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From Nutrition to Health: The Role of Natural Products – A Review

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1. Introduction

The word *natural* literally means something that is present in or produced by nature and not artificial or man-made (Spainhour, 2005). Although, many effective poisons are natural products (Schoental, 1965). When the word *natural* is used in written or verbiage form, many a times refer to something good or pure (Spainhour, 2005). Today, the term *natural products* are commonly understood to refer to herbs, herbal concoctions, dietary supplements, traditional medicine including Chinese traditional medicine, or other alternative medicine (Holt, and Chandra, 2002). In general, natural products are either of prebiotic origin or originate from microbes, plants, or animal sources (Nakanishi, 1999a; Nakanishi, 1999b). As chemicals, natural products include such classes of compounds as terpenoids, polyketides, amino acids, peptides, proteins, carbohydrates, lipids, nucleic acid bases, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and so forth. Natural products are an expression of organism's increase in life complexity by nature (Jarvis, 2000).

It is good to understand what 'nutrition' and 'a nutrition perspective' mean. It should be understood that food and nutrition are not the same. Nutrition is both the outcome and the process of providing the nutrients needed for health, growth, development and survival. Although food—as the source of these nutrients—is an important part of this process, it is not by itself sufficient. Good health management services, as well as good caring practices are other important and necessary inputs needed in maintaining good health apart from good nutrition (SCN, 2004).

2. World status of nutrition and health

During the past two to three decades there have been rapid changes in global economy accompanied by several significant changes in the nutritional status and health of developing countries (Evans et al., 2002). Significant reductions in the prevalence of undernutrition are some of the good changes recorded. The increased prevalence of obesity and diet-related chronic disease are some of the negative changes related to human nutrition (Hoffman, 2001). More also, on the increase is the data suggesting the existence of a biological link between poor nutrition in early life and chronic diseases in adulthood (Jackson et al., 2010; Langley-Evans and McMullen, 2010).

The prevalence of undernutrition in today's world varies greatly base on region and country, there has also been a decrease in global trends in wasting and stunting. However, the situation is still different in countries with extremely unstable governments and those with civil strife, with records of higher prevalence rate up to 20-30% (Bryce et al., 2008). Undernutrition in developed nations happen to be a problem among people living in rural areas, this could be due to the fact that inhabitants of rural areas mostly suffer from poor nutrition in terms of micronutrient deficiencies. Low income and poor access to nutritious foods is a common factor in poor urban societies leading to undernutrition (Shetty, 2009; Black et al., 2008). The prevalence of undernutrition remains moderate to high in developing nations, depending on the relative degree of economic development. These countries have relatively higher prevalence rate of children wasting and stunting of approximately 30-40% (Gutierrez-Delgado and Guajardo-Barron, 2009; Delisle, 2008).

3. Natural products and body anatomy

Most of the body structures like bones and muscle tissues are formed and nourished by natural products like calcium, phosphorus, vitamin D, proteins and so forth. Bone formation consists of a biological cascade through mesenchymal proliferation, chondrogenesis, osteogenesis, and remodelling (Reddi, 1994). For optimal bone mineral accrual in the developing skeleton, calcium and vitamin D are very important. Human skeleton is rich in calcium supply, with finely tuned mechanisms for release of calcium as needed. Calcium homeostasis is maintained during either low calcium intake or vitamin D status, through the regulation of parathyroid gland and kidneys, at the expense of bone. Adolescents are at risk for poor nutritional status in both calcium and vitamin D. Lack of calcium accumulation in the skeleton of an adolescent or a growing child can have negative consequences for achievement of peak bone mass (Bailey et al., 2000; Bachrach, 2001; Harkness and Bonny, 2005). Differentiation of mesenchymal stem cells into osteoblast to produce new bone tissue was capably induced by bone morphogenetic proteins (BMP), a phenomenon known as osteoinduction (Urist, 1965; Wozney, 2002). Growth factors contained in platelet-rich plasma (PRP) have been proposed to enhance bone grafts maturation and to support repair in the treatment of small bone defects in maxillofacial surgery, when in combination with an organic bovine bone (Roldan et al., 2004). The composition of collagens and noncollagenous matrix proteins defined the organic phase of mineralized tissues. Bone, dentin, and cementum contains collagen type I, cartilage contains collagen type II, and enamel is virtually free of collagen (Sommer et al., 1996). Proteins are the most important nutrients for maintaining body structures, they are the major component of muscles, it is generally believe that flesh makes flesh (Bischoff and Voit, 1860). Skin and bone contain a fibrous protein. Keratinocytes undergo a series of morphological and biochemical changes including the expression of large quantities of proteins which constitute cytoplasmic filamentous networks, keratohyalin granules and cornified envelopes in the course of differentiation (Manabe et al., 1997). Stiffness and rigidity to fluid biological components is provided by structural proteins most of which are fibrous proteins, actin and tubulin are globular and soluble as monomers, which upon polymerization form long, stiff fibres that comprise cytoskeleton, which allows the cell to maintain its shape and size. Connective tissue like cartilage has collagen and elastin as its main components, and keratin is an important component of hard or filamentous structures such as hair, nails, feathers, hooves, and some animal shells (Van Holde and Mathew, 1996).

4. Natural products and body physiology

Natural products are the potential sources of organic nutrients like carbohydrate, fats, proteins or amino acids and vitamins, as well as dietary minerals necessary for normal physiological functioning of the body.

Body physiological reactions involving nerve, muscle, blood, bone, endocrine and visceral tissues require constant renewal, a delicate balance of which human health is depended upon. Vital exchanges constantly occur, involving many enzymatic systems activated by minerals or trace elements (Speich et al., 2001). The contraction of skeletal, cardiac and smooth muscles aided by calcium ions and involving neuronal and hormonal interplay are responsible for a lot of vital functions in the body such as movements, heartbeats, blood circulation, respiration, parturition, micturition, digestion, and so forth. These activities are important for life maintenance, some of the crucial roles of natural products in maintaining body physiology such as cell signalling electrophysiology, muscle contraction, enzymes and hormones synthesis, etc. are outline below:---

5. Cell signalling

Natural products play important roles in a lot of cellular activities such as cell signalling that aids in cellular communications. Calcium and vitamin D are necessary for many cellular processes. Primarily, the role of calcium is to serve as a second messenger in virtually all cells. The most common signal transduction is the ionized calcium due to its ability to reversibly bind to proteins. Vitamin D receptors have been identified in most body cells such as the small intestine, colon, brain, skin, prostate, gonads, breast, lymphocytes, osteoblasts, B-islet cells, and mononuclear cells (Holick, 2004). At intracellular level, 1,25-dihydroxyvitamin D interacts with vitamin D receptors and retinoic acid X receptor to enhance or inhibit the transcription of vitamin D-responsive genes, including calcium-binding protein. Stimulation of many noncalcemic physiological functions including insulin production, thyroid hormone secretion, and activated T and B lymphocyte function has been shown to be promoted by 1, 25-dihydroxyvitamin D (Harkness and Bonny, 2005).

Apart from Vitamin D and calcium, Proteins are also involved in several cellular processes. Being the chief actors within the cell, proteins are said to be carrying out the duties specified by the information encoded in genes (Lodish et al., 2004). Most of the biological molecules are relatively inert elements upon which proteins act, with the exception of certain types of RNA (Voet and Voet, 2004). Within the cell proteins acts as enzymes that catalyse chemical reactions. Due to specific nature of enzymes they accelerate only one or few chemical reactions. Most of the reactions involved in metabolism, as well as manipulating DNA in processes such as DNA replication, DNA repair, and transcription are carried out by enzymes (Bairoch, 2000).

Cell signalling and signalling transduction are among the numerous processes involved by many proteins. Insulin is a good example of extracellular proteins that transmit a signal from a cell in which it was synthesized to other cells in distant tissues. Some proteins are membrane proteins that act as receptors, which function mainly to bind a signalling molecule and induce a biochemical response in the cell (Branden and Tooze, 1999). The protein components of adaptive immune system are the antibodies, whose main function is to bind antigens or foreign substances in the body, and target them for destruction. Antibodies are either secreted into the extracellular environment or anchored in the

membranes of specialized B cells called the plasma cells (Van Holde and Mathews, 1996). This phenomenon assists in maintaining body immunity.

6. Electrophysiology

Electrophysiological properties of some natural products serve as a means of communication or cell signalling in several body cells and glands. Many cellular functions, such as electrical signal generation in nerve and muscle cells, contraction in muscle cells, and secretion in nerve and gland cells depends on the significant role of widely distributed voltage-dependent calcium channels (Hagiwara, 1983; Hagiwara and Byerly, 1981). They exist not only in fully differentiated cells but also already in oocytes (Okamoto et al., 1977) and in developing nerve and muscle cells (Spitzer, 1979). There are several reports that calcium channels are restricted to, or more prominent in, the less differentiated states of excitable cells such as skeletal cells (Kano, 1975; Kidokoro, 1973; Kidokoro, 1975) and nerve cells (Matsuda et al., 1978; Mori-Okamoto et al., 1983; Spitzer and Baccaglini, 1976).

The involvement of calcium channels as well as sodium channels in generating action potentials in embryonic chick skeletal muscle cells has been established. (Fukuda et al., 1976; Kano, 1975; Kano and Yamamoto, 1977). The involvement of a chloride component has also been shown in addition to the sodium and calcium component of the action potential, in particular in the long-lasting plateau phase of the action potential in these muscle cells (Fukuda et al., 1976).The availability of ATP in mammalian neurones is due to its well-known role as a major energy carrier for cellular metabolism and has been reported to act as a fast transmitter in mammalian brain (Edwards and Gibb, 1993). An action potential is a transient depolarization of the membrane potential of excitable cells. They serve two main functions: to transmit and encode information, and to initiate cellular events such as muscular contraction. An action potential results from a transient change to the properties of the cell membrane, from a state where it is much more permeable to K^+ than Na^+, to a reversal of these permeability properties. Thus during the action potential an influx of Na^+ is responsible for the rapid depolarization and an efflux of K+ causes repolarization. Changes to membraneionic permeability are due to the opening and closing of voltage-gated ion channels, and the properties of such channels explain additional phenomena such as refractoriness, threshold and cellular excitability. Action potentials conduct with a finite velocity along nerve axons, and the actual velocity depends on a number of factors that include: fibre radius, temperature, functional ion channel number and the presence of a myelin sheath (Fry and Jabr, 2010). The cations Na^+, K^+, Mg^{2+}, and Ca^2, are involved in the propagation of nerve impulses and in muscle and heart contraction. Phosphorus (P), in phosphoric ester form (ATP), results from the third step of cell respiration. The active transport of Na^+ and K^+ through the plasma membrane involves the energy of ATP hydrolysed by Na^+ K^+ ATPase and activated by Mg^{2+}, constituting an essential cell function requiring around 25% of the energy metabolism of man at rest (Lehninger et al., 1994). The formation and the use of energy-rich bonds require Mg^{2+} (Durlach et al., 2000).

7. Muscle contraction

Although there are hormonal and neuronal interplay, diverse functions in the body like movement, respiration, digestion, blood circulation, heartbeat, micturition, parturition etc.

are facilitated by muscle contraction. Communication between muscle cells that lead to muscle contraction results from formation of action potential which is due to the electrophysiological properties of these tissues. It is an established fact that all muscle fibres use Ca^{2+} as their main regulatory and molecule signalling. Therefore, the variable expression of proteins involved in Ca^{2+} signalling and handling play a key role in the contractile properties of muscle fibres. Contraction and relaxation properties of a muscle fibre are largely determines by molecular diversity of the main proteins in the Ca^{2+} signalling apparatus otherwise known as the calcium cycle. The Ca^{2+} signalling apparatus includes: the ryanodine receptor that is the sarcoplasmic reticulum Ca^{2+} release channel, the troponin complex that mediates the Ca^{2+} effect to the myofibrillar structures leading to contraction, the Ca^{2+} pump responsible for Ca^{2+} reuptake into the sarcoplasmic reticulum, and calsequestrin--the Ca^{2+} storage protein in the sarcoplasmic reticulum. In addition, a multitude of Ca^{2+} binding proteins is present in muscle tissue including paryalbumin, calmodulin, S100 proteins, annexins, sorcin, myosin light chains, β-actin, calcineurin, and calpain. These Ca^{2+} binding proteins may either exert an important role in Ca^{2+} triggered muscle contraction under certain conditions or modulate other muscle activities such as protein metabolism, differentiation, and growth. Muscle diseases have been shown to be associated with alteration of several Ca^{2+} signalling and handling molecules. Pathophysiological conditions like malignant hyperthermia, dystrophinopathies and Brody's disease are seem to be associated with functional alterations of Ca^{2+} handling**.** These also underline the importance of the affected molecules for correct muscle performance (Berchtold et al., 2000).

8. Body electrolytes and homeostasis

The major electrolytes found in the body are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), bicarbonate (HCO_3^-), phosphate (HPO_4^2), and sulphate (SO_4^2) (Ahmad and Ahmad, 1993). For humans to be in an adequate physical condition and a highly efficient state, stable volume, osmotic concentration and electrolyte composition of internal fluids are necessary prerequisites (Zorbas et al., 2002). The macroelements Ca, Mg, K, Na, and phosphorus (P) are generally integrated into anatomic structures (bone elements, nucleic acids, membranes, proteins, enzymes) although they are also involved in the ionized active form and regarded as essential trace elements, as in voltage-gated ionic channels (Allain, 1996). In active form, they are of particular importance for metabolic balance in sports and during physical exercise (Maughan, 1999). Na^+ contributes to the maintenance of osmotic pressure, water regulation, and acid-base balance. Ca^{2+} controls vascular tonicity and coagulation of the blood (Lehninger et al., 1994).

9. Blood composition

Among the components of blood are protein (albumin, globulin, and fibrinogen), fat cholesterol, carbohydrate glucose, calcium, phosphorus, sodium chloride (NaCl), urea, uric acid, nonprotein nitrogen (N.P.N) compounds, and creatine. These natural products component are distributed by the blood to body cells and tissues for necessary physiological activities.

10. Red blood cells maturation

Red blood cells formation is important for maintaining normal red blood cells count and blood volume. The erythropoietic cells of the bone marrow are among the most rapidly growing and reproducing cells in the entire body, due to the continuing need to replenish red blood cells. Their maturation and rate of production are affected greatly by a person's nutritional status. For final maturation of the red blood cells two vitamins, vitamin B12 (cyanocobalamin) and folic acid are important. Both of these are essential for the synthesis of DNA, because each in a different way is required for the formation of thymidine triphosphate, one of the essential building blocks of DNA. Abnormal and diminished DNA and, as well as failure of nuclear maturation and cell division could be caused by lack of either vitamin B_{12} or folic acid (Guyton, 2006).

11. Haemoglobin formation

Haemoglobin serves as oxygen transportation medium through the formation of oxyhaemoglobin in the blood, which is distributed to other body cells and tissues. Maintenance of this role is achieved by maintaining the normal haemoglobin count. Initially, to form a pyrrole molecule, succinyl-CoA formed in the Krebs metabolic cycle, binds with glycine. In turn, to form the *heme* molecule, four pyrroles combine to form protoporphyrin IX, which then combines with iron. Finally, each heme molecule combines with a long polypeptide chain, a *globin* synthesized by ribosomes, forming a subunit of haemoglobin called a haemoglobin chain. Four of these chains in turn bind together loosely to form the whole haemoglobin molecule. The different types of chains base on the amino acid composition of the polypeptide portion are designated alpha chains, beta chains, gamma chains, and delta chains. The most common form of haemoglobin in the adult human being, haemoglobin A, is a combination of two alpha chains and two beta chains (Guyton, 2006).

12. Heredity

The role of natural products like deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in heredity is too important to be overlooked. It is a widely accepted hypothesis that deoxyribonucleic acid (DNA) is the genetic carrier of information and that ribonucleic acid (RNA) is an essential component in the expression of this information in polypeptide synthesis (Hurwitz and August, 1963). DNA molecule is a repository of genetic information. Therefore, there must be some precise mechanism for duplicating DNA so that the information within it can be handed down unchanged from one generation to the next. Inherited information resides in the precise sequence of bases in DNA and that this information is transferred to messenger RNA which can then specify the sequence of amino acids in some particular protein (Davern and Cairns, 1963).

13. Enzymes and hormones synthesis

Almost all process in a biological cell needs enzymes to occur at significant rates, the set of enzymes made in a cell determines which metabolic pathways occur in that cell. Pancreatic adaptation to the diet is a phenomenon due to the dietary induced modifications in enzyme composition of pancreatic tissue and secretion, which has been described in many species

(Poort and Poort, 1980; Corring, 1977; Ben Abdeljilil and Desnuelle, 1964; Reboud et al., 1966). A carbohydrate-rich diet results in an increase in the specific activity of amylase with a concomitant decrease in the specific activity of chymotrypsinogen. The converse is true for a protein-rich diet (Ben Abdeljilil and Desnuelle, 1964) and the same phenomenon has been described for the lipase-colipase system (Bazin et al., 1978). Such modifications of pancreatic content are now thought to be induced by changes in the biosynthetic rate of individual enzymes rather than by non-parallel secretion (Palade, 1975; Dagorn, 1978) or differential enzyme catabolism (Kramer and Poort, 1972). Changes in the individual rates of enzyme biosynthesis have been shown to occur in the developing embryonic pancreas (Kemp et al., 1972) and also after 30 days (Reboud et al., 1966) and more recently after 5 days of dietary adaptation in the adult rat (Poort and Poort, 1980). These long-term adjustments in enzyme synthesis have been correlated to concomitant adaptive modifications in pancreatic content (Reboud et al., 1966). However, no data are available to extend these conclusions to the short-term modifications in enzyme content that have been reported to occur within 24 hours (Deschodt-Lanckman et al., 1971). It became evident that rapid modulation of pancreatic enzyme synthesis was possible. Hormonal stimulation (Dagorn and Mongeau, 1977) or enteral administration of a product of digestion (Dagorn et al., 1977) produced changes in the biosynthetic rates of amylase, chymotrypsinogen and lipase within 15-30 min. It thus becomes possible that a meal may have an immediate regulatory function on pancreatic enzyme synthesis (Dagorn and Lahaie, 1981).

The entire organs functions are controlled by hormones; affecting diverse processes as growth and development, reproduction, and sexual characteristics. Energy storage and uses are also influence by hormones as well as controlling the volume of fluid and levels of salts and sugars in the blood. Large responses in the body could be triggered by very small amounts of hormones. Secretin and glucagon are members of a family of peptides, the vasoactive intestinal polypeptide (VIP)-secretin-glucagon family, which also includes pituitary adenylate cyclase-activating polypeptide (PACAP), gastric inhibitory polypeptide (GIP), parathyroid hormone (PTH), growth hormone-releasing hormone (GHRH), and exendins (Chow et al., 1997; Paul and Ebadi, 1993). All these peptides possess a marked amino acid sequence homology, are widely distributed in the body, and exert pleiotropic physiological effects, in many instances acting in a paracrine manner. The effects of these peptides are initiated by their specific interaction with cell-surface receptors, belonging to the superfamily of G-proteins-coupled receptors. These receptors are glycoproteins with a large hydrophilic extracellular domain followed by 7 highly conserved hydrophilic transmembrane helices, and their signalling mechanism primarily involves the activation of adenylate cyclase (AC)/protein kinase A (PKA) and phospholipase C (PLC)/PKC cascades (Arimura and Shioda, 1995; Chow et al., 1997; Fahrenkrug, 1989; Harmar and Lutz, 1994; Paul and Ebadi, 1993; Nussdorfer et al., 2000).

14. Natural products as nutritional supplements

Apart from being the major sources of nutrition in form of carbohydrate, protein, fat, etc. natural products are also used as nutritional supplements. According to the Dietary Supplement Health and Education Act of 1994 of the United States (Public Law 103-417, DSHEA), a dietary supplement is a product that is meant to supplement one's diet. Dietary

supplements contain one or more of the following ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, or another dietary substance, or a combination of these ingredients or their extracts. By definition, a dietary supplement is intended for ingestion in pill, capsule, tablet, or liquid form, but it is not for parenteral use. The most commonly used dietary supplement products are: enchinacea, ginseng, ginkgo, garlic, glucosamine, st. John's worth, peppermint, fish oils/omega-3 fatty acids, ginger, soy and so forth (Low Dog and Markham, 2007). Elemental analysis of garlic indicated that the powdered plant material contained mainly potassium, phosphorus, iron and calcium among others. While it's phytochemical screening revealed presence of chemical compounds like saponins, steroids, tannins, carbohydrates and cardiac glycosides (Mikail, 2010).

Vitamin/mineral supplements can be defined as products that are formulated to supply vitamin and/or mineral nutrients. They are often categorized as vitamin A, vitamin E, vitamin B-complex, multi-vitamins, calcium (Ca), iron (Fe), and multi-vitamins with mineral supplements (Kim, 1997; Kim-Park et al., 1991). In general, it has been found that school children select multi-vitamins with minerals and multi-vitamin supplements more frequently than other types of supplements (Bowering and Clancy, 1986). Vitamin/mineral supplement use has been reported to be influenced by several factors. With respect to young children, daily eating habits can be a particularly significant factor affecting supplement use, as mothers of children often adopt vitamin/mineral supplements as an insurance against possible poor or unbalanced meals. Supplements are also often given to promote appetite in young children (Song and Kim, 1998). This is perceived to be an important issue, as it is thought that young children have numerous eating problems including skipping meals, eating small meals and a strong dislike for some foods (Pipes, 1992). According to demographic characteristics, females, individuals in high socioeconomic categories, and individuals living in large cities tend to take vitamin/mineral supplements more often than their contrasting groups (Bowering and Clancy, 1986; Kim, 1997; Slesinski et al, 1995; Schellhorn et al., 1998; Kim and Keen, 2002).

Nutritional supplements aimed at improving physical performance or altering body compositions have become readily available worldwide. Athletes have been the greatest consumers of many of these products (Burk et al., 2006; Erdman et al., 2006; Huang et al., 2006) and their habits may be followed by other groups of individuals (Sobal and Marquart, 1994; Striegel et al., 2006), mainly those who exercise in gyms regularly (Morrison et al., 2004). The desire for achieving quick results has made the use of such substances very attractive (Rocha and Pereira, 1998). However, it is known that, in general, physically active people do not need additional nutrients apart from those obtained from a balanced diet (Rockwell et al., 2001; Costill, 2003; Silva, 2005; Goston and Correia, 2010).

15. Natural products roles in sanitation and personal care/cosmetics

Not only use as nutritional supplements, rather natural products have interesting roles in sanitation, personal care and cosmetic surgery. Large variety of products and formulations are considered as personal care products in the United States (US) and cosmetics in the European Union (EU), these products includes soaps, shampoos and shower products, sunscreens, skin and hair care products, hair dyes, make ups, lip sticks, toothpastes, dental care products, deodorants, personal hygiene products and many others(Antignac et al.,

2011). Decorative cosmetics are principally used to beautify or cover minor, visible imperfections. Shiny, oily, inhomogeneous colourings, as well as slight imperfections on skin surface are corrected by these kinds of cosmetics. These products play an important role, creating the effect of youthfulness and wholesomeness which are becoming more and more important in our society today (Valet et al., 2007).

Personal care products (PCP) from botanical ingredients include a variety of preparations, such as plant extracts, expressed juices, tinctures, waxes, vegetable oils, lipids, plant carbohydrates, essential oils, as well as purified plant components, such as vitamins, antioxidants or other substances with biological activity (Allemann and Baumann, 2009). For thousands of years, soap has been used as probably the oldest skin and cloth cleanser. Soap is produced from the saponification of fats and oils by alkali. The manufacturing process of soap involved saponification by which triglycerides (fats and oils) or fatty acids are transformed into the corresponding alkali salt mixtures of fatty acids (Friedman and Wolf, 1996). From the pulp industry soft and liquid soap are prepared from tall oil as tall resin by-products (Rappe et al., 1990). Products designed to improve the appearance of the aging face by altering the structure and function of the skin in ways that are important for cosmetic surgeons are termed cosmeceutics. Thus, cosmeceutics aids cosmetic operations, these products include alpha hydroxy acids, beta hydroxy acids, polyhydroxy acids, vitamins, retinoid, skin lightening agents, and sunscreens (Draelos, 1999).

16. Natural products as sources of drugs

Natural products have played an important role throughout the world for thousands of years in human diseases treatments and preventions. 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). An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market (Newman et al., 2003). In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products (Newman et al., 2000). This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs, are also good lead compounds suitable for further modification during drug development (Chin et al., 2006).

Natural products can come from anywhere. People most commonly think of plants first when talking about natural products, but trees and shrubs can also provide excellent sources of material that could provide the basis of a new therapeutic agent. Animals too, whether highly developed or poorly developed, whether they live on land, sea, or in the air can be excellent sources of natural products. Bacteria, smuts, rusts, yeast, moulds, fungi, and many other forms of what we consider to be primitive life can provide compounds or leads to compounds that can potentially be very useful therapeutic agents (Spainhour, 2005).

Some of the provision of nature to human kind over the years includes the tools for the first attempts at therapeutic intervention (Nakanishi, 1999a; Nakanishi, 1999b). The *Nei Ching* is one of the earliest health science anthologies ever produced and dates back to the thirtieth century BC (Nakanishi, 1999a; Nakanishi, 1999b). Some of the first records on the use of

natural products in medicine were written in cuneiform in Mesopotamia on clay tablets and date to approximately 2600 BC (Cragg and Newman, 2001a; Cragg and Newman, 2001b; Nakanishi, 1999a; Nakanishi, 1999b). Indeed, many of these agents continue to exist in one form or another to this day as treatments for inflammation, influenza, coughing, and parasitic infestations (Holt and Chandra, 2002; Spainhour, 2005). The best known natural products documentation is the Ebers Papyrus, which documents nearly 1000 different substances and formulations, most of which are plant-based medicines (Nakanishi, 1999a; Nakanishi, 1999b; Spainhour, 2005). More also, to date natural products continue to be the potential sources of new compounds or molecules that awaits further scientific elucidations, like the newly isolated alkylresorcinols from *Urginea indica* (Mikail et al., 2010).

The World Health Organization estimates that approximately 80% of the world's population relies primarily on traditional medicines as sources for their primary health care (Farnsworth et al., 1985). Over 100 chemical substances that are considered to be important drugs are either currently in use or have been widely used in one or more countries in the world have been derived from a little under 100 different plants. Approximately 75% of these substances were discovered as a result of chemical studies focused on the isolation of active substances from plants used in traditional medicine (Cragg and Newman, 2001a; Cragg and Newman, 2001b, Spainhour, 2005). A lot of natural products medications are derived from polyketides, which includes antibiotic, antifungal, anticancer, anthelmintic and immunosuppressant compounds such as erythromycins, tetracyclines, amphotericins, daunorubicins, avermectins, and rapamycins. These derivatives are used in treatment of host of disease situations affecting various body systems such as central nervous system, cardiovascular system, renal system, visual system and common integument.

17. Natural products as sources of antibiotics

Antibiotic is a word originally coined for those natural compounds with antimicrobial properties (Strohl et al., 2001; Overbye and Barrett, 2005; Palaez, 2006). The word antibiotic now a day no longer refers only to natural compounds; most of the marketed antibiotics are based on natural chemotypes. In the years 1982-2002 seventy out of the ninety antibiotics marketed originated from natural products (Newman et al., 2003; Palaez, 2006).The discoveries of sulphonamide antibiotics in the 1930s and penicillin in the 1940s have reduced the fatality rates of bacterial infections (Sneader, 2005; Newman et al., 2000; Drews, 2000). These has led to the discovery of most of the classes of antibacterial drug known today, many of which derived from natural products (Sneader, 2005; Walsh and Wright, 2005; Finch et al., 2003). The natural products-derived drugs mostly belong to five different structural classes namely: the β-lactam, the streptogramin, the macrolide, the tetracycline and the daptomycin (Butler and Buss, 2006).

Natural product-derived antibacterial drug prevalence may be due to the evolution of secondary metabolites as biologically active chemicals which conferred some selectional advantages to the producing organisms. There is likelihood of natural products to have evolved to penetrate the cell membranes and interact with specific proteins targets (Stone and Williams, 1992). The structural complexity of many natural products is required for the inhibition of many antibacterial protein targets (Butler, 2004; Koehn and Carter, 2005; Butler and Buss, 2006).

Some of the representative antibiotics of natural product origin include Daptomycin, Vancomycin, Ramoplanin, Tetracycline, Streptomycin, Erythromycin, Chloramphenicol, Penicillins, Cephalosporins, Carbapenems (Singh and Barret, 2006).However, as reported by Palaez (2006), Penicillins, Cephalosporins, Erythromycin, Thienamycin, Vancomycin, Fosfomycin, Mupirocin, Fusidic acid, Streptogramins, and Daptomycin are some of the marketed antibiotics that originated from microbial natural products. Some of the natural product-derived antibiotics currently in clinical development include the followings: Daptomycin, Dalbavancin, Telavancin, Oritavancin, Ramoplanin, Efiprestin, Lyostaphin and so forth (Clardy, et al., 2006).

18. Antivirals derived from natural products

Numerous compounds have been revealed through antiviral testing from structural classes that include peptides, terpenoids, polysaccharides, steroids and alkaloids that potentially inhibit both RNA and DNA viruses (Abad Martinez et al., 2008). Infections with viruses are counteracted by the host natural defences which prevent or limit the extent of these diseases. Interferon, a protein moiety produced in virus infected cells provides one of these defences. Interferon causes the production of a new protein that shuts off virus replication when attached to the cell membrane and consequently may lead to suppression of the viral infection. Therefore, antiviral compounds could be produce by the synthesis of drugs that induce interferon production before or after the infection in the sense that they activate certain host defence mechanisms (Becker, 1980). Marine compounds are good sources of Pharmacological agents. In the market today, there are over 40 pharmacological compounds, including alternative antiviral medicines or those being tested as potential antiviral drugs at preclinical and clinical stages (Yasuhara-Bell and Lu, 2010).

Some of the marine-derived antiviral agents circulating in market and are on clinical development include: Acyclovir, Ara-A (vidarabine), Ara-C (cytarabine), Avarol, Azidothymidine (zidovudine), and Cyanovirin-N (Yasuhara-Bell and Lu, 2010). Triterpenoids isolated from plants are biologically active natural products attracting considerable interest due to their variety of structures and their broad range of biological activities. Some compounds having significant anti-tumor activities in an in vivo assay have been reported. Some of these compounds are useful in the development of novel drugs with pharmacological actions (Barquero et al., 2006). Triterpenoidal saponins family of which Avicins is a member reduce both oxidative and nitrosative cellular stress, which result in developmental suppression of malignancies and other related diseases (Haridas et al., 2001).

Milk has been reported to contain antiviral agents (Matthews et al., 1976; Newburg et al., 1992). Lactoferrin is one of such agents that later shown to in vitro inhibit the human immunodeficiency virus (HIV-1), human herpes simplex virus (HSV-1 and -2), human cytomegalovirus, respiratory syncytial virus, poliovirus and rotavirus (Marchetti et al., 1999). Assayed chemically modified proteins presented antiviral activity against HSV-1 before, during and after infection. Higher concentrations of modified proteins are required if present before infection as compared to during or after infection. This therefore, suggests that targeted chemical modification of some natural products might provide antiviral compounds effective against HSV-1 infection (Oevermann et al., 2003).

19. Antiprotozoal potentials of natural products

Parasitic diseases are major public health problem especially in tropical developing countries, affecting hundred millions of people (Tagboto and Townson, 2001).

During phagocytosis reactive oxygen species are generated by neutrophilic granulocytes as a means of natural defence against invading microorganisms (Baehner et al., 1982). It is believed that this oxygen radicals formed by electron transfer processes have significant role in xenobiotic mechanism of action (Eberson, 1985; Halliwell and Gutteridge, 1985). Some antiprotozoal agents have been tested to possess this form of mechanism of action (Kovacic et al., 1989) although others may act in different ways.

Among the established antiprotozoal drugs from natural sources used in treating human protozoan infections are quinine from *Cinchona* species, artemisinin from *Artemisia annua* for malarial treatment and *Psychotria ipecacuanha* for treating amoebiasis (Tagboto and Townson, 2001). Three alkaloids namely quinidine, cinchonine, and cinchonidine together with quinine have significant antimalarial activity. All of these compounds were isolated from *Cinchona* trees. Totaquine is an antimalarial agent containing all the four alkaloids used in the past as a cheap alternative to quinine sulphate (Dobson, 1998). Seven out of 14 anti-parasitic drugs approved from 1981-2006 are natural products derivatives including artemisinin (Newman and Cragg, 2007). Apart from the established antiprotozoal drugs, natural products still possess the potentials of providing more alternative sources of antiprotozoal medications that needs further scientific elucidations. *Allium sativum* has been shown to possess trypanocidal activity both in vitro and in vivo (Mikail, 2009a). There are several other plants that possess this activity (Mikail, 2009b).

20. Antifungal property of natural products

Antifungal drugs are used in treating any of the following disease conditions: allergic reactions to fungal proteins, toxic reactions to toxins present in certain fungi and infectious mycoses which is the most serious and difficult to diagnose and treat due to the fact that mycoses come in many forms (Barret, 2002). Polyene natural product amphotericin B is the most commonly drug used in treating these disease conditions (Gallis et al., 1990; Wingard et al., 1999). Other various newer lipid formulations are also used in handling such disease conditions (Hiemenz and Walsh, 1996). Griseofulvin which was first isolated from the fungus *Penicillium griseofulvin* has been used in the treatment of dermatophyte infections for the past 30 years (Finkelstein et al., 1996). Polyene antifungal antibiotic nystatin, is used for prophylaxis and treatment of candidiasis of the skin and mucous membranes (Waugh, 2008). In Brazil, many plants biomes, such as the Cerado (savannah), the Atlantic and the Amazon rain-forest, have been used in the treatment of several tropical diseases, such as leishmaniasis, malaria, schistosomiasis, fungal and bacterial infections. These are mostly used by local populations as natural medicines (Alves et al., 2000).

21. Anthelminthic activity of natural products

More than 1 billion people are reported by the World Health Organization to suffer from neglected tropical diseases such as helminthiasis. This disease condition is a major health problem throughout developing countries and is also a food safety issue worldwide (Savioli, 2009). Th2 immunity is the key for protective immunity to all helminths, although the final

effector mechanisms for helminths expulsion are distinct for each helminths, which could be due to the different invasion strategy of each helminth (Shigeo Koyasu et al., 2010). Worm expulsion is dependent on Th2 immune responses. Critical for worm expulsion are Th2 cytokines, IL-4 and IL-13. Both of these cytokines significantly delays worm expulsion (Finkelman et al., 2004). Anthelmintic act rapidly and selectively on neuromuscular transmission of nematodes, agonism at nicotinic acetylcholine receptors of nematode muscle and cause spastic paralysis, organophosphorus cholinesterase antagonism, increasing the opening of glutamate-gated chloride (GluCl) and produce paralysis of pharyngeal pumping, increasing calcium permeability, while other anthelmintics have a biochemical mode of action (Martin, 1997).

Ivermectin was discovered from a microorganism, *Streptomyces avermitilis,* isolated from an Oceanside golf course soil in japan, it was found to have potent bioactivity. It has systemic anti-parasitic activities, effective against helminths, arachnids, and insects, but not against protozoa, bacteria, flatworms or fungi (Omura, 2008) Ivermectin was the first ' endoectoparasites' discovered due its proven activity against endo- and ectoparasites , at unprecedented low doses it could be easily used orally, topically and parentally (Arena et al., 1992; Omura, 2002). *Digenea simplex* and *Chondria armata* are two Japanese red algae, which have been used for their potent anthelminthic properties for more than 1000 years. Elimination of intestinal worms, such as parasitic round worms (*Ascaris lumbricoides*), tape worms (*Taenia* spp), and wip worms (*Trichuris trichura*) are some of the anthelminthic properties of these Japanese algae. Domoic acid and kainic acid are two closely related compounds isolated from these red algae, which are responsible for these curative properties (Gerwick et al., 2007). A wide range of plant and plant extracts has been used as potential alternative anthelminthic strategy for the treatment of helminth infections. Many species of fig tree from the genus Ficus and the papaya tree, *Carica papaya*, the crude latex was extracted and used successfully against ascarids, tapeworms, whipworms and hookworms in the early 19th century (Berger and Asenjo, 1940; Waller et al., 2001; Tagboto and Townson, 2001; Stepek et al., 2004).

22. Role of natural products in treating non infectious diseases

Although natural products are the origin of several drugs used in the treatment of many infectious diseases, they also play a significant role in the treatment of several non-infectious disease conditions.

23. Diabetes mellitus and obesity

Hyperglycaemia is the unifying feature of this heterogeneous endocrine disorder. Every year the number of diabetic patients is rising by 4-5% (Wagman and Nuss, 2001). Plant extract and complex microbial secondary metabolites of natural products have attracted the attention of scientific world for their potential use as drugs for the treatment of chronic diseases such as Type II diabetes (Bedekar et al., 2010). Acarbose was discovered from compounds isolated from *Actinomycetes species*, which are potent inhibitors of digestive enzymes such as α-amylase, sucrase, and maltase. Acarbose is the most widely used digestive enzyme inhibitor among the numerous antidiabetic drugs used for the treatment of Type-II diabetes (Bedekar et al., 2010). Maglitol which was derived from 1-deoxynorjirimycin is one of the widely used α-glucosidase inhibitors used in the treatment of Type II diabetes. Nojirimycin, deoxynojirimicin, and their derivatives are new compounds

with inhibitory properties derived from various *Bacillus* and *Streptomyces* strains (Schmidt et al., 1979; Tan, 1997). Another α-glucosidase inhibitor used as antidiabetic drug mostly in Asia is voglibose, which is synthesized from valiolamine isolated from fermentation broth of *Streptomyces hydroscopicus* subsp. *Limoneus* (Matsuo et al., 1992; Goke et al., 1995).

Interestingly, polyphenols natural compounds such as flavonoids have demonstrated numerous health benefits, by addressing the issue of obesity and diabetes due to their digestive enzyme inhibition activity, induction of apoptosis in adipose tissue, etc. (Nelson-Dooley et al., 2005). A subgroup of flavonoids, the anthocyanins is water-soluble plant pigments responsible for the blue, purple and red coloration of many plant tissues. Anthocynanins are extracted mostly from plants or plant waste in a form of a mixture. Anthocyanidins are the aglycon forms of anthocynanins of which 17 of them are found in nature. Anthocyanins have antioxidant and antihypertensive activities, they have also demonstrated the inhibition of lipid oxidation. Anthocyanins specifically inhibit α-glucosidase activity and have the potential to reduce blood glucose levels after starch-rich meals. (Matsui et al., 2001a; Bedekar, 2010). Through influencing signalling molecules natural products can prevent both adult and childhood obesity. During physiological conditions such as exercise, hypoxia, the presence of reactive oxygen species (ROS), and ischemia/reperfusion activated protein kinase (AMPK) is activated, which is the master regulator of metabolic processes. Natural products also activate AMPK to reduce obesity through the regulation of fatty acid metabolism-related proteins such as acetyl-coenzyme A (CoA) carboxylase (ACC), sterol regulatory element-binding protein (SREBP), fatty acid synthase (FAS) and so forth (Hwang et al., 2011).

24. Hypertension

The hypothesis that meat is a source of peptides that are effective in preventing and reducing chronic life style-related diseases (CLSRDS) such as hypertension has been tested. Empowering hypertensive people in quality life such as offering nutritional food rich in antioxidant vitamins, and proteins or biologically active peptides, can lower blood pressure, possibly by preventing an underlying cause of the condition. Provision of these forms of functional food is useful even to the normotensive individuals nutritionally. The underlying aetiology to clinical hypertension may be due to a deficiency in proteins from meat origins, along with abnormalities in carbohydrate and fat metabolism. Proteolysis of meat muscle generate multiple number of amino acid peptides with nutrafunctional roles, the have strong angiotensin-converting enzyme inhibitory activity, which perhaps lower blood pressure (Ahmed and Muguruma, 2010). Dietary supplements promote cholesterol-lowering benefits, some of these supplements reported to have significant low-density lipoprotein-cholesterol (LDL-C) lowering properties are soluble plant fibre (oats, psyllium, pectin, flaxseed, barley, guar gum, cellulose, lignins, wheat bran), plant sterols, soy proteins, nuts (almonds, pecan, walnut) and red yeast rice supplements (Nijjar et al., 2010).

25. Analgesia and recreaction

Pain is simply an undesirable physical or emotional experience. For the past 7000 years ago natural products have been used to treat pain disorders. A good example is opium poppy *(Papaver soniferum)* and the bark of willow tree (*Salix* spp.). In 19th century some individual components of different natural products remedies were identified and purified. One of the

most widely used and available compounds for the management of mild pain is Aspirin or acetylsalicylic acid derived from salicylic acid, which is extracted from Willow tree (*Salix alba*). Opioid is a name given to all compounds having the same mechanism of action as the constituents of opium. These are derived from opium juice from *Papaver somniferum;* examples of these groups of drugs include morphine, codeine and thebaine. These drugs are also use for recreational purposes apart from their use as analgesics (McCurdy and Scully, 2005). Cocaine interact with voltage-gated ion channels and blocks sodium channels which is responsible for its local anaesthetic activity. Cocaine has the ability to block the dopamine transporter due to its ability to create a euphoric state, meaning it is also use for recreational purposes (McCurdy and Scully, 2005). Caffeine is the most widely used psychoactive drug in the world, found in a number of plant sources. Coffee (*Coffea arabica*, native to Africa), tea (*Camellia sinensis*, native to China), and cacao (Theobroma cacao, native to South and Central America), from which chocolate is made. Other caffeine-containing plants include kola (*Cola acuminate*), guarana (*Paullinia cupana*), and yerba mate (*Ilex paraguarienis*). Theophyllines found in tea and theobromines found in cacao are other botanical methylated xanthines closely related to caffeine with psychoactive effects. Nicotine from tobacco plant (*Nicotiana tabacum*, *Nicotiana rustica*) and related species are other psychoactive substances. *Cannabis* plant is the source of cannabinoids such as marijuana and hashish which also possess psychoactive effects in form of relaxation, sedation, intensification of thoughts and feelings, alterations of perception, and increased appetite (Presti, 2003).

26. Antipsychotics

From ancient times to present in Indian ayurvedic medicine, extracts of the snakeroot plant, *Rauwolfia serpentine,* have been used to treat psychotic symptoms. Reserpine was isolated and identified in the 20th century from *R. serpentine,* and was found to cause decreases in the activity of monoaminergic neurons using the neurotransmitters dopamine, norepinephrine, and serotonin (Presti, 2003). Polygalasaponins is an extract of a plant (*Polygala tenuifolia* Willdenow) that has been used as antipsychotic for hundred years in Korean traditional medicine. Polygalasaponin has been shown to have dopamine and serotonin receptor antagonism properties in vivo, suggesting its possible utility as an antipsychotic agent (Chung et al., 2002).

27. Antidepressants

Saint John's wort (*Hypericum perforatum*) for centuries in Europe, the extract of this plant has been used for their antidepressant effects (Presti, 2003). Pharmacophores are natural products derived from chemically defended marine organisms related to serotonin or clinically utilized antidepressant drugs. Aaptamine and 5,6-dibromo-*N,N*-dimethyltryptamine are two marine natural products which produced significant antidepressant-like activity in the forced swim tests. In the tail suspension test antidepressant-like effects of 5,6-dibromo-*N,N*-dimethyltryptamine were confirmed, whereas aaptamine has not produce significant results (Diers et al., 2008).

28. Wound healing (angiogenesis)

The plant Saint John's wort when used in topical preparations facilitates wound healing. Its healing properties were mentioned in the ancient medical texts of Hippocrates, Pliny, and

Galen (Presti, 2003). Honey has been shown to possessed various antimicrobial activities in addition to its wound healing effect, a good example is the manuka honey (*Leptospermum scoparium*). Preparations of aloe vera (*Aloe barbadensis*), cocoa and oak bark extracts have been used to treat various ailments especially those of the skin (Davis and Perez, 2009). Upon injury papaya and fig trees produce latex rich in proteolytic enzymes, the juices extracted from the stem or fruit of plants such as the pineapple, contain large amount of cysteine proteinases (Rowan et al., 1990). Chymopapain, is one of these enzymes used in medicine to treat intervertebral disc prolapse with a similar success rate to surgery (Smith and Brown, 1967). For burn injuries ananain and comosain are used as debriding agents (Rowan et al., 1990). Bromelain, papain, and ficin have been used to replace glucocorticoids and non-steroidal anti-rheumatics as anti-inflammatory drugs (Lotz-Winner, 1990; Maurer, 2001; Stepek et al., 2004).

29. Role of natural products in preventive medicine

Natural products like medicinal plants and foodstuffs are used for their preventive effects against life-style related diseases such as coronary heart diseases, hypertension, thrombosis, allergic inflammation, arteriosclerosis, diabetes and cancer, although clinical basis and experimental evidence are insufficient and unclear. However, biochemical and pharmacological study of isolated natural compounds from various medicinal plants and foodstuffs indicate that fucoidan (polysaccharides), carp oil (fatty acids) and triterpenoids inhibited the tumour growth and/or metastasis in the liver, through the inhibition of tumour induced neovascularization, in tumour-bearing mice. The inhibition of thrombin-induced adhesion molecule through protein C kinase activation inhibition has been demonstrated by baicalein (flavones) isolated from *Scutellaria baicalensis* roots. Furthermore, through endothelium-dependent nitric oxide production, xanthoangelol (chalcones) isolated from *Angelica keiskei* roots inhibited catecholamine-induced vasoconstriction (Kimura, 2005). Many plants are used in traditional medicine as active agents against various effects induced by snakebite. *Baccharis trimera* (Asteraceae), known in as *carqueja* in Brazil, has been shown to inhibit haemorrhagic and proteolytic activity caused by *Bothrops* snake vemons (Januario et al., 2004). Biologicals like vaccines and antisera have a great role in preventive medicine. Polyclonal antibodies are mixture of antibody specificities which all recognize the same antigen. Blood serum that contains polyclonal antibodies is known as antiserum. Polyclonal antibodies are used in medicine to confer passive immunity to certain diseases. For instance, transfusion of serum antibodies from a human survivor of Ebola virus is the only effective treatment for the viral infection. Antiserum is also used in medicine as antitoxin or antivenin, which contain antibodies specific for venom from poisonous reptiles, arachnids and insects. People who have been bitten or stung by these animals are treated with this antiserum. Vaccine is a biological preparation that improves immunity to a particular disease made from attenuated or killed forms of a microbe or its toxins. Vaccines are used for either prophylaxis or therapy against certain disease conditions such as smallpox. Smallpox vaccine was the first successful vaccine to be developed in 1796 by Edward Jenner (Stewart and Devlin, 2006).

30. References

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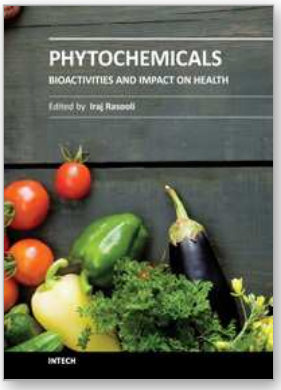

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Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.

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