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Drugs from the Natural Bio Sources for Human Disease

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Abstract: From the past few decades to the future life natural products have played a vital role throughout the world in treating and preventing human disease. The value of natural product in this regard can be based on 3 criteria, (i) The rate of introduction of new chemical entities of wide structural diversity, (ii) The number of disease treated or prevented by these substances and (iii) Their frequency of use in treatment of disease. Microbes have made a phenomenon contribution to the health and well being of people throughout the world. In addition to many primary metabolites such as amino acid, vitamins and nucleotide they also capable of making secondary metabolites, which constitute 1/3 of the pharmaceutical in the market today and provides many essential products to the environment. The new millennium will see further advanced discovery that will keep the sentence Prevention is better than cure.

Key words: Bio sources, natural drugs, synthetic drugs, terrestrial and marin organisms

INTRODUCTION

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates (Newman *et al.*, 2000). Therapeutic drugs have played a major role in increasing average life expectancy in the United States in the last century. However, while many of the drugs are in use for the last fifty years or more have been of synthetic or semi-synthetic origin, the pharmacopoeias prior to that period were of natural origin. The medicinal value of plants has been recognized by almost every society on this planet. In the nineteenth and earlier centuries, natural product extracts, particularly those derived from botanical species, provided the main source of folk medicines. However, in the latter part of the nineteenth century, biologically-active organic molecules began to be isolated in relatively pure form for medicinal use. For example, Salicylic acid, the precursor of aspirin, was isolated in 1874 from willow bark. Various more potent painkillers, such as morphine and codeine, were isolated from the opium poppy. The anti-malarial agent, quinine, was separated from cinchona (china bark). The leaves of the purple foxglove plant provided an excellent source of digitalis that was purified for use against heart disease. There are numerous other

examples. Although synthesis of the first synthetic pharmaceutical drug, aspirin, occurred in the latter half of the nineteenth century, it was not until the early 1900s that the recognition of aspirin as a universal pain reliever was realized and this discovery spawned the era of therapeutic agents.

However, it was not until the recognition that many infectious diseases were caused by microorganisms that the real impetus in the development of therapeutic agents, both natural and non-natural, began to occur. Concurrent with the discoveries in medical microbiology were major advances in synthetic organic chemistry and biochemistry that provided further momentum in the area of therapeutic agents. Synthetic sulfa drugs, the natural antibiotic, penicillin, from *Penicillium notatum* (Alexander Fleming), the semi-synthetic antibiotic, tetracycline, produced from natural chlortetracycline elaborated by *Streptomyces aureofaciens* (Benjamin Duggar) and the anti-tubercular aminoglycoside, streptomycin, from *Streptomyces griseus* (Salman Waksman) were all landmark discoveries of the 1930s and 1940s. The importance of vitamins and diseases caused by their deficiencies were also being uncovered during this period. During the next several decades advances in X-ray crystallography, NMR spectroscopy and, mass spectrometry and developments in electrophoresis, ultracentrifugation, HPLC and other technologies contributed to the discovery of additional chemical entities with therapeutic activities and to the development of some vaccines natural products with

industrial applications can be produced from primary or secondary metabolism of living organisms (plants, animals or microorganisms). Owing to technical improvements in screening programs, and separation and isolation techniques, the number of natural compounds discovered exceeds 1 million. Among them, 50-60% is produced by plants (alkaloids, flavonoids, terpenoids, steroids, carbohydrates, etc.) and 5% have a microbial origin. Of all the reported natural products, approximately 20-25% show biological activity, and of these approximately 10% have been obtained from microbes. Furthermore, from the 22-500 biologically active compounds that have been obtained so far from microbes, 45% are produced by actinomycetes, 38% by fungi and 17% by unicellular bacteria (Berdy, 2005). The increasing role of microorganisms in the production of antibiotics and other drugs for treatment of serious diseases has been dramatic. However, the development of resistance in microbes and tumor cells has become a major problem and requires much research effort to combat it. Raja *et al.* (2010) reported new antibiotics that are active against resistant bacteria are required. Bacteria have lived on Earth for several billion years. During this time, they encountered in nature a wide range of naturally occurring antibiotics. To survive, bacteria developed antibiotic resistance mechanism (Hoskeri *et al.*, 2010).

REASONS FOR DEVELOPING NEW ANTIBIOTICS

New antibiotics that are active against resistant bacteria are required. Bacteria have lived on the Earth for several billion years. During this time, they encountered in nature a wide range of naturally occurring antibiotics. To survive, bacteria developed antibiotic resistance mechanisms. Therefore, it is not surprising that they have become resistant to most of the natural antimicrobial agents that have been developed over the past 50 years. This resistance increasingly limits the effectiveness of current antimicrobial drugs. The problem is not just antibiotic resistance but also multidrug resistance. In 2004, more than 70% of pathogenic bacteria were estimated to be resistant to at least one of the currently available antibiotics (Katz *et al.*, 2006) The so-called superbugs (organisms that are resistant to most of the clinically used antibiotics) are emerging at a rapid rate.

S. aureus, which is resistant to methicillin, is responsible for many cases of infections each year. The incidence of multidrug-resistant pathogenic bacteria is increasing. The Infectious Disease Society of America (IDSA) reported in 2004 that in US hospitals alone, around 2 million people acquire bacterial infections each

year. *S. aureus* is responsible for half of the hospital-associated infections and takes the lives of approximately 100 000 patients each year in the USA alone (Balaban and Dell'Acqua, 2005). The bacteria produce a biofilm in which they are encased and protected from the environment. Biofilms can grow on wounds, scar tissues and medical implants or devices, such as joint prostheses, spinal instrumentations, catheters, vascular prosthetic grafts and heart valves. More than 70% of the bacterial species producing such biofilms are likely to be resistant to at least one of the drugs commonly used in anti-infectious therapy. In hospitals, there are also other examples of Gram-positive (*Enterococcus* and *Streptococcus*) and Gram-negative pathogens (*Klebsiella*, *Escherichia*, *Enterobacter*, *Serratia*, *Citrobacter*, *Salmonella* and *Pseudomonas*); these hospital-inhabiting microbes are called 'nosocomial bacteria. More than 60% of sepsis cases in hospitals are caused by Gram-negative bacteria. Among them, *Pseudomonas aeruginosa* accounts for almost 80% of these opportunistic infections. They represent a serious problem in patients hospitalized with cancer, cystic fibrosis and burns, causing death in 50% of cases. Other infections caused by *Pseudomonas* species include endocarditis, pneumonia and infections of the urinary tract, central nervous system, wounds, eyes, ears, skin and musculoskeletal system. This bacterium is another example of a natural multidrug-resistant microorganism. Although many strains are susceptible to Gentamicin, Tobramycin and Amikacin, resistant forms have also developed. These multidrug-resistant bacteria make hospitals dangerous places to be especially if you are sick but even if not.

CHEMICALLY SYNTHESIZED DRUGS ORIGINATING FROM NATURAL PRODUCTS

Drugs of natural origin have been classified as (1) original natural products (2) products derived or chemically synthesized from natural products (3) synthetic products based on natural product structures. Evidence of the importance of natural products in the discovery of leads for the development of drugs for the treatment of human diseases is provided by the fact that close to half of the best selling pharmaceuticals in 1991 were either natural products or their derivatives (Cragg *et al.*, 1997). In this regard, of the 25 top-selling drugs reported in 1997, 42% were natural products or their derivatives and of these, 67% were antibiotics. Today, the structures of around 140 000 secondary metabolites have been elucidated. It is important to understand that many chemically synthesized drugs owe their origin to natural sources. Applications of chemically synthesized natural metabolites include the use of a natural product derived

from plant salicylic acid derivatives present in white willow, wintergreen and meadowsweet to relieve pain and suffering. Concoctions of these plants were administered by Hippocrates back in the year 500 BC, and even earlier in Egypt and Babylonia, for fever, pain and childbirth. Synthetic salicylates were produced initially by Bayer in 1874, and later in 1897, Arthur Eichengrun at Bayer discovered that an acetyl derivative (aspirin), reduced acidity, bad taste and stomach irritation. These plant-based systems continue to play an essential role in health care, and it has been estimated by the World Health Organization (WHO) that approximately 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care (Farnsworth *et al.*, 1985).

FREQUENCY OF DRUGS

Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases (48/55), including as antibacterial, anticancer, anticoagulant, antiparasitic, and immunosuppressant agents, among others. There was no introduction of any natural products or related drugs for 7 drug categories (anesthetic, antianginal, anti histamine, anxiolytic, chelator and antidote, diuretic, and hypnotic) during 1981 to 2002. In the case of antibacterial agents, natural products have made significant contributions as either direct treatments or templates for synthetic modification. Of the 90 drugs of that type that became commercially available in the United States or were approved worldwide from 1982 to 2002, ~79% can be traced to a natural product origin (Newman *et al.*, 2003).

Frequency of use of natural products in the treatment and prevention of disease can be measured by the number and economic value of prescriptions, from which the extent of preference and/or effectiveness of drugs can be estimated indirectly. According to a study by Grifo and colleagues, 884 of a representative 150 prescription drugs in the United States fell into the category of natural products and related drugs. They were prescribed predominantly as anti-allergy/pulmonary /respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases. Another study found that natural products or related substances accounted for 40, 24, and 26%, respectively, of the top 35 worldwide ethical drug sales from 2000-2002. Of these natural product-based drugs, paclitaxel (ranked at 25 in 2000), a plant-derived anticancer drug, had sales of \$1.6 billion in 2000 (Oberlies and Kroll, 2004).

DRUG DISCOVERY FROM TERRESTRIAL PLANTS

Terrestrial plants, especially higher plants, have a long history of use in the treatment of human

diseases. Several wellknown species, including licorice (*Glycyrrhiza glabra*), myrrh (*Commiphora* species), and poppy capsule latex (*Papaver somniferum*), were referred to by the first known written record on clay tablets from Mesopotamia in 2600 BC, and these plants are still in use today for the treatment of various diseases as ingredients of official drugs or herbal preparations used in systems of traditional medicine. Furthermore, morphine, codeine, noscapine (narcotine), and papaverine isolated from *P. somniferum* were developed as single chemical drugs and are still clinically used. Hemisuccinate carbenoxolone sodium, a semi-synthetic derivative of glycyrrhetic acid found in licorice is prescribed for the treatment of gastric and duodenal ulcers in various countries (Dewick, 2002). From terrestrial plant-derived secondary metabolites, several new chemical entities are undergoing clinical trials including four that are derivatives of known anticancer drugs Such as camptothecin, paclitaxel, epipodophyllotoxin, and vinblastine (Butler, 2005).

DRUG DISCOVERY FROM TERRESTRIAL MICROORGANISMS

Until the development of penicillin in the early 1940s, most natural product-derived drugs were obtained from terrestrial plants. The success of penicillin in treating infection led to an expansion in the area of drug discovery from microorganisms. Terrestrial microorganisms are a plentiful source of structurally diverse bioactive substances, and have provided important contributions to the discovery of antibacterial agents including penicillins, cephalosporins, aminoglycosides, tetracyclines, and polyketides. Current therapeutic applications of metabolites from microorganisms have expanded into immunosuppressive agents (eg., cyclosporins and rapamycin), cholesterol-lowering agents (eg., lovastatin and mevastatin), antihelmintic agents (eg, ivermectin), an antidiabetic agent (acarbose), and anti cancer agents (eg., pentostatin, peplomycin, and epirubicin) (Sneader, 2005).

DRUG DISCOVERY FROM MARINE ORGANISMS

Unlike the long-standing historical medical uses of terrestrial plants, marine organisms have a shorter history of utilization in the treatment and prevention of human disease.

Among the first bioactive compounds from marine sources, spongouridine and spongostatin from the Caribbean sponge (*Cryptotheca crypta*), were isolated serendipitously in the early 1950s. They were approved as an anticancer drug (cytosine arabinoside, Ara-C) and an antiviral drug (adenine arabinoside, Ara-A), respectively, years later. (Newman and Cragg, 2004a) The secondary metabolites of marine organisms have been studied

extensively over the past 30 years, since a small number of academic chemists began to isolate and elucidate novel compounds from marine sources in the 1970's. Drug discovery research from marine organisms has been accelerating and now involves interdisciplinary research including biochemistry, biology, ecology, organic chemistry, and pharmacology (Capon, 2001) Recently, much attention has been given to marine organisms due to their considerable biodiversity that has been found in the widespread oceans that cover over 70% of the world. Structurally unique secondary metabolites have been isolated and identified from marine organisms and, consequently, a compound based on new chemical template has been developed and launched in 2004, while numerous other candidates are in clinical trials (Newman and Cragg, 2004b).

DRUG DISCOVERY FROM TERRESTRIAL VERTEBRATES AND INVERTEBRATES

During the course of research on human physiology and pathology, many biochemical molecules have been discovered and their functions have been investigated. Since these biochemical compounds are related to biological action in the human body, an excess or deficiency of them has often caused pathological problems in humans. Neurohormones (adrenaline, levodopa, and histamine), peptide hormones (insulin and glucagons), sex hormones (estrogens, progesterone, and testosterone), other hormones (hydrocortisone and aldosterone), and prostaglandins (prostaglandin E 1 and E 2) are examples of compounds used for the treatment of diseases related to their physiological action. Besides human biochemicals and their analogs, other drugs in this category have been discovered from various terrestrial vertebrates and invertebrates, including an inhibitor of Angiotensin Converting Enzyme (ACE) developed from teprotide, which was isolated from the venom of Brazilian viper (*Bothrops jararaca*) after the venom was found to cause a sudden and massive drop in blood pressure. Two drugs from vertebrates and invertebrates have been approved from 2000 to the present.

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