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Natural products sources and their active compounds on disease prevention: A Review

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Abstract

Natural products represent major approach for the discovery and development of new drugs. Phytochemicals are the naturally occurring, biologically active compounds found in plants which have capabilities of inhibiting various diseases. Antioxidants defend molecules from oxidation if they are attacked by free radicals. In this way prevention from many diseases and food spoilage is possible. Almost 47 % of anticancer drugs came from the natural products.

Key words: Phytochemicals, natural products, bioactive compounds, diseases, prevention

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1. Introduction:

Thousands of years ago natural products have been used for disease prevention and health care. Ancient civilizations of Chinese, North Africans and Indians provide evidence for use of the natural sources in curing various types of diseases. The oldest known document is four thousand years old called Sumerian clay tablet used for various diseases [1]. Similarly mandrake was used for relief of pain. Turmeric was used for blood clotting. Gall bladder infections were treated by the roots of endive plants. Raw garlic was used to treat the circulatory disorders [2]. These old medicines are still used in many countries as the alternative medicines. Until nineteenth century active components were not isolated from medicinal plants [3].

In 1806 Friedrich Sertürner was a scientist who isolated morphine from the *Papaver somniferum*. Then natural products were extensively screened to obtain medicines. Atropine was obtained from the *Atropa belladonna* [4].

According to modern search it was revealed by World Health Organization that almost 80% of world's population depends on the traditional medicines. Almost 121 drugs used in USA in these days come from the natural sources. From these 90 drugs come from plant sources indirectly or directly [5]. Almost 47 % of anticancer drugs come from the natural products. Between years from 1981 to 2006 about 100 anticancer agents were developed. From these 25 were the derivatives of natural products, 18 were mimics of natural products and 11 were derived from the natural product called pharmacophore. There were also 9 anticancer agents which were purely natural products. Thus the natural sources are significant source of caring in the health system [6-7].

2. Natural products:

The organic compounds which are formed by living systems are called natural products. The major areas of organic chemistry are synthesis, biosynthesis and elucidation of the structures of natural products [8]. Three major categories can be used to divide natural compounds. In the first category there are those compounds which are present in all cells of the organisms and play a central role in the metabolism and reproduction in them. They are called primary metabolites. Nucleic acids, common amino acids and sugars are included in them. In the second category there are polymeric materials with high molecular weights such as lignins, cellulose and proteins made up of cellular structures. In the third category there are those compounds which may be present in smaller amounts. They are called secondary metabolites [9]. The difference in primary and secondary metabolites is that, the biological effect of primary metabolites is exerted within the cell or organisms body which is responsible for the production. But secondary metabolites have their biological effect within the organisms and also on the other organisms. Biological active components of poisonous, commercial and medicinal plants had been studied during development of the organic

chemistry. Most of these are the secondary metabolites [10]. Many screening programs exist for the bioactive compounds which led to the new drug discovery e.g. taxol for cancer treatment. They play an ecological role in regulating interactions between insects, microorganisms, plants and animals. They may be attractants, pheromones, antifeedants and defensive substances [11].

3. Natural products as phytochemicals:

The secondary metabolites of plants have been mentioned as phytochemicals. Phytochemicals are the naturally occurring, biologically active compounds found in plants which have capabilities of disease inhibiting [12-13]. Phytochemicals are much effective in preventing disease because of antioxidant effect. Antioxidants defend molecules from oxidation if they are attacked by free radicals. They also prevent them from reactive oxygen. In this way prevention from many diseases and food spoilage is possible [14-15]. Before the introduction of orthodox medicines medicinal plants were used. Flowers, leaves, stems, seeds, roots, bark and fruit are constituents of the herbal medicines. Component of phytochemicals represent medicinal value of the natural plants [16-17]. Phytochemicals perform physiological actions on human body. Important phytochemicals are tannins, alkaloids, phenolic compounds and flavonoids [18].

4. Microorganisms as a source of natural products:

Until the discovery penicillin, microorganisms were not source of the potential drugs. After that large number of the marine and terrestrial microorganisms was screened to discover the drugs [19]. Microorganisms have wide variety of the active substances so they led to discovery of the antibacterial agents. Examples are cephalosporins, acarbose and epirubicin [20].

5. Marine organisms as source of natural products:

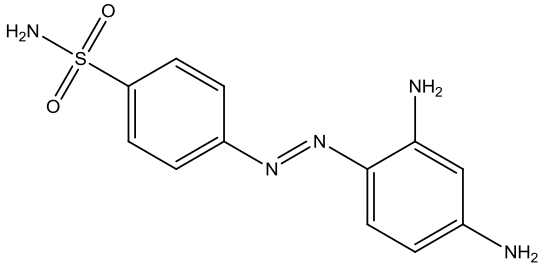
Two active compounds were isolated first time from the marine species. These were spongothymidine and spongouridine derived from Carribean sponge known as *Cryptotheca crypta* in 1950s [21]. The above compounds were nucleotides and represented great potential in the form of antiviral and anticancer agents. Discovery of these compounds led to the extensive research for the identification of novel drugs from the marine sources [22]. Almost 70% of earth's surface is mainly covered by oceans. A number of marine organisms show sedentary lifestyle. So they synthesize complex and potent chemicals for the purpose of their defense from the predators. These chemicals may serve as remedies for ailments like cancer. Example is discodermolide isolated from marine sponge [4]. *Discodermia dissolute* is a natural product having similar action to paclitaxel and possesses antitumor activity. This also have better solubility in water compared to paclitaxol. Combination of these two drugs led to reduce the tumor growth in various types of cancers [21-23].

6. Animals as a source of natural products:

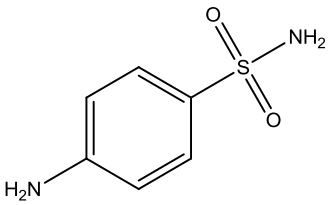
Animals have been a major source of the interesting compounds which were used as drugs. Epibatidine is obtained from skin of the Ecuadorian frog which is poisonous. It is 10 times more effective than the morphine [24].Toxins and venoms obtained from animals played an important role in the curing of several diseases. Example is Teprotide, extracted from the Brazilian viper. It led to development of the captopril and cilazapril which were effective against the hypertension [25].

7. Natural products as antibacterials:

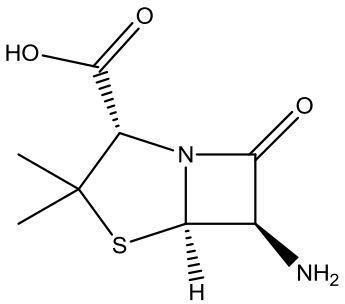
The introduction of sulfonamides was exemplified by the Prontosil which led to introduction of the synthetic antibacterials. Its first clinical report was in 1933 which lead to award of Nobel Prize for the Medicines in 1938 received by Domagk [26]. In antibiotic field the active sulfanilamide is structural analogue of the *para*-aminobenzoic acid. It competitively inhibits the dihydropteroate synthase. So it causes inhibition of the folic acid and also causes bacterial death. Following are the examples of antibacterials [27].



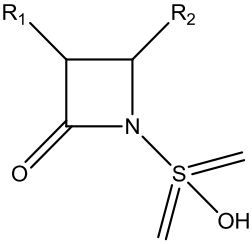
(Prontosil)



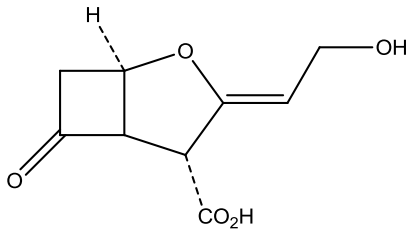
(Slfanilamide)



(6-amino-penicillanic acid)



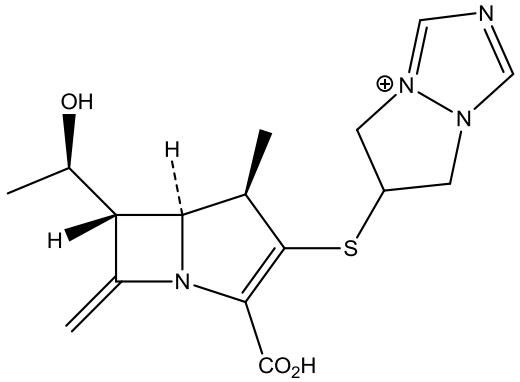
(Monobactam nucleus)



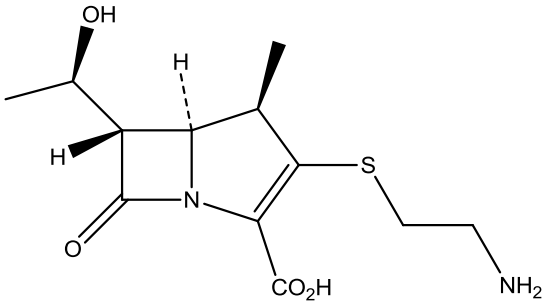
(Clavulanic acid)[28]

8. Actinomycins, tetracyclins, erythromycines and aminoglycosides as sources of natural products:

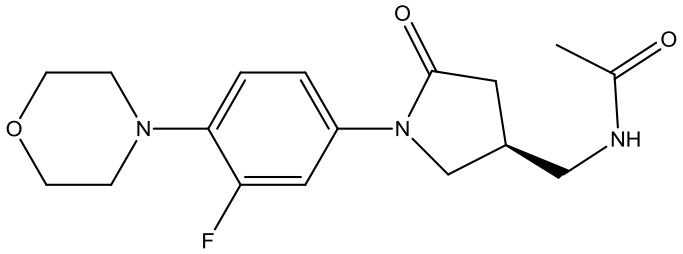
In 1943 aminoglycoside streptomycin was separated from the *Streptomyces griseus.* Inspite of activity against *M. tuberculosis* it was also active against wide variety of the other types of pathogenic organisms. Additional work over next twenty years yielded more number of the similar type of glycosidic based antibacterials [29-30].



(Biapenem)



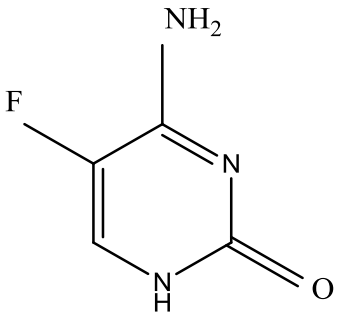
(Thienamycin)



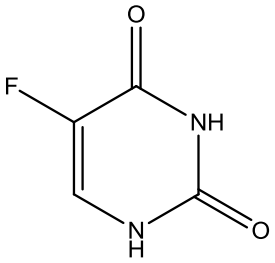
(Linezolid) [31]

9. Antifungals as a source of natural products:

Fungi are the eukaryotes, number of targets where differences between microbes and hosts are smaller as compared to the bacteria, such as they have differences in the primary processes of metabolism as architecture of their membranes and cell walls [32]. A specific number of the bacterial targets cannot show eukaryotic counterparts. Following are the examples of antifungals [33].



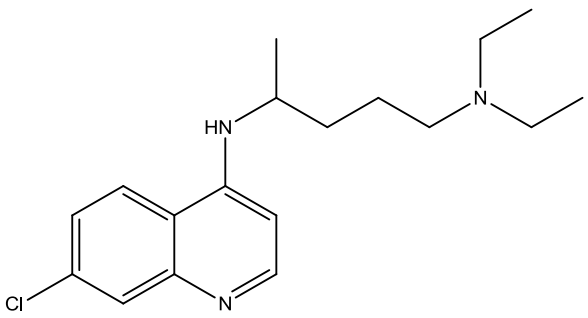
(5-fluorocytosine)



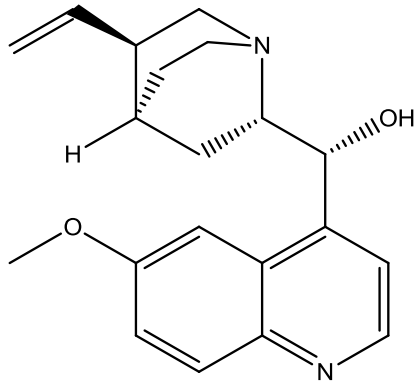
(5-fluorouracil) [34]

10. Antiparastics as a source of natural products:

Natural products represent major approach for the discovery and development of new drugs. Use of the medicinal plants for treatment of the parasitic diseases is documented from earlier times [35]. Discovering natural sources of the novel antiprotozoal extracts from the nature remained as challenge and so the source of combinatorial genomics and chemistry. Quinine has been used as anti-malarial in past. Following are the examples of antiparastic [36-37].



(Chloroquine)



(Quinine) [37]

11. Classes of natural products

There are following classes of secondary metabolites [38], [39]

- Polyketides and fatty acids
- Terpenoids and steroids
- Phenylpropanoids
- Alkaloids
- Specialized amino acids and peptides [38]
- Carbohydrates
- Flavonoids

Polyketides are the secondary metabolites having a large number of structures and few of them are veterinary or medicinal agents. Tetracyclines and erythromycin are examples of antibiotics. Daunorubicin is example of anti-cancer and avermectin is example of anti-helminthic [40]. Polyketides are formed due to stepwise condensation of the acetate units. Alternate C atoms are present in the resultant C chain due to CH_3 and COOH groups of acetate. In fatty acids reduction of COOH group of acetate units occur during course of chain assembly [41]. Unsaturated fatty acids can be obtained subsequently by oxidative processes and dehydrogenation. Oxygenation occurs on alternate carbon atoms in these compounds [42]. Fatty acids are present in fats in the form of free acids and mostly in combined form as alcohols with esters such as cholesterol and glycerol. Mostly even number of carbon atoms is present in fatty acids, typically C_{12} to C_{20} [43]. These are linked together by a straight chain and maximum four double bonds may be present in a chain. The double bonds are non-conjugated and show cis geometry. Plants contain corresponding alcohols and fatty acids in their seed coating and leaf waxes [44]. Differences between fatty acid and polyketides biosynthesis are due to different types and numbers of the acyl precursors, position, pattern of cyclization of products and extent of the keto-group reductions. So polyketide and fatty acid biosynthesis are related mechanistically and precursor molecules used in their biosynthesis are same [45-46]. Polyketides are found in plants, fungi, bacteria and include important clinical drugs like daunorubicin, tetracycline, erythromycin, and lovastatin and rapamycin. Biologically unparallel activities are included in modern search of polyketide which are commercially useful for modern drug discovery [47]. Secondly mechanism, catalytic reactivity and extraordinary structure of polyketides provide an opportunity for the investigation of enzyme catalysis mechanism, protein–protein interaction and molecular recognition. Thirdly amenability and remarkable versatility of polyketides that allow generation of the novel compounds [48-49].

Terpenoids are natural products derived from isoprene units having five carbon atoms. The structutes of most terpenoids are multi cyclic having difference of functional groups. The carbon skeletons of terpenoids also differ from one another [50]. These are natural lipids which may be found in each class of the living things. This is the reason that they are considered as largest group of the natural products. Most terpenoids have been commercially interesting due to their use as fragrances and flavours in cosmetics and foods. The examples are sclareol and menthol. They are important due to quality of the agricultural products like fragrance of the flowers and flavour of the fruits. Terpenes are widely spread in the nature especially in those plants having essential oils as constituents. They are formed of hydrogen idoprene, CH_2=C (CH_3)-CH=CH_2 [51]. Hemiterpenoids contain single type of isoprene unit. Single type of hemiterpene is isoprene but derivatives of the isoprene containing oxygen such as prenol and isovaleric acid is also included in hemiterpenoids [52]. Monoterpenoids consist of two units of isoprene. Related monoterpenoids can be produced by biochemical changes of monoterpenes like rearrangement or oxidation. Acyclic or cyclic monoterpenes may be present in monoterpenoids. Examples are eucalyptol, geranyl pyropho- sphate, limonene, pinene, citral and camphor [53]. Sesquiterpenes consist of three units of *isoprene*. Examples of acyclic sesquiterpenes are fernesol, artemisinin, oil of flowers and bisabolol. The examples of cyclic sesquiterpene are eudesmol which is present in the eucalyptus oil [54-55]. Diterpenes consist of four units of isoprene. They are derived from the geranylgeranyl pyrophosphate. Examples of diterpenes are kahweol, cembrene, cafestol and taxadiene. Diterpenes are used as base for biologically active compounds such as phytol, retinol and retinal [56]. Triterpenes have six units of isoprene from these squalene and lanosterol are found in olives and wheat germ [57].

Alkaloids are also a major class of natural products. The constituents of alkaloids are nitrogen atoms in heterocyclic form. The nature of alkaloid constituents is basic. That's why the name of alkaloids is derived from "alkaline" as it is used to explain the base containing nitrogen [58]. Alkaloids are present naturally in organisms including plants, animals, fungi and bacteria. In research work of 19th century, medicinal plants were studied to isolate the natural products. It was seen that alkaloids were obtained from these plants which contained nitrogen bases [59]. These were also called vegetable alkalies and were used as stimulants and local anesthetics. Almost all alkaloids show bitter taste and quinine is bitterest one. Alkaloids are very numerous among natural products and have a wide variety of structures that their classification is difficult. So they are classified in families on the basis of hetero cyclic rings. Nomenclature of the alkaloids is not systematized. That's why the names of alkaloids are derived from plant names or from their physiological activities. Following are classes of the alkaloids on the basis of ring system [60]. Pyrrolidine alkaloids have tetrahydropyrrole ring system. The example is hygrine present in *Erythroxylum* of the coca

leaves [61]. Pyridine alkaloids contain hexahydropyridine ring system. The examples are piperine, coniine and isopelletierine [62]. Pyrrolidine pyridine alkaloids contain heterocyclic ring systems. This ring system is called Pyrrolidinepyridine. The examples are nicotine alkaloid and myosmine present in *Nicotiana tabacum* [63]. Pyridine piperdine alkaloids have ring system of pyridine. The pyridine rings join to form piperidine ring system. Simplest member of pyridine piperdine is anabasine alkaloid which is isolated from poisonous plant called anabasis aphyllan [64]. Quinoline alkaloids have ring system of quinolone which is heterocyclic. The example is quinine present in bark of the cinchona tree. It has long been used as medicine for the malaria treatment. Now a day's synthetic drug primaquinine have replaced quinine because it can also be used as antimalarial. Isoquinoline alkaloids have ring system of isoquinoline which is heterocylic. Examples are opium alkaloids such as papaverine, narcoti morphine, heroine and codeine [65].

12. Roles of amino acids in immune function:

Among amino acids alanine is the major substrate to synthesize glucose which is significant substrate of energy for the leucocyte. Alanine also influences the immune function. Now days some information is accessible regarding to effects of the dietary supplementation along with alanine on immune responses in animal species. In patients with the total parenteral nutrition, addition of alanine might be beneficial for leucocyte metabolism and supporting gluconeogenesis [66].

13. Arginine, ornithine and citrulline:

Arginine is an amino acid which is synthesised by citrulline as immediate precursor and is present virtually in all types of cells. Citrulline is another amino acid which is synthesized in small intestine of mammals but ferrets and cats cannot synthesize them in their small intestine. Citrulline is synthesized by proline, glutamine and glutamate. Arginine must be provided from diet for supporting the nitrogen balance. It also promotes health of humans and animals. Because of depolarization of membrane coupled with transport of amino acid with positive charge, arginine is the effective secretagogue for growth hormone, insulin and prolactin [67].

14. Imbalance in the antioxidant defence and natural antioxidant therapy:

Modern search has revealed that genetic and multiple acquired factors may alter the homeostatic balance in body and favour multiple types of diseases. The solution of this problem is that homeostatic balance must be restored. Majority of disorders are due to imbalance between anti-oxidant and pro-oxidant homeostatic phenomenon in body. If free radicals are more in body then pro-oxidant conditions are dominated. Free radicals are produced due to respiration and immune functions in body. Other reasons are smoke, pollution, radiations etc. The protective antioxidants in body fight against free radicals [68]. A homeostatic balance is established between oxidants and antioxidant defence. Enzymztic and non-enzymatic agents also effect the antioxidant defense [69].

15. Screening of the bioactive compounds:

The basic scheme shows the work flow which can be used for screening of natural products obtained from marine sources including natural marine resources, green extraction techniques, functional characterization, chemical characterization, different extraction methods, bioactivity in-vitro assays and advanced analytical methods [70].

16. Functional Foods and nutraceuticals:

Functional foods having active components, from animal or plant sources enhance health. Functional foods do not behave magic bullet for the poor habits of health [71]. Increasing consumption of the vegetables, fruits and grains is a strategy for the consumers. It optimizes their health while reducing risk of the chronic diseases. So use of the functional foods, nutraceuticals and dietary supplements is going to increase. However it is important to obtain more information for health benefits and the possible risks for ensuring the safety and efficacy of the dietary supplements. It is to improve health by increasing nutrient requirements for disease prevention. It must be believed that evidences suggest antioxidants as best obtained from food consumption as compared to a pill [72].

17. Conclusions:

A careful review of previous studies revealed presence of the medicinally important components in various living organisms. A number of evidences obtained from earlier studies confirmed and identified the phytochemicals as bioactive compounds. Studies confirmed that presence of the phytochemicals contribute to physiological and medicinal properties of plants for treatment of the different ailments. That's why extracts obtained from such plants may be seen as a good source for the useful drugs. Traditional medicinal practice must be recommended for such plants as it may be suggested that more work may purify, charaterize and isolate active constituents which are responsible for activity of such plants. Additional work must be encouraged for the elucidation of possible mechanisms of actions of such extracts [73].

References:

[1] D.J. Newman, G.M. Cragg. (2007). Natural Products as Sources of New Drugs over the Last 25 Years⊥. Journal of natural products. 70(3): 461-477.

[2] D.J. Newman, G.M. Cragg, K.M. Snader. (2003). Natural products as sources of new drugs over the period 1981-2002. Journal of natural products. 66(7): 1022-1037.

[3] Y.-W. Chin, M.J. Balunas, H.B. Chai, A.D. Kinghorn. (2006). Drug discovery from natural sources. The AAPS Journal. 8(2): E239-E253.

[4] B. Haefner. (2003). Drugs from the deep: marine natural products as drug candidates. Drug discovery today. 8(12): 536-544.

[5] F.E. Koehn, G.T. Carter. (2005). The evolving role of natural products in drug discovery. Nature Reviews Drug Discovery. 4(3): 206-220.

[6] J.D. Phillipson. (2001). Phytochemistry and medicinal plants. Phytochemistry. 56(3): 237-243.

[7] J.-M. Kong, N.-K. Goh, L.-S. Chia, T.-F. Chia. (2003). Recent advances in traditional plant drugs and orchids. Acta Pharmacologica Sinica. 24(1): 7-21.

[8] M.A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann. (2005). Charting biologically relevant chemical space: a structural classification of natural products (SCONP). Proceedings of the National Academy of Sciences of the United States of America. 102(48): 17272-17277.

[9] P. Cos, L. Ying, M. Calomme, J.P. Hu, K. Cimanga, B. Van Poel, L. Pieters, A.J. Vlietinck, D.V. Berghe. (1998). Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. Journal of natural products. 61(1): 71-76.

[10] H. Budzikiewicz, C. Djerassi, D.H. Williams. (1964). Structure elucidation of natural products by mass sp ectrometry.

[11] A.L. Harvey. (2008). Natural products in drug discovery. Drug discovery today. 13(19): 894-901.

[12] F. Abdurraham. Studies on natural products chemistry of the Moraceae in African traditional medicine and management of psychiatry in Borno state. M. Sc. Thesis, University of Maiduguri, Nigeria, 1992.

[13] E. Farombi, J. Nwankwo, G. Emerole. (1998). Effect of methanolic extract of browned yam flour diet on 7, 12 Dimethylbenzanthracene (DMBA) and 3-methylcholanthrene (3-MC)-induced toxicity in the rat. Proceedings of the Federation of African Society on Biochemistry and Molecular Biology. 1: 5-10.

[14] J. Chetia, S. Upadhyaya, L. Saikia. (2014). Phytochemical Analysis, Antioxidant and Antimicrobial Activity and Nutrient Content analysis of Ocimum gratissimum linn. From dibrugarh, NE India. International Journal of Pharmaceutical Sciences Review & Research. 25(1).

[15] I.I. Koleva, H.A. Niederländer, T.A. van Beek. (2000). An on-line HPLC method for detection of radical scavenging compounds in complex mixtures. Analytical Chemistry. 72(10): 2323-2328.

[16] A.C. Akinmoladun, E. Ibukun, E. Afor, E. Obuotor, E. Farombi. (2007). Phytochemical constituent and antioxidant activity of extract from the leaves of Ocimum gratissimum. Sci. Res. Essay. 2(5): 163-166.

[17] J. Pascaline, M. Charles, C. Lukhoba, O. George. (2011). Phytochemical constituents of some medicinal plants used by the Nandis of South Nandi district, Kenya. J Anim Plant Sci. 9: 1201-1210.

[18] U. Kolak, G. TOPÇU, S. Birteksöz, G. Ötük, A. Ulubelen. (2009). Terpenoids and steroids from the roots of Salvia blepharochlaena. Turkish Journal of Chemistry. 29(2): 177-186.

[19] H.B. Woodruff. (1980). Natural products from microorganisms. Science. 208(4449): 1225-1229.

[20] G. Strobel, B. Daisy, U. Castillo, J. Harper. (2004). Natural Products from Endophytic Microorganisms⊥. Journal of natural products. 67(2): 257-268.

[21] V. Bernan, M. Greenstein, W. Maiese. (1997). Marine microorganisms as a source of new natural products. Advances in applied microbiology. 43: 57-90.

[22] G.M. König, S. Kehraus, S.F. Seibert, A. Abdel-Lateff, D. Müller. (2006). Natural products from marine organisms and their associated microbes. ChemBioChem. 7(2): 229-238.

[23] L.-A. Tziveleka, C. Vagias, V. Roussis. (2003). Natural products with anti-HIV activity from marine organisms. Current topics in medicinal chemistry. 3(13): 1512-1535.

[24] G.M. Cragg, D.J. Newman, K.M. Snader. (1997). Natural products in drug discovery and development. Journal of natural products. 60(1): 52-60.

[25] A.M. Clark. (1996). Natural products as a resource for new drugs. Pharmaceutical research. 13(8): 1133-1141.

[26] A. Brantner, K. Pfeiffer, H. Brantner. (1994). Applicability of diffusion methods required by the pharmacopoeias for testing antibacterial activity of natural compounds. Die Pharmazie. 49(7): 512-516.

[27] D.J. Payne, M.N. Gwynn, D.J. Holmes, D.L. Pompliano. (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery. 6(1): 29-40.

[28] F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich. (2006). Antibacterial natural products in medicinal chemistry—exodus or revival? Angewandte Chemie International Edition. 45(31): 5072-5129.

[29] P. Cos, A.J. Vlietinck, D.V. Berghe, L. Maes. (2006). Anti-infective potential of natural products: how to develop a stronger in vitro 'proof-of-concept'. Journal of ethnopharmacology. 106(3): 290-302.

[30] A. Raja, P. Prabakarana. (2011). Actinomycetes and drug-an overview. Am. J. Drug Discovery Dev. 1: 75-84.

[31] V.C. Verma, S.K. Gond, A. Kumar, A. Mishra, R.N. Kharwar, A.C. Gange. (2009). Endophytic actinomycetes from Azadirachta indica A. Juss.: isolation, diversity, and anti-microbial activity. Microbial ecology. 57(4): 749-756.

[32] L. Scorzoni, T. Benaducci, A. Almeida, D. Silva, V. Bolzani, M. Mendes-Giannini. (2009). Comparative study of disk diffusion and microdilution methods for evaluation of antifungal activity of natural compounds against medical yeasts Candida spp and Cryptococcus sp. Revista de Ciências Farmacêuticas Básica e Aplicada. 28(1): 25-34.

[33] M. Vicente, A. Basilio, A. Cabello, F. Pelaez. (2003). Microbial natural products as a source of antifungals. Clinical microbiology and infection. 9(1): 15-32.

[34] A.L. Gunatilaka. (2006). Natural Products from Plant-Associated Microorganisms: Distribution, Structural Diversity, Bioactivity, and Implications of Their Occurrence⊥. Journal of natural products. 69(3): 509-526.

[35] A. Sher, R. Coffman. (1992). Regulation of immunity to parasites by T cells and T cell-derived cytokines. Annual review of immunology. 10(1): 385-409.

[36] C.S. Lantz, J. Boesiger, C.H. Song, N. Mach, T. Kobayashi, R.C. Mulligan, Y. Nawa, G. Dranoff, S.J. Galli. (1998). Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. Nature. 392(6671): 90-93.

[37] O. Kayser, A. Kiderlen, S. Croft. (2003). Natural products as antiparasitic drugs. Parasitology Research. 90(2): S55-S62.

[38] R.T. Schuh, J.A. Slater. (1995). True bugs of the world (Hemiptera: Heteroptera): classification and natural history. Cornell University Press: pp.

[39] M. Saxena, J. Saxena, R. Nema, D. Singh, A. Gupta. Journal of Pharmacognosy and Phytochemistry.

[40] J. Crosby, D.H. Sherman, M.J. Bibb, W. Peter Revill, D.A. Hopwood, T.J. Simpson. (1995). Polyketide synthase acyl carrier proteins from< i> Streptomyces</i>: expression in< i> Escherichia coli</i>, purification and partial characterisation. Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology. 1251(1): 32-42.

[41] R.W. Hoffmann. (1987). Stereoselective Syntheses of Building Blocks with Three Consecutive Stereogenic Centers: Important Precursors of Polyketide Natural Products [New Synthetic Methods (68)]. Angewandte Chemie International Edition in English. 26(6): 489-503.

[42] L. Du, B. Shen. (2001). Biosynthesis of hybrid peptide-polyketide natural products. Current opinion in drug discovery & development. 4(2): 215-228.

[43] M. Sommerfeld. (1983). < i> Trans</i> unsaturated fatty acids in natural products and processed foods. Progress in lipid research. 22(3): 221-233.

[44] W.A. Pryor, J. Stanley. (1975). Suggested mechanism for the production of malonaldehyde during the autoxidation of polyunsaturated fatty acids. Nonenzymic production of prostaglandin endoperoxides during autoxidation. The Journal of organic chemistry. 40(24): 3615-3617.

[45] W.P. Revill, M.J. Bibb, D.A. Hopwood. (1996). Relationships between fatty acid and polyketide synthases from Streptomyces coelicolor A3 (2): characterization of the fatty acid synthase acyl carrier protein. Journal of bacteriology. 178(19): 5660-5667.

[46] D.A. Hopwood, D.H. Sherman. (1990). Molecular genetics of polyketides and its comparison to fatty acid biosynthesis. Annual review of genetics. 24(1): 37-62.

[47] J. Staunton, K.J. Weissman. (2001). Polyketide biosynthesis: a millennium review. Natural product reports. 18(4): 380-416.

[48] B. Shen. (2003). Polyketide biosynthesis beyond the type I, II and III polyketide synthase paradigms. Current opinion in chemical biology. 7(2): 285-295.

[49] K.J. Weissman, P.F. Leadlay. (2005). Combinatorial biosynthesis of reduced polyketides. Nature reviews microbiology. 3(12): 925-936.

[50] D.H. Barton, J.E. Corrie, D.A. Widdowson, M. Bard, R.A. Woods. (1974). Biosynthesis of terpenes and steroids. Part IX. The sterols of some mutant yeasts and their relationship to the biosynthesis of ergosterol. J. Chem. Soc., Perkin Trans. 1. 1326-1333.

[51] D. Barton, P. Marshall, D. Widdowson. (1973). Biosynthesis of terpenes and steroids: VII. Unified scheme for the biosynthesis of ergosterol in Saccharomyces cerevisiae. Bioorganic chemistry. 2(4): 363-373.

[52] A.J. Barlow, H. Becker, K.P. Adam. (2001). Biosynthesis of the hemi-and monoterpene moieties of isoprenyl phenyl ethers from the liverwort< i> Trichocolea tomentella</i>. Phytochemistry. 57(1): 7-14.

[53] M. Baig, D. Banthorpe, S. Branch. (1989). Hemi-and mono-terpenoids from callus of Santolina chamaecyparissus. Fitoterapia. 40: 184-186.

[54] H. Matsuda, K. Ninomiya, T. Morikawa, M. Yoshikawa. (1998). Inhibitory effect and action mechanism of sesquiterpenes from Zedoariae Rhizoma on D-galactosamine/lipopolysaccharide-induced liver injury. Bioorganic & medicinal chemistry letters. 8(4): 339-344.

[55] D.E. Cane. (1990). Enzymic formation of sesquiterpenes. Chemical Reviews. 90(7): 1089-1103.

[56] S.L. Richheimer, M.W. Bernart, G.A. King, M.C. Kent, D.T. Beiley. (1996). Antioxidant activity of lipid-soluble phenolic diterpenes from rosemary. Journal of the American Oil Chemists' Society. 73(4): 507-514.

[57] B.-S. Min, J.-J. Gao, N. Nakamura, M. Hattori. (2000). Triterpenes from the spores of Ganoderma lucidum and their cytotoxicity against meth-A and LLC tumor cells. Chemical & pharmaceutical bulletin. 48(7): 1026-1033.

[58] D.J. Faulkner. (2001). Marine natural products. Natural product reports. 18(1): 1R-49R.

[59] L.F. Tietze, A. Modi. (2000). Multicomponent domino reactions for the synthesis of biologically active natural products and drugs. Medicinal research reviews. 20(4): 304-322

[60] Velioglu, Y., G. Mazza, et al. (1998). "Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products." Journal of agricultural and food chemistry 46(10): 4113-4117.

[61] Asano, N., A. Kato, et al. (1997). "The effects of calystegines isolated from edible fruits and vegetables on mammalian liver glycosidases." Glycobiology 7(8): 1085-1088.

[62] Herrmann, K. (1978). "Review on nonessential constituents of vegetables. III. Carrots, celery, parsnips, beets, spinach, lettuce, endives, chicory, rhubarb, and artichokes (author's transl)." Zeitschrift für Lebensmittel-Untersuchung und-Forschung 167(4): 262.

[63] Nkafamiya, I., S. Osemeahon, et al. (2010). "Nutritional status of non-conventional leafy vegetables, Ficus asperifolia and Ficus sycomorus." African Journal of Food Science 4(3): 104-108.

[64] Chang, S.-S., M.-L. Wu, et al. (1999). "Poisoning by Datura leaves used as edible wild vegetables." Veterinary and human toxicology 41(4): 242-245.

[65] C. Ringmichon, B. Gopalkrishnan, A. Dixit. Journal of Pharmacognosy and Phytochemistry.

[66] Li, P., Y.-L. Yin, et al. (2007). "Amino acids and immune function." British Journal of Nutrition 98(02): 237-252.

[67] Parry-Billings, M., R. Budgett, et al. (1992). "Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system." Medicine and science in sports and exercise 24(12): 1353-1358.

[68] Ng, T., F. Liu, et al. (2000). "Antioxidative activity of natural products from plants." Life sciences 66(8): 709-723.

[69] A.K. Tiwari. (2001). Imbalance in antioxidant defence and human diseases: Multiple approach of natural antioxidants therapy. Curr. Sci. 81(9): 1179-1187.

[70] E. Ibañez, M. Herrero, J.A. Mendiola, M. Castro-Puyana, Extraction and characterization of bioactive compounds with health benefits from marine resources: macro and micro algae, cyanobacteria, and invertebrates. In *Marine Bioactive Compounds*, Springer: 2012; pp 55-98.

[71] Ng, T., F. Liu, et al. (2000). "Antioxidative activity of natural products from plants." Life sciences 66(8): 709-723.

[72] Alzamora, S. M., D. Salvatori, et al. (2005). "Novel functional foods from vegetable matrices impregnated with biologically active compounds." Journal of Food Engineering 67(1): 205-214.

[73] Stuchlík, M. and S. Zak (2002). "Vegetable lipids as components of functional foods" Biomedical papers-palacky University in olomouc 146(2): 3-10.