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Natural products chemistry: A pathway for drugs discovery

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Abstract
Long before the era of high through-put screening and genomics, drug discovery relied heavily on natural products. Drug discovery involves the identification of New Chemical Entities (NCEs) of potential therapeutic value, which can be obtained through isolation from natural sources, through chemical synthesis or a combination of both. However, the success stories for the discoveries Penicillin from *penecilium rubens*, Paclitaxel *yew tree* and marketed as Taxol, Aspirin from Willow bark of *Salix alba* tree etc. have pave way for scholars in the field of natural product and organic chemistry to focus their research work in drug-derived from plants and microorganisms. Natural products derived from these sources are rich in bioactive compound, which have been use over years throughout human history and evolution as remedies for various ailments. This paper however, X-rayed the sources and classes of natural products, pharmaceuticals derived from Natural product, and uses of natural products. The paper also recommended among others that, government should fund research in the area of natural products, pharmaceutical chemistry and Pharmacognocy.

Keywords: Natural products, chemistry, drug, plant, microorganisms, metabolism

Introduction
Sand is a natural product, but we will not cover the chemistry of silica. Natural products of interest are those organic compounds that contain at a minimum the element carbon. Carbon (chemical symbol: C) has a valency of 4 and is bound to another carbon either as a single, double, or triple bond. Carbon is also attached to other elements, such as carbons, hydrogen (H), oxygen (O), and nitrogen (N); and also sulfurs (S) and phosphorous (P). The various combinations lead to the bewildering array of natural products structures (Cooper and Nicola, 2015) [12]. Starting from the late 19th century there had been much account by scientists and physicians on the antibacterial properties of the different types of moulds including the mould penicillium but they were unable to discern what process causing the effect. The effect of mould penicillium was finally being isolated in 1928 by Scottish scientist Alexander Fleming, in his work that seems to have been independent of those earlier observations (Greenwood, 2008). Similarly, recent literature also revealed how drugs were reportedly discovered through the natural products process due to prevalence of many diseases without suitable medical products available. Among the various pharmaceutical industrial processes used for drug discovery, the Research and Development process is one of the pioneer processes (Cutler, 2000) [14]. The meaning of natural Products has been over the time defined as the naturally occurring compounds that are end products of primary metabolites; often they are unique compounds for particular organisms (El-Olemyl *et al.,* 1994) [21]. Metabolites are intermediates in metabolic processes in nature and are usually small molecules. A primary metabolite is directly involved in normal growth, development, and reproduction, for example, fermentation products (ethanol, acetic acid, citric and lactic acid) and cell constituents (lipids, vitamins, and polysaccharides). In contrast, secondary metabolite is not directly involved in those processes and usually has a function but is not that important for the organism (e.g., antibiotics, pigments, and carotenoids), (Cooper and Nicola, 2015) [12]. Long before the era of high through-put screening and genomics, drug discovery relied heavily on natural products (Bahl and Bahl, 2006) [8]. In fact, many of the drugs available today contain active ingredients extracted from natural products. Since 1994, nearly half of all drugs were discovered using natural products (Hamburger and Hostettman, 1991) [25]. Furthermore, there were thirteen (13) new drugs based on natural products that entered the commercial market. These include ixabepilone, retapamullin, trabectedin, and the peptides exenatide and ziconotide (Sofowora, 1984). Natural product drug discovery continues to play a significant role in the clinical development of new therapies in the biopharmaceutical industry (Hamburger and Hostettman, 1991) [25]. NaturalProduct is a chemical compound or substance produced by a living organism that is, found in nature. In the broadest sense, natural products include any substance produced by life (Hanson, 2003). Natural products remain the best sources of drugs and drug leads, and this remains true today despite the fact that many pharmaceutical companies have deemphasized natural products research in favor of HTP screening of combinatorial libraries during the past 2 decades. From 1940s to date, 131 (74.8%) out of 175 small molecule anticancer drugs are natural product-based/inspired, with 85 (48.6%) being either natural products or derived there from. From 1981 to date, 79

(80%) out of 99 small molecule anticancer drugs are natural product-based/inspired, with 53 (53%) being either natural products or derived there from. Among the 20 approved small molecule New Chemical Entities (NCEs) in 2010, a half of them are natural products (Samuelson, 1999). Drug discovery involves the identification of New Chemical Entities (NCEs) of potential therapeutic value, which can be obtained through isolation from natural sources, through chemical synthesis or a combination of both. The field of natural products drug discovery, despite the success stories of penicillin, paclitaxel, etc., also had aspects that made it less attractive. In the traditional approach, drug targets were exposed to crude extracts, and in case of evidence of pharmacological activity the extract was fractionated and the active compound isolated and identified. This method was slow, labor intensive, inefficient, and provided no guarantee that a lead from the screening process would be chemically workable or even patentable (Williams *et al.*, 2002). As natural products usually are molecules with more complex structures, it was more difficult to extract, purify or synthesize sufficient quantities of a NCEs of interest for discovery and development activities (Hunter *et al.*, 2008).

Classification of Natural Product

- Alkaloids
- Tannins
- Saponins
- Terpenoids
- Steroids
- Flavonoids
- Alkaloids: These are any of a class of naturally occurring organic nitrogen-containing bases. Alkaloids have diverse and important physiological effects on humans and other animals. Well-known alkaloids include morphine, strychnine, quinine, ephedrine, and nicotine. Alkaloids are found primarily in plants and are especially common in certain families of flowering plants. More than 3,000 different types of alkaloids have been identified in a total of more than 4,000 plant species (Cooper and Nicola, 2015) [12]. In general, a given species contains only a few kinds of alkaloids, though both the opium poppy (*Papaver somniferum*) and the ergot fungus (*Claviceps*) each contain about 30 different types. Certain plant families are particularly rich in alkaloids; all plants of the poppy family (Papaveraceae) are thought to contain them, for example. The Ranunculaceae (buttercups), Solanaceae (nightshades), and Amaryllidaceae (amaryllis) are other prominent alkaloid-containing families (Sadiq *et al*., 2015).

Alkaloids (meaning alkali-like) are nitrogenous heterocyclic organic compounds mostly of plant origin that show significant physiological or toxic effect on humans (El-Olemyl *et al.*, 1994) [21]. Alkaloids are classified based on prominent heterocyclic ring system present in the molecule. These are:

- Pyridine alkaloids e.g. Nicotine
- Piperidine alkaloids e.g. coniine, Piperine
- Quinoline alkaloids e.g. quinine
- Isoquinoline alkaloid e.g. papaverine, morphine
- Indole alkaloids e.g. gramine, strychnine.

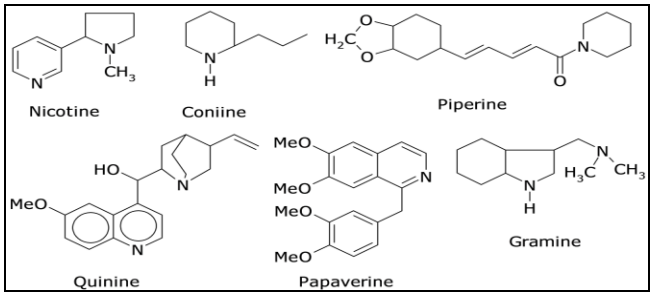

Fig 1: Structure of same alkaloids use as drugs

- **Tannins:** Tannins are non-crystallizable higher molecular weight (1000 – 5000) complex Phenolic compounds (Zaki, 2000, Oboh and Abulu, 1997). These compounds possess both ant-nutritive and medicinal properties. These compounds exhibit their ant-nutrient ability by precipitating dietary proteins and digestive enzymes to form complexes not readily digestible (Zaki, 2000). Other anti-nutritional effects include, damage to the gastrointestinal tract, interference with the absorption of iron and possibly, a carcinogenic effect. Medicinally, they are used in the treatment of diarrhea and skin burns (El-Olemyl *et al.*, 1994). Tannins are classified as hydrolysable tannins (i.e. a mixture of carbohydrates and polyphenols-gallic acid) and condensed tannins (i.e. complex flavonoid polymers) (Sofowora, 1993).

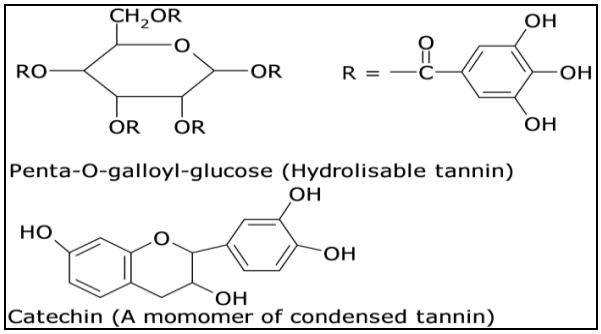

Fig 2: Structures of Some Tannin

- **Saponins:** Saponins are a group of naturally occurring plant glycosides, characterized by their strong foam-forming properties in aqueous solution. The presence of saponins has been reported in more than 100 families of plants out of which at least 150 kinds of natural saponins have been found to possess significant anti-cancer properties. There are more than 11 distinguished classes of saponins including dammaranes, tirucallanes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes and steroids (Cooper and Nicolar, 2015) [12]. Due to the great variability of their structures, saponins always display anti-tumorigenic effects through varieties of antitumor pathways (Shuli *et al*., 2010).
- **Terpenoids:** Terpenoids are widely found in nature and are referred to as terpenes or isoprenoids, they are the largest group of natural compounds found in the plants and are synthesized from five-carbon building block. Based on the number of building blocks, terpenoids are

Classified as monoterpenes, Sequiterpenes, diterpenes, sesterpenes, triterpenes, tetraterpenes and poly terpenes (Rabi and Bishayee, 2009) [35]. With almost 40,000 different terpenoids having been isolated from plants, animal and microbial species (Setzer and Setzer, 2003). One example is triterpenoids recently emerged as a unique group of phytochemicals with multi-functional anticancer activities. Terpenes commonly occur in the oils that give plants their fragrance. Originally the term *terpene* was restricted to only hydrocarbons; it is now used to include substituted derivatives too. The fundamental building block of terpenes is the isoprene unit, C_5H_8. The larger structures are assembled from several isoprene units, usually by head-to-tail linked isoprene units. Terpenes can be cyclic or acyclic, with a large range of structural.

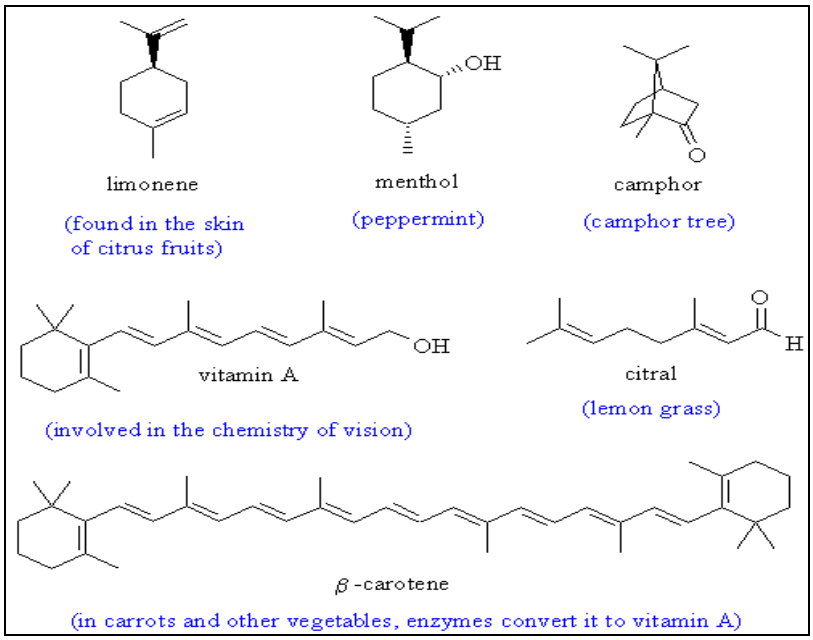

Fig 3: structures of terpenoids

- **Steroids:** steroid is a type of organic compound that contains a characteristic arrangement of four cycloalkane rings joined to one another. Examples of steroids include the dietary lipid cholesterol, the sex hormones estradiol and testosterone, bile acids, and drugs such as the anti-inflammatory agent dexamethasone (Han *et al*., 2013 [26], Lednicer, 2011) [31].

The steroid core is composed of seventeen carbon atoms bonded together in the form of four fused rings: three cyclohexane rings (designated as rings A, B and C in the figure to the left) and one cyclopentane ring (the D ring). The following is a list of the major classes of steroid hormones and some prominent members, with examples of major related functions (Han *et al*., 2013) [26].

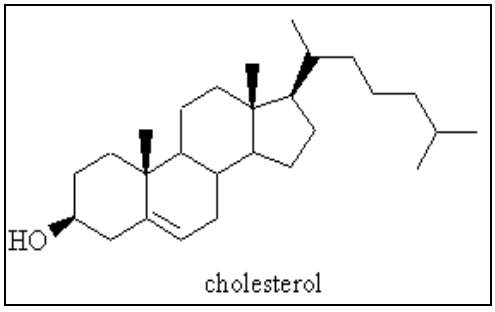

Fig 4

- **Flavonoids:** They are the most abundant polyphenols in human diet, representing about 2/3 of all those ones ingested. Like other phytochemicals, they are the products of secondary metabolism of plants and, currently, it is not possible to determine precisely their number, even if over 4000 have been identified. In fruits and vegetables, they are usually found in the form of glycosides and sometimes as acylglycosides, while acylated, methylated and sulfate molecules are less frequent and in lower concentrations. They are water-soluble and accumulate in cell vacuoles (El-Olemyl *et al.* 1994 [21]: Abdulmuhit *et al.* 2010 [2]: Adzu *et al.* 2001) [3].

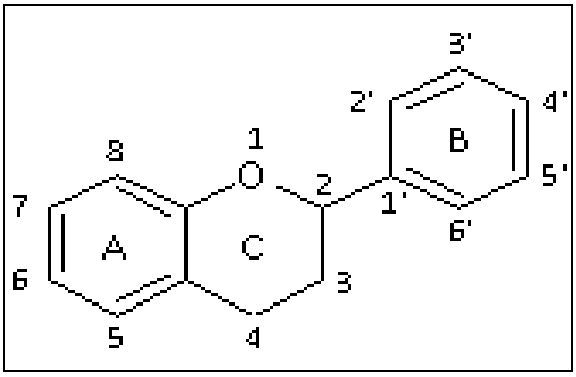

Fig 4: Skeleton of Diphenylpropane

Sources of Natural Products

Historically, the most important sources for biologically active natural products have been terrestrial plants and microorganisms such as fungi and bacteria. Terrestrial and aquatic species of plants and microorganisms, especially those of marine origin, produce unique bioactive substances yielding a large variety of valuable therapeutics and lead structures for potential new drugs.

- **Plants source of natural product:** A significant number of drugs have been derived from plants that were traditionally employed in ethnomedicine or ethnobotany (the use of plants by humans as medicine as in Ayurvedic or Traditional Chinese Medicine), while others were discovered initially (through random screening of plant extracts in animals) or later, by determining their *in vitro* activity against HIV or cancer cell lines (Li *et al*., 2009). An avenue that may have influenced ethnopharmacology suggests that some traditionally used remedies may have arisen from observations of self-medication by animals. Studies have clearly shown that wild animals often consumed plants and other material for medical rather than nutritional reasons, treating parasitic infections and possible viral and bacterial diseases (Bhat *et el.,* 2005). For drug discovery, the chemical and pharmacologic investigation of ethnobotanical information offers a viable alternative to high-through put screening and the body of existing ethnomedical knowledge has led to great developments in health care. It would appear that selection of plants, based on long-term human use in conjunction with appropriate biological assays that correlate with the ethnobotanical uses, should be most successful (Kliebenstein, 2004).
- **Microorganisms Source of Natural Product:** Microorganisms were identified as sources of valuable natural products as evidenced by the discovery of penicillin from the fungus *Penicillium rubens* by Alexander Fleming in 1928. Historically, microorganisms (amongst them mostly bacteria and fungi) have played an important role in providing new structures, like antibiotics for drug discovery and development. The terrestrial microbial populations are immensely diverse which is also reflected in the number of compounds and metabolites isolated from these microorganisms (Rogers, 2011). As mentioned above, the similarity of many compounds from marine invertebrates like sponges, ascidians, soft corals and bryozoans to those isolated from terrestrial microbes led to the hypothesis that associated microorganisms might be responsible for their production. Over time it became more and more evident, that a significant number of marine natural products are actually not produced by the originally assumed invertebrate but rather by microbes living in symbioses with their invertebrate host (Boal, 2006) [11].

Uses of Natural Products Chemistry

Natural products sometimes have pharmacological activity that can be of therapeutic benefit in treating diseases. As such, natural products are the active components of many traditional medicines. Furthermore, synthetic analogs of natural products with improved potency and safety can be prepared and therefore natural products are often used as starting points for drug discovery (Cochrane, Vederas, 2016). Natural product constituents have inspired numerous drug discovery efforts that eventually gained approval as new drugs by the U.S. Food and Drug Administration.

- **As a traditional medicine:** Indigenous peoples and ancient civilizations experimented with various plant and animal parts to determine what effect they might have. Through trial and error in isolated cases, traditional healers or shamans found some sources to provide therapeutic effect, representing knowledge of a crude drug that was passed down through generations in such practices as traditional Chinese medicine and Ayurveda (Saxena *et al.,* 2014). Extracts of some natural products led to modern discovery of their active ingredients and eventually to the development of new drugs (Saxena *et al.,* 2014).
- **Modern natural product-derived drugs:** A large number of currently prescribed drugs have been either directly derived from or inspired by natural products. A few representative examples are listed below. Some of the oldest natural product based drugs are analgesics. The bark of the willow tree has been known from antiquity to have pain relieving properties. This is due to presence of the natural product salicin which in turn may be hydrolyzed into salicylic acid. A synthetic derivative acetylsalicylic acid better known as aspirin is a widely used pain reliever. Its mechanism of action is inhibition of the cyclooxygenase (COX) enzyme. Another notable example is opium is extracted from the latex from *Papaver somniferous* (a flowering poppy plant). The most potent narcotic component of opium is the alkaloid morphine which acts as an opioid receptoragonist (Hallett *et al.,* 2013). A more recent example is the N-type calcium channel blocker ziconotide analgesic which is based on a cyclic peptide cone snail toxin (ω-conotoxin MVIIA) from the species *Conus magus*(Hallett *et al.,*2013). A significant number of anti-infectives are based on natural products. The first antibiotic to be discovered, penicillin, was isolated from the mold *Penicillium*. Penicillin and related beta lactams work by inhibiting DD-transpeptidase enzyme that is required by bacteria to cross link peptidoglycan to form the cell wall(Hallett *et al.,*2013). Several natural product drugs target tubulin, which is a component of the cytoskeleton. These include the tubulin polymerization inhibitor colchicine isolated from the *Colchicum autumnale* (autumn crocus flowering plant), which is used to treat gout (Alvin *et al.,*2014) [7]. Colchicine is biosynthesized from the amino acids phenylalanine and tryptophan. Paclitaxel, in contrast, is a tubulin polymerization stabilizer and is used as a chemotherapeutic drug. Paclitaxel is based on the terpenoid natural product taxol, which is isolated from *Taxus brevifolia* (the pacific yew tree) (Alvin *et al.,* 2014) [7]. Classes of drugs widely used to lower cholesterol are the HMG-CoA reductase inhibitors, for example atorvastatin. These were developed from mevastatin, a polyketide produced by the fungus Penicillium citrinum (Alvin *et al*. 2014)

[7]. Finally, a number natural product drugs are used to treat hypertension and congestive heart failure. These include the angiotensin-converting enzyme inhibitor captopril. Captopril is based on the peptidic bradykinin potentiating factor isolated from venom of the Brazilian arrowhead viper (Bothrops jararaca).

Natural Product-derived Pharmaceuticals

Natural products constitute a key source of pharmacologically active ingredients in a variety of novel agents with therapeutic potential in a wide range of diseases. Pharmaceuticals containing natural products or compounds derived from natural product scaffolds or templates have to undergo the same stringent approval process as drugs obtained from purely synthetic origin.

- **Drug:** Drug has been define in a myriad ways, Okeye, (2001) define drug as a substance that could bring about a change in the biological functions through its chemical actions. It is also considered as a chemical that modifiers of the living tissues that could bring about psychological and behavioral changes (Olalekan *et al*, 2014) [34]. Moreover, drug is defined as a substance that modifies perceptions, cognition mood, behavior and general body function (Balogun, 2006) [9]. Comprehensively, drug is any chemical substance, natural or man-made (usually excluding nutrients, water, or oxygen), that by its chemical nature alters biological structure or functioning when administered and absorbed (Dewick, 2009) [19]. Pharmacology is the discipline that studies drug effects on living systems (Dewick, 2009) [19].

Classification of Drug

Drugs can be categorized in a number of ways. In the world of medicine and pharmacology, a drug can be classified by its chemical activity or by the condition that it treats.

- Narcotics
- Depressants
- Stimulants
- Hallucinogens
- Anabolic steroids

- **Depressants**. Drugs that suppress or slow the activity of the brain and nerves, acting directly on the central nervous system to create a calming or sedating effect. This category includes barbiturates (phenobarbital, thiopental, butalbital), benzodiazepines (alprazolam, diazepam, clonazepam, lorazepam, midazolam), alcohol, and gamma hydroxybutyrate (GHB). Depressants are taken to relieve anxiety, promote sleep and manage seizure activity (Dewick, 2009) [19].
- **Stimulants.** Drugs that accelerate the activity of the central nervous system. Stimulants can make you feel energetic, focused, and alert. This class of drugs can also make you feel edgy, angry, or paranoid. Stimulants include drugs such as cocaine, crack cocaine, amphetamine, and methamphetamine. According to the recent World Drug Report published by the United Nations Office on Drugs and Crime, amphetamine-derived stimulants like ecstasy and methamphetamine are the most commonly abused drugs around the world after marijuana (Strobel, 2003).
- **Hallucinogens**. Also known as psychedelics, these drugs act on the central nervous system to alter your perception of reality, time, and space. Hallucinogens may cause you to hear or see things that don't exist or imagine situations that aren't real. Hallucinogenic drugs include psilocybin (found in magic mushrooms), lysergic acid diethylamide (LSD), peyote, and dimethyltryptamine (DMT) (Zaffiri *et al.*, 2012).
- **Inhalants.** These are a broad class of drugs with the shared trait of being primarily consumed through inhalation. Most of the substances in this class can exist in vapor form at room temperature. As many of these Substances can be found as household items, inhalants are frequently abused by children and adolescents. These include substances such as paint, glue, paint thinners, gasoline, marker or pen ink, and others. Though ultimately all of these substances cross through the lungs into the bloodstream, their precise method of abuse may vary but can include sniffing, spraying, huffing, bagging, and inhaling, among other delivery routes (Zaffiri *et al.*, 2012).
- **Cannabis**. Cannabis is a plant-derived drug that is the most commonly used illicit drug worldwide. It acts through the cannabinoid receptors in the brain. Cannabis is abused in various forms including bhang, ganja, charas, and hashish oil. (Strobel, 2003).

Conclusion/Recommendation

Compounds isolated from nature have long been known to possess biological profiles and pharmaceutical potential far greater than anything made by man. However, natural products are notoriously cumbersome to isolate and very challenging to synthesize. Natural products have played a central role in advancing synthetic and biosynthetic chemistry, medicine, and our understanding of nature. The training of chemists and pharmacognocists in the area of microscale chromatographic purification and spectroscopy is ever increasing to tackle the challenging questions in bioorganic chemistry and molecular biology. To this end the authors recommended that, federal and state government should fund research in the area of natural products chemistry, organic chemistry and biochemistry. Similarly, Nigerian universities in collaboration Non-governmental Organizations NGOs such as WHO to open centre for research in drugs derived from natural products.

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