NIGERIAN MEDICINAL PLANTS: IDENTIFYING, PURIFYING, AND PRODUCING DRUGS FOR THE TREATMENT AND CURE OF HUMAN DISEASES

EMMA ONUA

Abstract

Plants have been well documented for their medicinal uses for thousands of years. They have evolved and adapted over millions of years to withstand bacteria, insects, fungi, and weather, to produce unique, structurally diverse, secondary metabolites. Their ethnopharmacological properties have been used as a primary source of medicines for early drug discovery (McRae et al, 2007; Fellows and Scofield, 1995). According to the World Health Organization (WHO), 80% of people still rely on plant-based traditional medicines for primary health care (Fansworth et al, 1985) and 80% of 122 plant-derived drugs were related to their original ethnopharmacological purpose (Fabricant and Farnsworth, 2001). The knowledge associated with traditional medicine (complementary or alternative herbal products) has promoted further investigations of medicinal plants as potential medicines and has led to the isolation of many natural products that have become well-known pharmaceuticals. The use of herbal medicines among Nigerians and the tendency by patients to combine this class of medicines with allopathic drugs while on hospital admission is on the increase (Fakeye and Onyemadu, 2008). The reasons for this include the affordability of these remedies as well as superstitious beliefs commonly spread by the traditional herbal medicine practitioners, and their patrons alike, contribute immensely to the increase in consumption of these herbal remedies (Calixto, 2000; Kaplowitz, 1997; Shaw et al, 1997).

INTRODUCTION

Historically, natural products have been used since ancient times and in folklore for the treatment of many diseases and illnesses. Classical natural product chemistry methodologies enabled a vast array of bioactive secondary metabolites from terrestrial and marine sources to be discovered (Dias et al, 2012). The earliest records of natural products were depicted on clay tablets in cuneiform from Mesopotamia (2600 B.C.), which documented oils from *Cupressus sempervirens* (Cypress) and *Commiphora* species (myrrh), and which are still used today to treat coughs, colds, and inflammation (Cragg et al, 2005). It has been well documented that natural products played critical roles in modern drug development, especially for antibacterial and antitumor agents. Even though the popularity of the synthetic products increased, due to its production cost, time effectiveness, easy quality control, stringent regulation, and quick effects, still their safety and efficacy always remained questionable, resulting in the depend-

ence on the natural products by more than 80% of the total population in the developing world, because of its time-tested safety and efficacy. A huge number of natural product-derived compounds in various stages of clinical development highlighted the existing viability and significance of the use of natural products as sources of new drug candidates (Veeresham, 2012).

Owing to the high diversity of terrestrial and marine organisms, natural products (secondary metabolites) are some of the most successful sources of drug leads for the treatment of many diseases and illnesses (David *et al*, 2014). In the 1990s, advancements in automation [high-throughput screening (HTS)] and isolation technologies resulted in the surge in research towards natural products both in the fields of human health and agriculture. These strategies and techniques generated a substantial shift towards this 'green Eldorado', a real 'Green Rush' between 1990 and 2000. However, in the early 2000s, most of the big Pharmas terminated their HTS and bioprospecting endeavors. But, to date, the low productivity of combinatorial chemistry and rational drug design is silently positioning pharmacognosy back on the rails and natural product discovery is remerging as a reputable source of current drugs on the market (Chen *et al*, 2003., Butler, 2004., David, *et al*., 2014).

Meanwhile, the World Health Organization has come to the realization of the importance of biodiversity, which would be able to offer affordable, therapeutic solutions to a majority of the world population. The preservation of the world's biodiversity and its access is a critical issue, which could hamper a serene utilization of natural products in the developing world, with herbal-based phytopharmaceuticals representing a significant share of the total world pharmaceutical market. This review presents an industrial perspective that discusses natural product drug discovery, lead research, botanicals, pro-drugs, synergy effects, drug interactions with botanicals, traditional medicines, reverse Pharmacognosy, and presents the difficulties in accessing biodiversity (David *et al*., 2014).

Akande et al (2012) explored the biochemical constituents of a locally prepared herbal remedy (Agbo) in Nigeria and observed that they contained tannin, saponin, alkaloids, and flavonoids in various amounts. They recommended that there is a need for standardization of dosage regimens and scrutiny of the pedigree of the peddlers of these herbal remedies by appropriate government agencies. Traditional medicine is still the predominant means in the Third World for the preservation of health of the rural majority that constitutes over 70% of the total population (Okoli et al, 2007).

A review of the Malaysian experience with medicinal plants, conducted by Muhammad and Awaisu (2008), noted that about one-third of the

world's population still lacks regular access to essential drugs, and this figure is believed to be rising to over 50% in the poorest parts of Africa and Asia. They further noted that traditional medicine, therefore, offers a major and accessible source of treatment and continues to play an important role in healthcare management. According to the International Federation of Pharmaceutical Manufacturers & Associations, the process of pharmaceutical research and development (R&D) is a complex, costly, risky, and long undertaking. It requires a sustained mobilization of substantial human and financial resources over a long period before a new drug finally reaches the patient. On average, this process takes between 10-15 years, and the estimated average cost of developing a new medicine exceeds $800 million. In the course of the R&D process, more than 8,000 compounds are tested on average, of which only one is developed into a potent and safe drug (IFPMA). As a result, Pharmaceutical R&D is largely dominated by private multinational companies known to possess the financial capacities, expertise, know-how, and technical excellence that guarantee the sustainability of the whole process (Muhammad and Awaisu, 2008).

MATERIALS AND METHODS

Extensive reviews of publicly available records, published literature, and the author's personal experiences as a pharmaceutical research scientist of nearly thirty years were the sources utilized for this article.

THE BASICS OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D)

The research and development (R&D) of modern pharmaceuticals follow some general principles. Whether the starting material is of natural sources (herbs, extracts from roots or seeds, fermentation products, etc.) or synthesized through elaborate chemical processes, an active pharmaceutical ingredient (API) must be isolated, characterized, tested for safety and efficacy, and the proper dosage set for the intended indication. If an API successfully scales through these initial hurdles, it is subjected to rigorous processes for consistent manufacturability, including characterization of the parent compound and metabolites, elucidation of its degradation products, storage stability, and determination of appropriate storage conditions. Following the completion of these activities, (which could take up to 6 to 10 years), a dossier of all the Safety and Efficacy data generated for the drug is compiled by the development sponsor and submitted to the relevant regulatory agencies for review and possible approval. Of course, there are unknown factors that play a role in pharmaceutical R&D, includ-

ing the specific activities required for the particular drug, the time interval required from initiation to completion of these activities, as well as the cost of development.

Fundamentally, drug discovery and development is a multi-disciplinary endeavor, requiring the collective effort of scientists in various areas including Chemistry Computational, Chemistry, Organic, Chemistry Synthetic, Chemistry Analytical, Biology, Physiology, Mathematics, Statistics, Computer Science, Law (Patent and Proprietary), etc. The sub-disciplines that have developed under these broad subjects, such as Biochemistry, Pharmacology, Enzymology, Process Chemistry and Toxicology, all play important roles in the process as well. Typical processes for Pharmaceutical R&D include some or all of the following:

1) Synthesis or isolation of a pharmacologically active ingredient (a potential drug)
2) Purification and Scale-up
3) Preclinical Development and Optimization
4) Pre-clinical and Clinical testing
5) Commercialization (Scale-up, Chemistry, Manufacturing, Control etc.)
6) Regulatory Approval
7) Marketing and post-approval safety monitoring

SYNTHESIS OR ISOLATION OF A PHARMACOLOGICALLY ACTIVE INGREDIENT

The process of synthesizing a pharmacologically active molecule is usually driven by a computer-aided drug design approach. A known or suspected target of pharmacological activity is identified, and if a molecule registers a "hit" on the target, it is said to have drug-like properties. The design and synthesis effort requires close collaboration between systems biologists, computer drug modeling experts, and the chemists who would eventually translate the designed molecule into an actual substance in the laboratory. Usually, tens or hundreds of molecules are generated from a common chemical scaffold (backbone), with specific modifications introduced to enhance or diminish certain characteristics. These compounds are then screened in assays to determine their drug-like characteristics, which would inform further development efforts.

Alternatively, a pharmacologically active ingredient may be isolated from a herbal preparation that has demonstrated pharmacological activity in the past. The biggest challenge for herbal preparations is that they contain a multitude of chemical substances with varying levels of pharmacologi-

cal activity. Unfortunately, these preparations do not only contain desirable pharmacological properties but often do contain undesirable attributes as well. Therefore, selecting one of the components of a herbal preparation requires careful and methodical application physico-chemical separation techniques to isolate the compounds of interest. Thereafter, the isolated molecules are subjected to elaborate tests to identify the specific molecules that are responsible for the observed pharmacological activity.

PURIFICATION AND SCALE-UP

Often, the initial synthetic chemical products contain impurities, which do not have known or beneficial pharmacological characteristics. Herbal preparations are even worse in this regard because they usually contain other compounds that may have undesirable characteristics. In each of these cases, there is a need for isolation and purification of the preparations, so that only the compound of interest is available at the end of the process.

The purification processes that are available to Chemists include electrophoretic separation, liquid chromatography, fraction collection, etc. Following purification and characterization, the next challenge is to scale up production of the pure form of the molecule from the laboratory scale of a few milligrams required for initial testing during the Drug Discovery phase, to a "Development" batch of several grams or even kilogram amounts. The larger amount will be utilized in the multiple studies that are part of R&D activities.

PRECLINICAL DEVELOPMENT AND OPTIMIZATION

In this phase of pharmaceutical R&D, the molecule of interest is subjected to a battery of tests in a combination of *in vitro* (Latin for "in a test tube") and *in vivo* (in a living organism) setting. The reason for starting most of the preclinical tests is that putting untested molecules into animal testing is both unethical and expensive. It is unethical, because the potential toxicity of a compound is largely unknow in the early stages of R&D, and testing compounds in animals without indicating the side effects would be frowned upon by society.

Using *in vitro* tools, such as liver microsomes, hepatocytes, cell cultures, and isolated perfused organ systems, etc., potential drug molecules are evaluated for drug-like properties, such as metabolic stability, metabolic profile, the potential for interaction with other co-administered drugs, protein binding, the potential to cause reactive metabolites, etc. The results of these tests would help re-design or make modifications to a molecule, in order to decrease it. The *in vivo*

tests would involve the use of animal species (mouse, rat, dog, and monkeys), to generate safety and dose-setting data that would permit a reasonable extrapolation into human doses.

CLINICAL TESTING

Following compilation and evaluation of preclinical data for a likely drug candidate, a decision is then made to proceed to clinical studies involving human subjects. Clinical studies are organized in phases, starting from a Safety evaluation in healthy volunteers, and culminating in large-scale studies using complex statistical designs and blinded treatments to verify Safety and Efficacy of the drug candidate.

COMMERCIALIZATION
(Scale-up, Chemistry, Manufacturing, Control)

If a potential drug meets the pre-defined clinical end-points for a particular disease indication, then, the molecule is manufactured on a large scale for commercialization. Scale-up of chemical manufacturing is often complicated when the lab-scale synthesis is changed to commercial volumes. The use of different reaction volumes, equipment, and processes do not always translate directly from lab-scale to commercial scale. To ensure that the output is consistent in quality and purity, the so-called CMC (Chemistry Manufacturing and Controls) processes are particularly important, because the drug product at this stage is ready for a larger audience. Each batch of the drug compound is subjected to rigorous physical and chemical tests to confirm their identity, purity, and other specifications before they are released for use.

REGULATORY APPROVAL

At the time of submitting a Dossier to a relevant regulatory authority, all the known information about a potential drug is assembled to demonstrate its safety and efficacy. The regulatory agency will then review the entire package of data. If the regulatory agency is satisfied that the drug molecule is what the sponsor claims that it is and that it is safe, and efficacious against the claimed disease condition, they will approve its use in the general population. Sometimes, the drug is restricted to a segment of the population for which adequate information exists for a claim of safety and efficacy. For other indications or an expanded use, the regulatory agency may request additional information, additional studies, or a modification of the application in accordance with the new request. In the U.S.A., the regulatory agency is the Food and Drug Administration

(FDA), whereas, in Nigeria, it is the National Agency for Food and Drug Administration and Control (NAFDAC). The NAFDAC process for the production of herbal medicines (and its derivatives, presumably) is contained in NAFDAC Doc. Ref. No. DER-GDL-006-00, effective 2018-2020.

CHALLENGES OF DEVELOPING DRUGS FROM NATURAL PRODUCTS IN NIGERIA

The pharmaceutical sector in Nigeria is made up of the academia, administrative, regulatory, community (retail), industry and hospital practice areas and is regulated by the Pharmacists Council of Nigeria (PCN) (Ekpenyong et al, 2018). They reported that there are 21,892 registered pharmacists in Nigeria. However, the data suggest that only 12,807 (58.5%) are in active professional practice as indicated by the number of licensed pharmacists in 2016. The challenges of developing drugs from natural products are discussed in detail in the works of Akande et al, 2012., Agbo and Mboto, 2012., Walubo, 2013., Shakya, 2016., Habtamu and Melaku, 2018).

In a keynote speech delivered by Farouk Gumel (Partner, Price Waterhouse) in 2014, he projected that the global pharmaceutical market would grow to $1.3 trillion by 2020. Unfortunately, Nigeria was not listed in the countries where the anticipated growth would take place. He reported annual average GDP growth of 6.8% for Nigeria, but this growth does not include a significant contribution from the pharmaceutical sector.

THE ECONOMICS OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT

The cost of developing a new drug from *de novo* synthesis to marketing is estimated to cost between $600 million and $800 million (Adams and Brantner, 2006, Prasad and Mailankody, 2017). Between 2009 and 2018, the median cost of developing a new drug was $985 million, while the average sum totaled $1.3 billion (Wouters et al, 2020). The high cost is mostly linked to the high attrition rate of molecules in the drug discovery and development pipeline. It is estimated that for every 10-20 molecules that emerge from pharmaceutical research and enters the development pipeline, about 10,000 molecules would have to be isolated, synthesized and screened for pharmacological activity (Torjsen, 2015). Essentially, pharmaceutical drug discovery and development is a very expensive and capital-intensive enterprise, without assurance of success. The cost could be considerably cheaper if the starting material is a naturally occurring compound, likely extracted from roots, leaves, bark, and fermentation of

microbes or other constituents of the animal and plant kingdoms. Another area of very high costs is the conduct of clinical trials.

Whereas on the surface, drug discovery and development does appear to be an expensive proposition, nonetheless, it is a high-cost and high-paying enterprise. For the sake of comparison, in 2018, a total of $25.08 billion was remitted by Nigerians in diaspora into the country (PricewaterhouseCoopers, 2019). This represents about 83% of the federal government's 2018 budget in value (equivalent to N8.7 trillion Naira @ N350=$1). In the same year, Nigeria's total receipts from the sale of crude oil were estimated to be between $16.1 billion and $26 billion.

On the other hand, the top-five pharmaceutical companies reported the following gross revenue figures in their publicly-issued financial records: Pfizer ($53.6 billion), BMS ($20.8 billion), Novartis ($51.9 billion), Merck ($42.3 billion), Johnson & Johnson ($81.7 billion), Eli-Lilly ($35.9 billion), Bayer (£39.6 billion), and GlaxoSmithKline (£30.8 billion). If Nigeria were to develop drugs from common plants that are known to have pharmaceutical properties, the cost of discovery and development would, almost certainly, be overshadowed by the revenues from marketing such drugs.

IMPORTANT MEDICINAL PLANTS IN NIGERIA

Chukwuma et al (2015) and El-Ghani (2016) have provided excellent and comprehensive reviews of medicinal plants in Nigeria. The African Regional Standard Organisation (ARSO), an intergovernmental body formed by the African Union (AU), has identified ten medicinal plants from Nigeria:

- Moringa oleifera (drumstick tree),
- Bitter kola (*Garcinia kola*),
- Bitter leaf (*Vernonia amygdalina*),
- Cashew (*Anarcadium occidentale*),
- Scent leaf (*Ocimum gratissimum*),
- African bush mango (*Irvingia gabonensis*),
- Yellow yam (*Dioscorea bulbifera*),
- Prunus Africana for prostate cancer,
- Baobab (*Adansonia digitata*), and
- Hibiscus sabdariffa (zobo).

The plants, and their associated pharmaceutical properties, sourced from the works of Muanya, 2017, Tilaye et al. 2018, Biswas et al, 2002, Okpanyi and Ezeukwu, 1981, Neuwinger. 2000, Franz and Franz, 1988, Ali et al. 1991), are the following:

Moringa oleifera (the drumstick tree, Odudu oyibo, Okochi egbu, Okwe olu, Okwe oyibo):

This plant is thought to be a natural energy booster, strengthens the immune system, has antibiotic properties, cures headaches, migraines, asthma, ulcers, reduces arthritic pains and inflammations, restricts tumor growth, increases milk production in nursing mothers, and nourishes malnourished children, who gained more weight after the leaves were added to their diets.

Garcinia kola (bitter kola, aku-*ilu* or *ugolo*):

Nigerian scientists have confirmed in clinical settings and in animal models that eating moderate quantities of bitter kola enhances sexual activity, and it has clinically significant analgesic/anti-inflammatory effects in knee osteoarthritis patients. Nigerian scientists have also patented eye drops made with bitter kola for preventing blindness in patients with glaucoma.

Vernonia amygdalina (Bitter Leaf, *onugbu*):

This plant is thought to be an effective treatment for diabetes, cancer, drug-resistant microbial infections. Indeed, a bitter-leaf-based herbal anti-diabetic medication has passed human clinical trials and received a United States Patent 6531461. It is also a phytochemotherapy (treatment based on plant chemicals) for cancer made from aqueous extracts of leaves of Bitter leaf, which has received a United States Patent 6849604. In a study of acetaminophen-induced hepatic damage in mice (DILI = Drug-Induced Liver Injury), bitter leaf extracts protect the liver by eliciting hepatoprotectivity through antioxidation (Tilaye et al, 2018).

Anacardium occidentale (Cashew):

Cashew seed extract has anti-diabetic effects, anti-inflammatory properties, have a beneficial effect on blood pressure, prevents insulin resistance among diabetics, and helps control diarrhea, dysentery and hemorrhoids. It has also been shown that gram-positive bacteria, which cause tooth decay, acne, tuberculosis, and leprosy, are killed by chemicals in cashew nuts, cashew pulp, and cashew shell oil.

Ocimum gratissimum (Basil or *nchuanwu* or *arigbe*):

Arigbe or *nchanwu* leaf is a relatively well-studied herb, with research that has demonstrated that it can radically and speedily improve anxiety and depression and reduce stress. It has also been used for the treatment of headaches, diarrhea, wart, worms, and kidney infections. The leaves of certain varieties of *nchuanwu* are said to contain thymol oil, which is highly antiseptic and also used to prevent mosquito bite.

Irvingia gabonensis (native mango, *ugiri* or *ogbono*):

Ugiri and ogbono seeds help to lower body weight in overweight persons, reduce abdominal fat, lower cholesterol, chances of developing diabetes, chances of developing heart diseases, chances of developing cancer, chances of developing stroke, and chances of developing kidney failure.

Dioscorea bulbifera (yellow yam):

Yellow yams are used in the treatment of piles, dysentery, syphilis, ulcers, cough, leprosy, diabetes, asthma, and cancer. It is a raw material for local contraceptives in Nigeria. In other areas of the world (Asia), they are used externally, usually

as a poultice, to treat wounds, sores, boils and inflammations; in dressings for treating dermal parasitic and fungal infections; or crushed, mixed with palm oil, and massaged onto areas of rheumatism, and for troubles of the breasts and for jiggers. The tuber is used as a diuretic and can be used as a remedy for diarrhea and hemorrhoids.

Prunus Africana (red stinkwood, African cherry, African prune):

African sherry seeds are used to treat benign prostatic hyperplasia (enlargement of the prostate), erectile dysfunction and enhanced sexual vitality, urinary tract disorders, kidney disease, male baldness, stomach upset, chest pain and inflammation.

Adansonia digitate (baobab):

Baobab leaves, bark, and seeds have been used to treat "almost any disease," including malaria, tuberculosis, fever, microbial infections, diarrhea, anemia, toothache, and dysentery. The leaves and fruit pulp have been used to reduce fever and stimulate the immune system.

Hibiscus sabdariffa (zobo):

Hibiscus sabdariffa has been used to treat high blood pressure, liver diseases, and fevers. Hibiscus tea is a mild laxative in large amounts. In Iran, it is a traditional treatment for high blood pressure, which is the focus of several studies, and for cholesterol reduction.

Azadirichta indica (NEEM or *Dogonyaro*):

Dogonyaro has been used for the treatment of malaria, intestinal worms, skin ulcers, diabetes, gum disease (gingivitis), birth control, leprosy, cough, and asthma. Also, the oil is also used for healthy hair, to improve liver function, detoxify the blood, and balance blood sugar levels.

CONCLUSION

According to a UNIDO country profile of the pharmaceutical sector in Nigeria report (2011), the key challenges confronting Nigeria's pharmaceutical market include counterfeit medicines, poor healthcare infrastructure, and the limited spending power of citizens. While foreign pharmaceutical companies operating in Nigeria simply import and market finished or semi-finished drugs, very little basic and applied research is conducted by the Nigerian pharmaceutical industry. Indeed, the lofty goal of sourcing APIs locally has never been realized, despite the academic research conducted in Nigerian universities.

Some of the biggest challenges confronting prospective R&D activities in Nigeria, in addition to the ones identified above, include paucity of capital (Nigerians are more likely to trade in finished commodities than manufacture them locally), the length of time it takes to bring a drug to the market, the challenge of setting up and operating high-quality laboratories for Research-scale operations and scaling such up to commercial manufacturing. Besides, a steady source of reagents that are critical to the operation of a standard R&D facility may not be assured, due to fluctuations in economic policies, uncertainty in the availability of foreign exchange, availability of competent scientists, and technical operators.

Finally, there is an abundance of natural sources of potential pharmaceutical raw materials in Nigeria. The pharmaceutical properties of some plants have been described in the literature in university labs, but adequate attention has not been given to the development of drugs from those raw materials. With the availability of a dedicated workforce and capital, it is possible to establish major pharmaceutical R&D facilities in Nigeria, which would extract, refine, identify, characterize and develop drugs from the medicinal plants that abound in Nigeria. These facilities would produce the active pharmaceutical ingredients needed by pharmaceutical producers. The potential earnings from such an industry could earn enough foreign exchange for Nigeria to dwarf the dwindling receipts from the sale of crude oil. Nigeria and Nigerians would benefit immensely from investment in this area. They only need the discipline to stay focused on the long-term benefits that could result from the effort.

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Emma Onua*, is currently a Senior Research Scientist (Pharmacokinetics & Drug Metabolism) at ELANCO (formerly Eli Lilly & Co Animal Health Division), Indianapolis, Indiana, U.S.A.*