realisation that the chemical diversity of natural products is a better match to that of successful drugs than the diversity of collections of synthetic compounds [43,44], the interest in applying natural chemical diversity to drug discovery appears to be increasing once again [45]. As noted above, most of the leads from natural products that are currently in development have come from either plant or microbial sources. Earlier publications have pointed out that relatively little of the world's plant biodiversity has been extensively screened for bioactivity and that very little of the estimated microbial biodiversity has been available for screening [8,46].Hence, more extensive collections of plants or further advances in the ability to culture microbes could provide many novel chemicals for use in drug discovery assays. In the microbial area, the main sources to date have been fungi and terrestrial actinomycetes. There is growing interest in samples from marine actinomycetes [47–49], particularly with the discovery of species unique to the marine environment and the demonstration that they can produce chemically novel bioactive metabolites. For example, salinosporamide A from Salinospora tropica potently inhibits the 20S proteasome and has anti-cancer activity in experimental models [48]; it is undergoing clinical trials. Many technical hurdles still have to be overcome before wide-scale bioprospecting in marine bacteria is a realistic activity [49]. Another marine source of bioactive compounds that is receiving increasing attention is cyanobacteria [50]. These have yielded curacin A and dolastatin 10 which are being evaluated as anti-cancer agents or have triggered the creation of analogues with better drug-like properties. Over 120 cyanobacterial alkaloids were published between 2001 and 2006, and they have wide structural diversity and a variety of biological actions, such as cytotoxicity, sodium channel

modulation, anti-fungal and inhibition of proteases. Although the mostly untapped microbial diversity of marine environments is recognised, continued productive use of terrestrial bacteria has been limited by difficulties in culturing the vast majority of species. This has led to the interest in various genetic manipulation techniques such as combinatorial genetics [46,51]. Most of the research in this area focuses on polyketide pathways in bacteria or fungi [52], and this has led, for example, to the creation of rapamycin analogues with a range of activities [53]. There are, however, concerns about the applicability of the approach [54] and many of the specialist biotech companies that were founde to exploit the technology have not survived. Molecular biological techniques have also been applied to use bacteria to produce drug like isoprenoid compounds originally isolated from plants [55], and to produce novel flavanones and dihydroflavonols [56]. A bioinformatics approach has also been used to predict which microbes will produce novel chemicals on the basis of the gene sequences encoding polyketide synthesis; this has led to the discovery of novel compounds with potential anti-fungal and anticancer activities [57]. More recently, a metagenomics approach has been used to access a wider range of synthetic capabilities from bacteria [58,59]. This involves sampling all the bacterial DNA from an environmental sample and cloning the DNA in host organisms such as E. coli. Recombinant bacteria can then be cultured and tested for the expression of bioactive metabolites. Similar work has explored the peptide synthetase genes and polyketide synthase genes of cyanobacteria [60]. The metagenomics approach has led to the discovery of novel compounds with antibiotic activity, the turbomycins [61] .

Another approach is to adapt the strategy long used to improve the activity of naturally occurring antibiotics by applying combinations of synthetic and enzymatic methods to produce complex natural products. 'Mutasynthetic' methods [62] have been used t create macrocyclic compounds related to the antibiotic daptomycin (Fig. 1) and the anti-cancer compound cryptophicin [63], and vancomycin analogues have been made with th aid of oxidative modifications carried out by cytochrome P450 enzymes [64]. Natural products have inspired many developments in organic chemistry [65,66], leading to advances in synthetic methodologies and to the possibility of making analogues of the original lead compound with improved pharmacological or pharmaceutical properties [67]. Natural product scaffolds have also been well recognized as being'privileged' structures in termsof their ability to be the basis for successful drugs. Such scaffolds are being used as cores of compound libraries made by combinatorial techniques. There are several examples of libraries based on alkaloids, polyketides, terpenoids [68] and flavonoids [69]. There is also a description of computational methods to compare the natural product likeness of compound libraries [70].With the application of various techniques to create analogues and derivatives of natural products, it becomes possible to derive novel compounds that can be patented, even when the original structure was previously disclosed.

Anti-Cancer Drug Discovery

The first agents introduced in clinical use were vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the *Catharanthus roseus* G. Don. (Apocynaceae).These drugs were discovered during an investigation for oral hypoglycemic agents. Recently semi-synthetic analogues of vinca alkaloids are vinorelbine (VRLB) and vindesine (VDS). These are primarily using alone or in combination with other chemotherapeutic drugs to combat a variety of cancers. VLB is using for the treatment of lymphomas, leukemias, breast cancer, testicular cancer, lung cancers, and Kaposi's sarcoma. VCR had also showed efficacy against leukemia, particularly acute lymphocytic leukemia in childhood [71]. Extensive research studies at Sandoz Laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide, **Podophyllotoxin Derivatives** as clinical agents which are being used in the treatment of lymphomas and bronchial and testicular cancers[72].

A more recent advancement in the development of plant derived chemotherapeutic agents is the development of a class of molecules called taxanes. Paclitaxel also names as taxol was first isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae). Paclitaxel is used in the treatment of wide variety of cancers including breast, ovarian and non-small-cell lung cancer, and has also shown efficacy against Kaposi sarcoma. Docetaxel, a semisynthetic derivative, is primarily used in the treatment of breast cancer. The importance of this class of anti-cancer agents can be evaluate by the fact that more than one dozen taxanes analogues are in clinical or preclinical development[73].

Another advancement that was made in the anti-cancer drug is the class of clinically-active agents derived from camptothecin. Campothecin was first isolated from the Chinese ornamental

tree, *Camptotheca acuminata* Decne (Nyssaceae). Camptothecin was introduced to clinical trials by the National Cancer Institute in the 1970s, but withdrawn soon because of reports of severe bladder toxicity. Extensive researches performed by several organizations for a search of more effective camptothecin derivatives and Topotecan (Hycamtin) was developed by SmithKline Beecham (now Glaxo SmithKline), and Irinotecan was developed by the Japanese company, Yakult Honsha, are now in clinical use. Topotecan is used for the treatment of ovarian and small-cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers [74].

Other plant-derived agents, which are in clinical use, are homoharringtonine. Homoharringtonine was originally isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea* (Cephalotaxaceae),. Elliptinium was isolated from species of several genera of the Apocynaceae familyincluding *Bleekeria vitensis*, a Fijian medicinal plant with reputed anti-cancer properties. A racemic mixture of harringtonine and homoharringtonine (HHT) is being used successfully in China to combat acute myelogenous leukemia and chronic myelogenous leukemia [75].

Antidiabetic drugs derived from plants

Metformin, the mainstay drug in treatment of type 2 diabetes, is derived from the guanidines which were obtained from Galegine officinalis [76]. Antidiabetic drugs derived from animals Insulin The discovery of insulin from animals marked a major breakthrough in the treatment of diabetes. Historically, in 1921, in Ontario Canada, a young surgeon Frederick Banting, and his assistant Charles Best, kept a severely diabetic dog alive for 70 days by injecting it with a murky concoction of canine pancreas extract. Banting and co-workers later administered a more refined extract of insulin to Leonard Thompson, a young boy dying of diabetes. Within 24 hours, Leonard's dangerously high blood sugars had dropped to near normal levels [77]. Exenatide Exenitide, a 39-amino-acid peptide, is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster (Heloderma suspectum) that was first isolated by Dr. John Eng in 1992 [78]. This drug has been approved for the management of type 2 diabetes mellitus. Antidiabetic drugs derived from micro-organisms Acarbose is a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes. It is an alpha-glucosidase inhibitor used in type 2 diabetes

Challenges in drug discovery from medicinal plants

Despite the evident successes of drug discovery from medicinal plants, future endeavors face many challenges. Pharmacognosists, phytochemists, and other natural product scientists will need to continuously improve the quality and quantity of compounds that enter the drug development phase to keep pace with other drug discovery efforts (Butler, 2004). The process of drug discovery has been estimated to take an average of 10 years upwards (Reichert, 2003) and cost more than 800 million dollars (Dickson and Gagnon, 2004). Much of this time and money is spent on the numerous leads that are discarded during the drug discovery process. In fact, it has been estimated that only one in 5000 lead compounds will successfully advance through clinical trials and be approved for use. Lead identification is the first step in a lengthy drug development process. Lead optimization (involving medicinal and combinatorial chemistry), lead development (including pharmacology, toxicology, pharmacokinetics, ADME [absorption, distribution, metabolism, and excretion], and drug delivery), and clinical trials all take a considerable length of time.

CONCLUSION:

Despite a period in which pharmaceutical companies cut back on their use of natural products in drug discovery, there are many promising drug candidates in the current development pipeline that are of natural origin. Technical drawbacks associated with natural product research have been lessened, and there are better opportunities to explore the biological activity of previously inaccessible sources of natural products. With the increasing acceptance that the chemical diversity of natural products is well suited to provide the core scaffolds for future drugs, there will be further developments in the use of novel natural products and chemical libraries based on natural products in drug discovery campaigns

REFERENCES:

1 Kinghorn, A.D., 2001. Pharmacognosy in the 21st century. Journal of Pharmacy and Pharmacology 53 (2), 135 – 148.

2 Samuelsson, G., 2004. Drugs of Natural Origin: a Textbook of Pharmacognosy, 5th Swedish Pharmaceutical Press, Stockholm.

3 Newman, D.J., Cragg, G.M., Snader, K.M., 2000. The influence of natural products upon drug discovery. Natural Product Reports 17 (3), 215 – 234.

4 Butler, M.S., 2004. The role of natural product chemistry in drug discovery. Journal of Natural Products 67 (12), 2141 – 2153.

6 Newman, D.J. and Cragg, G.M. (2007) Natural products as sources of new drugs over the last 25 years. J. Nat. Prod. 70, 461–477

7 Butler, M.S. (2008) Natural products to drugs: natural product-derived compounds in clinical trials. Nat. Prod. Rep. 25, 475–516
7 Chin, Y.-W. et al. (2006) Drug discovery from natural sources. AAPS J. 8, E239–E253
8 Lam, K.S. (2007) New aspects of natural products in drug discovery. Trends Microbiol. 15, 279–289
9 Ganesan, A. (2008) The impact of natural products upon modern drug discovery. Curr. Opin. Chem. Biol. 12, 306–317
10 Singh, S.B. and Barrett, J.F. (2006) Empirical antibacterial drug discovery– foundation in natural products. Biochem. Pharmacol. 71, 1006–1015
11 Baker, D.D. et al. (2007) The value of natural products to future pharmaceutical discovery. Nat. Prod. Rep. 24, 1225–1244
12 McChesney, J.D. (2007) Plant natural products: back to the future or into extinction? Phytochemistry 68, 2015–2022
13 Rishton, G.M. (2008) Natural products as a robust source of new drugs and drug leads: past successes and present day issues. Am. J. Cardiol. 101 (Suppl.), 43D– 49D
14 Baker, J.T., Borris, R.P., Carte´, B., Cordell, G.A., Soejarto, D.D., Cragg, G.M., Gupta, M.P., Iwu, M.M., Madulid, D.R., Tyler, V.E., 1995. Natural products drug discovery and development: new perspectives on international collaboration. Journal of Natural Products 58 (9), 1325 – 1357.
15 Tyler, V.E., 1999. Phytomedicines: back to the future. Journal of Natural Products 62 (11), 1589 – 1592.
16 Cardellina II, J.H., 2002. Challenges and opportunities confronting the botanical dietary supplement industry. Journal of Natural Products 65 (7), 1073 – 1084.
17 Ley, S.V., Baxendale, I.R., 2002. New tools and concepts for modern organic synthesis. Nature Reviews Drug Discovery 1 (8), 573 – 586.
18 Geysen, H.M., Schoenen, F., Wagner, D., Wagner, R., 2003. Combinatorial compound libraries for drug discovery: an ongoing challenge. Nature Reviews Drug Discovery 2 (3), 222 – 230.
19 Lombardino, J.G., Lowe III, J.A., 2004. The role of the medicinal chemist in drug discovery—then and now. Nature Reviews Drug Discovery 3 (10), 853 – 862.
20 Newman, D.J., Cragg, G.M., Snader, K.M., 2003. Natural products as sources of new drugs over the period 1981 – 2002. Journal of Natural Products 66 (7), 1022 – 1037.
21 Clardy, J., Walsh, C., 2004. Lessons from natural molecules. Nature 432 (7019), 829 – 837.
22 Nicolaou, K.C., Snyder, S.A., 2004. The essence of total synthesis. Proceedings of the National Academy of Sciences of the United States of America 101 (33), 11929 – 11936.
23 Peterson, E.A., Overman, L.E., 2004. Contiguous stereogenic quaternary carbons: a daunting challenge in natural products synthesis. Proceedings of the National Academy of Sciences of the United States of America 101 (33), 11943 – 11948.
24 Koehn, F.E., Carter, G.T., 2005. The evolving role of natural products in drug discovery. Nature Reviews Drug Discovery 4 (3), 206 – 220.
25 Lee, M.L., Schneider, G., 2001. Scaffold architecture and pharmacophoric properties of natural products and trade drugs: application in the design of natural product-based combinatorial libraries. Journal of Combinatorial Chemistry 3 (3), 284 – 289
26 Feher, M., Schmidt, J.M., 2003. Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. Journal of Chemical Information and Computer Sciences 43 (1), 218 – 227.
27 Piggott, A.M., Karuso, P., 2004. Quality, not quantity: the role of natural products and chemical proteomics in modern drug discovery. Combinatorial Chemistry and High Throughput Screening 7 (7), 607 – 630.
28 Hall, M.G., Wilks, M.F., Provan, W.M., Eksborg, S., Lumholtz, B., 2001b. Pharmacokinetics and pharmacodynamics of NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione) and mesotrione, inhibitors of 4- hydroxyphenyl pyruvate dioxygenase (HPPD) following a single dose to healthy male volunteers. British Journal of Clinical Pharmacology 52 (2), 169 – 177
29 Eldridge, G.R., Vervoort, H.C., Lee, C.M., Cremin, P.A., Williams, C.T., Hart, S.M., Goering, M.G., O'Neil-Johnson, M., Zeng, L., 2002. High-throughput method for the production and analysis of large natural product libraries for drug discovery. Analytical Chemistry 74 (16), 3963 – 3971.
30 Burke, M.D., Berger, E.M., Schreiber, S.L., 2004. A synthesis strategy yielding skeletally diverse small molecules combinatorially. Journal of the American Chemical Society 126 (43), 14095 – 14104.
31 Ganesan, A., 2004. Natural products as a hunting ground for combinatorial chemistry. Current Opinion in Biotechnology 15 (6), 584 – 590.
32 Tan, D.S., 2004. Current progress in natural product-like libraries for discovery screening.

Combinatorial Chemistry and High Throughput Screening 7 (7), 631 – 643.

33 Kramer, R., Cohen, D., 2004. Functional genomics to new drug targets. Nature Reviews Drug Discovery 3 (11), 965 – 972.

34 Hoessel, R., Leclerc, S., Endicott, J.A., Nobel, M.E., Lawrie, A., Tunnah, P., Leost, M., Damiens, E., Marie, D., Marko, D., Niederberger, E., Tang, W., Eisenbrand, G., Meijer, L., 1999. Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases. Nature Cell Biology 1 (1), 60 – 67.

35 Eisenbrand, G., Hippe, F., Jakobs, S., Muehlbeyer, S., 2004. Molecular mechanisms of indirubin and its derivatives: novel anticancer molecules with their origin in traditional Chinese phytomedicine. Journal of Cancer Research and Clinical Oncology 130 (11), 627 – 635.

36 Hwang, B.Y., Lee, J.H., Koo, T.H., Kim, H.S., Hong, Y.S., Ro, J.S., Lee, K.S., Lee, J.J., 2001. Kaurane diterpenes from Isodon japonicus inhibit nitric oxide and prostaglandin E2 production and NF-nB activation in LPSstimulated macrophage RAW264.7 cells. Planta Medica 67 (5), 406 – 410.

37 Lee, J.H., Koo, T.H., Hwang, B.Y., Lee, J.J., 2002. Kaurane diterpene, kamebakaurin, inhibits NF-kappa B by directly targeting the DNA-binding activity of p50 and blocks the expression of antiapoptotic NF-kappa B target genes. Journal of Biological Chemistry 277 (21), 18411 – 18420

38 Blaskovich, M.A., Sun, J., Cantor, A., Turkson, J., Jove, R., Sebti, S.M., 2003. Discovery of JSI-124 (cucurbitacin I), a selective Janus kinase/signal transducer and activator of transcription 3 signaling pathway inhibitor with potent antitumor activity against human and murine cancer cells in mice. Cancer Research 63 (6), 1270 – 1279

39 Li, Y., Sun, X., LaMont, J.T., Pardee, A.B., Li, C.J., 2003. Selective killing of cancer cells by beta-lapachone: direct checkpoint activation as a strategy against cancer. Proceedings of the National Academy of Sciences of the United States of America 100 (5), 2674 – 2678.

40 Pisha, E., Chai, H., Lee, I.S., Chagwedera, T.E., Farnsworth, N.R., Cordell, G.A., Beecher, C.W., Fong, H.H., Kinghorn, A.D., Brown, D.M., Wani, M.C., Wall, M.E., Hieken, T.J., Das Gupta, T.K., Pezzuto, J.M., 1995. Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. Nature Medicine 1 (10), 1046 – 1051.

41 Tan, Y., Yu, R., Pezzuto, J.M., 2003. Betulinic acid-induced programmed cell death in human melanoma cells involves mitogen-activated protein kinase activation. Clinical Cancer Research 9 (7), 2866 – 2875.

42 Cichewicz, R.H., Kouzi, S.A., 2004. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and 438 M.J. Balunas, A.D. Kinghorn / Life Sciences 78 (2005) 431 – 441 treatment of cancer and HIV infection. Medical Research Reviews 24 (1), 90 – 114

43 Feher, M. and Schmidt, J.M. (2003) Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. J. Chem. Inf. Comput. Sci. 43, 218–227

44 Grabowski, K. and Schneider, G. (2007) Properties and architecture of drugs and natural products revisited. Curr. Chem. Biol. 1, 115–127

45 Galm, U. and Shen, B. (2007) Natural product drug discovery: the times have never been better. Chem. Biol. 14, 1098–1104

46 Harvey, A.L. (2000) Strategies for discovering drugs from previously unexplored natural products. Drug Dis. Today 5, 294–300

47 Lam, K.S. (2006) Discovery of novel metabolites from marine actinomycetes. Curr. Opin. Microbiol. 9, 245–251

48 Fenical, W. and Jensen, P.R. (2006) Developing a new resource for drug discovery: marine actinomycete bacteria. Nat. Chem. Biol. 2, 666–673

49 Bull, A.T. and Stach, J.E. (2007) Marine actinobacteria: new opportunities for natural product search and discovery. Trends Microbiol. 15, 491–499

50 Tan, L.T. (2007) Bioactive natural products from marine cyanobacteria for drug discovery. Phytochemistry 68, 954–979

51 Harvey, A.L. (2007) Natural products as a screening resource. Curr. Opin. Chem. Biol. 11, 480–484

52 Cox, R.J. (2007) Polyketides, proteins and genes in fungi: programmed nanomachines begin to reveal their secrets. Org. Biomol. Chem. 5, 2010–2026

53 Zhang, M.Q. and Wilkinson, B. (2007) Drug discovery beyond the 'rule-of-five'. Curr. Opin. Biotechnol. 18, 478–488

54 Floss, H.G. (2006) Combinatorial biosynthesis–potential and problems. J. Biotechnol. 124, 242–257

55 Chang, M.C.Y. and Keasling, J.D. (2006) Production of isoprenoid pharmaceuticals by

engineered microbes. Nat. Chem. Biol. 2, 674–681
56 Chemler, J.A. et al. (2007) Combinatorial mutasynthesis of flavonoid analogues from acrylic acids in microorganisms. Org. Lett. 9, 1855–1858
57 McAlpine, J.B. et al. (2005) Microbial genomics as a guide to drug discovery and structural elucidation: ECO-02301, a novel antifungal agent, as an example. J. Nat.
Prod. 68, 493–496
58 Kennedy, J. et al. (2007) Metagenomic approaches to exploit the biotechnological potential of the microbial consortia of marine sponges. Appl. Microbiol. Biotechnol. 75, 11–20
59 Lefevre, F. et al. (2008) Drugs from hidden bugs: their discovery via untapped resources. Res. Microbiol. 159, 153–161
60 Barrios-Llerena, M.E. et al. (2007) Genetic analysis of polyketide synthase and peptide synthetase genes in cyanobacteria as a mining tool for secondary metabolites. J. Ind. Microbiol. Biotechnol. 34, 443–456
61 Gillespie, D.E. et al. (2002) Isolation of antibiotics turbomycin a and B from a metagenomic library of soil microbial DNA. Appl. Environ. Microbiol. 68, 4301– 4306
62 Kennedy, J. (2008) Mutasynthesis, chemobiosynthesis, and back to semi-synthesis: combining synthetic chemistry and biosynthetic engineering for diversifying natural products. Nat. Prod. Rep. 25, 25–34
63 Kopp, F. and Marahiel, M.A. (2007) Where chemistry meets biology: the chemoenzymatic synthesis of nonribosomal peptides and polyketides. Curr. Opin. Biotechnol. 18, 513–520
64 Lamb, D.C. et al. (2007) Cytochromes P450 and drug discovery. Curr. Opin. Biotechnol. 18, 504–512
65 Wilson, R.M. and Danishefsky, S.J. (2006) Small molecule natural products in the discovery of therapeutic agents: the synthesis connection. J. Org. Chem. 71, 8329– 8351
66 Newman, D.J. (2008) Natural products as leads to potential drugs: an old process or the new hope for drug discovery? J. Med. Chem. 51, 2589–2599
67 Sunazuka, T. et al. (2008) Efficient total synthesis of novel bioactive microbial metabolites. Acc. Chem. Res. 41, 302–314
68 Boldi, A.M. (2004) Libraries from natural product-like scaffolds. Curr. Opin. Chem. Biol. 8, 281–286
69 Yao, N. et al. (2007) Synthesis of flavonoid analogues as scaffolds for natural product-based combinatorial libraries. J. Comb. Chem. 9, 668–676
70 Ertl, P. et al. (2008) Natural product-likeness score and its application for prioritization of compound libraries. J. Chem. Inf. Model. 48, 68–74
71 Gueritte F., Fahy J., The vinca alkaloids. In Anticancer Agents from Natural Products, edited by Cragg GM, Kingston DGI, Newman DJ. Brunner-Routledge Psychology Press, Taylor & Francis Group, Boca Raton, Chapter 7. 23. 2005.
72 Lee K.H., Xiao Z., Podophyllotoxins and analogs. In Anticancer Agents from Natural Products, edited by Cragg GM, Kingston DGI, Newman DJ. Brunner-Routledge Psychology Press, Taylor & Francis Group, Boca Raton, Chapter 5. 71. 2005.
73 Kingston D. G. I., Taxol and its analogs. In Anticancer Agents from Natural Products, edited by Cragg GM, Kingston DGI, Newman DJ. Brunner-Routledge Psychology Press, Taylor & Francis Group, Boca Raton, Chapter 6. 89. 2005.
74 Rahier N.J., Thomas C. J., Hecht S. M., Camptothecin and its analogs. In Anticancer Agents from Natural Products, edited by Cragg GM, Kingston DGI, Newman DJ. Brunner-Routledge Psychology Press, Taylor & Francis Group, Boca Raton, Chapter 2. 5. 2005
75 Itokawa H., Ibraheim Z. Z, Ya F. Q., Takeya K., Anthraquinones, naphthohydroquinones and naphthohydroquinone dimmers from Rubia cordifolia and their cytotoxic activity. *Chemical and Pharmaceutical Bulletin*, 41(10). 1869. 1993.
76. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod. 2012;75(3):311-5. D01: 10.1021/np200906s.
77. Sattley M. The History of Diabetes. Diabetes Health Newsletter; 2008. Available: http://diabeteshealth.com/read/2008/12/17/715/the-history-of-diabetes/. British Journal of Pharmaceutical Research, 4(17): 2075-2095, 2014 2091
78. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancrease. J Biol Chem. 1992;267(11):7402-5.