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THE NEED FOR ENHANCEMENT OF RESEARCH, DEVELOPMENT, AND COMMERCIALIZATION OF NATURAL MEDICINAL PRODUCTS IN NIGERIA: LESSONS FROM THE MALAYSIAN EXPERIENCE*.

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Abstract

The use of natural medicinal products in modern medicine as complementary and alternative therapies is of the increase globally. More so in developing and third world countries where the cost of research and development of synthetic drugs is prohibitive and technological facilities as well as expertise are lacking. These, coupled with the crumbling health care management systems in many of such countries make herbal medicines attractive alternatives. The potential medicinal values of these plant products are not being properly harnessed and research and development (R&D) in this area are lagging behind. R&D and consultancy services span from phytochemical analysis, standardization and quality control of herbs, and dosage forms design to preclinical and clinical trials. This paper tries to highlight all the necessary steps needed to conduct research and development in this area and proposes the nitty – gritty needed to impose statutory regulations on ensuring the quality, safety, efficacy, and commercial distribution of such products. The paper examines these important issues and highlights by way of examples, some of the steps taken and the positive achievements of the people and government of Malaysia towards self reliance in the area of natural medicinal plant research. It is primarily intended to map out strategies on how Nigeria in conjunction with research and academic institutions can be actively involved in natural products R&D, taking the Malaysian experience as a prototype. It is also aimed at urging government's efforts to encourage research in this area and impose regulations for commercial production and distribution of such products.

Key words: research, development, commercialization, natural medicinal products, Nigeria.

Introduction

Natural medicinal products are gaining increasing popularity and use worldwide as complementary alternative therapies (WHO, 2003a). Among such therapeutic preparations are plant-derived phytomedicines, nutraceuticals and cosmeceuticals. Reasons for the popularity are multifaceted, based partly on the fact that the raw materials are available naturally and in abundance with an estimated record of 10⁶²⁻⁶³ potentially beneficial substances (Drew, 2000). About one-third of the world's population still lacks regular access to essential drugs, and the figure is believed to be rising to over 50% in the poorest parts of Africa and Asia. Traditional medicine therefore offers a major and accessible source of treatment and continues to play an important role in health care

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management. In many parts of the world, traditional medicine is the preferred form of health care (WHO, 2002), and remains the most easily available and affordable form of therapy in low income countries. It is also a known and disturbing fact that research and development of conventional, largely synthetic drugs, in many developing and third world countries is either limited in scope or non-existent due to the prohibitive costs involved. The average cost of developing a new pharmaceutical drug exceeds \$800 million. These, coupled with the rather poor healthcare management systems in many developing countries, have made the use of herbal and other alternative therapies, attractive alternatives. The industrial revolution of the 1960's led to the proliferation of synthetic chemicals used as drugs. The synthetic drugs have largely supplanted and surpassed the popularity of the herbal medicines as at then. However, due to the skyrocketing costs of these synthetic agents, lack of easy accessibility to the common man, and new advances in natural products R&D, there is resurgence in the use of these natural products. In the developed world, popularity in complementary and alternative medicines and the decreasing attraction to the use of conventional chemosynthetic therapies in spite of availability is partly also traceable to the increasing costs of personal health maintenance (Hoareau and DaSilva, 1999) and to the inherent problems of adverse effects increasingly becoming obvious, especially with longer life expectancy that carries with it the associated risks of developing chronic, debilitating diseases like cardiovascular, diabetic, cancer and mental disorders (WHO, 2002).

The momentum for change in the pharmaceutical industry and the opportunities it provides for integrating compounds isolated from natural products into the discovery process have already been pointed out (Seidl, 1999). In pharmaceutical industries, medicinal plants have now become an integral component of research as they represent an unparalleled source of molecular diversity for drug discovery and development. The synergy of natural-products research and biotechnology will in the near future drive new plant-drug development. In spite of the wide spread use, traditional medicines have not yet been integrated into the national health care systems of many developing countries. To date, no more than 25 countries have an established national policy for traditional medicine, even though regulations or registration procedures for herbal products exist in nearly 70 countries (WHO, 2003a), such as that developed by the Nigerian regulatory agency, NAFDAC (NAFDAC, 2004; Hashim, 2006). Traditional and complementary alternative medicines have developed within different cultures in different regions and there has not been parallel development of methods for evaluating them to meet either national or international standards. Consequently, knowledge of their adverse effect potentials and efficacy is limited hence; strong reservations and often frank disbelief about their acclaimed benefits. For instance, the reported immuno-stimulant effect of traditional medicines and their roles in the fight against AIDS remains controversial.

The increasing use of traditional medicines, the general lack of research, the growing concern by stakeholders vis-à-vis the demands for patenting rights, evidence of safety, efficacy, good quality traditional medicinal products and a range of other ethical issues (Gamaniel and Jsselmuiden, 2004) coupled with the need for integration and maximization of their potential as a source of health care are some of the pressing challenges that must be tackled for acceptable use of traditional and alternative medicines in modern therapeutics. In response to these challenges, WHO has developed guidelines and strategies for traditional medicines (WHO 2000; WHO 2002) to enable this form of health care better contribute to health security. Furthermore, in recognition of the threatened extinction of medicinal plants as a result of continued deforestation, WHO similarly endorses call for international cooperation and coordination to establish conservation programmes for medicinal plants, to ensure that adequate quantities are available for future generations and has similarly drawn guidelines on good agricultural and collection practices for medicinal plants (WHO, 2003b).

Countries like India and China have long been recognized to have fairly well-established practices and policies for traditional medicines that have gained worldwide acceptance and are being practiced along side modern medicines. In America, herbal remedies and dietary supplements with established scientific validation are sold as over-the-counter medications (OTC) and are popular among medical professionals. The European Agency for the evaluation of medicinal products has recently approved guidelines that specify the test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products (EMA, 1999). Medicinal plants constitute a source of valuable foreign exchange for many developing countries and the global market for herbs and medicinal plants runs into several billion dollars per annum. Countries like Bulgaria, Germany, Poland, and others in Africa and Asia are recognized as major exporters of plant-based medicinal products and raw materials for overseas medicinal plant industries (Hoareau and DaSilva, 1999). Plethora of literature has indicated that the global market for herbal medicines currently stands at over US\$ 43-60 billion annually and is growing steadily (Enwonwu, 2003). Over US\$ 2.4 billion Traditional Chinese Medicines were sold and 400 million US\$ worth of Traditional Chinese Medicines were exported out of China in 1993; about 60 million US\$ was realized from herbs in 1996 in Malaysia (Elujoba, 2005). Medicinal plants and other natural substances are an integral component of ethno-veterinary medicine and human health notably in the areas of cardiac, cancer (Cragg & Newman, 2005) and microbial (Ríos

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and Recio, 2005) chemotherapies. The recent development and therapeutic success of plant derived antimalarial, artemisinin, amidst increasing microbial resistance to conventional drugs is worthy of note. Unfortunately, research, development and commercial production of medicinal plant-based products particularly in the developing world are hampered greatly by the absence of essential infrastructure in both the public (such as universities and other governmental institutions) and private sectors, compounded by lack of governmental interest and financial support.

Malaysia is one of such countries whose commendable efforts in natural medicinal products R & D are encouraging and worthy of emulation by other developing nations. The Malaysian Natural Products Society formed in 1994 oversees and coordinates activities relating to medicinal plant research and development and aim to eventually release the Malaysian Pharmacopoeia. The Malaysian government through relevant establishments and agencies is playing a leading and commendable role of financing and encouraging research and development of herbal and complementary alternative medicines. In conjunction with drug industries and other stakeholders, the people and government of Malaysia have laid a very good foundation for the development of this sector and have recorded great successes evidenced by the increasing number of good quality herbal products in the market. The designation of Malaysia as WHO's center for regulatory control in 1996 is an eloquent testimony of their effort and determination to achieve an internationally acceptable standard in the pharmaceutical industry.

Drug Research and Development: Synthetic versus Natural Medicinal Products

Synthetic drug research and development is a lengthy and costly process. It involves the preparation of new drugs from available chemicals for eventual therapeutic application to both humans and animals. The process commences with the use of starting materials that are combined together in a series of chemical reaction processes to form either an intermediate product or the target compound. Both the intermediate and target products can be pharmacologically useful compounds. When subjected to further chemical and structural modifications, they may also bring about new compounds that may prove therapeutically more promising. The starting materials can be inorganic, organic or organo-metallic in nature. Advances in organic, analytical and combinatorial chemistry, as well as robotics have made it possible for pharmaceutical industries to create a virtual library, a computational enumeration of all possible structures of a given pharmacophore from all available reactants. Out of the thousands to millions of virtual compounds, a selection based on established criteria of potentially useful compounds is made for actual synthesis. The syntheses of targeted drug molecules with specific and potentially useful characteristics constitute the Research aspect of Pharmaceutical R & D. The second part, Development, involves making the drug molecule undergo numerous steps of stringent testing for its development into a final medicinal product. For a whole circle of drug R & D therefore, very different skills and capacities are required and include among others, the analytical chemists, pharmacologists, toxicologists, industrial pharmaceutical technologists as well as clinical pharmacists and physicians that would be involved in clinical trials and post marketing surveillance of the prospective drug.

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 long period of time 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.

From theoretical and technical standpoints, the processes of R & D in herbal and natural medicinal products are similar to those employed for modern synthetic drugs. The introduction of modern technology in the commercial production of herbal products has resulted in a paradigm shift from traditional forms of preparations into modern pharmaceutical dosage forms. Herbal medicines are prepared using herbs/plants or parts such as the root, stems, bark leaves, flowers, fruits or the seeds, harvested from the wild or conservation parks. The essential processing steps include inspection, cleaning, drying under controlled temperatures (to preserve active phytochemicals), grinding (size reduction), and extraction of chemical constituents using water and/or organic solvents and fractionation (of pure phytochemicals). Standardization, to which the process of fractionation is part, is a very important step. This process involving isolation, identification and purification of active constituents is a critical step that defines the modern approach to drug development from plants. It enables phytochemists to determine the available constituents of plants, which of them is/are responsible for biological activity and in what concentrations. Sensitive and sophisticated chromatographic techniques such as TLC, GLC and HPLC are required for separation and isolation

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procedures whilst spectroscopic techniques including UV, IR, MS and NMR are employed for structural elucidation. Standardization is vital in ascertaining the consistency of chemical constituents in medicinal plant preparations and by implication their biological potency. Plant tissue culture, functional genomics like transcriptomics, proteomics, metabolomics and other high throughput screening technologies allow the production and testing of thousands of samples at very short time intervals and can also be used in identification and standardization both chemically and biologically of active compounds in complex mixtures (Haylands, 2000; Robert 2005) without reliance on single active ingredient or mechanism of action. Unfortunately, these methods and novel technologies also applicable in herbal drug development, require large investments in equipment and running costs, which are far above the average budgets of local, largely small and medium scale industries (SMI), while multinational pharmaceutical industries having facilities and expertise hesitate to venture into traditional medicinal plant production, because of issues connected to patenting and intellectual property rights (IPRs). It is therefore reasonable to expect that universities and relevant governmental institutions in developing nations, in partnership with indigenous pharmaceutical SMI, would work in concert for research and development of natural products for the benefit of humanity. Interestingly, herbal medications can be produced for consumption in their crude extract forms without having to undergo isolation and preparation of the phytochemical constituents responsible for biological activity. The essential requirements for the commercial production of natural medicinal products are scientific evidence of safety and efficacy as well as good manufacturing procedures to ensure the consumption of safe and qualitative medications. Other desired safeguards would include the enforcement of regulations on storage, product labeling as well as post marketing surveillance to ensure that herbal products are not dubiously adulterated with chemo-active agents and other harmful substances. These recommendations provide ample opportunity for greater diversification of R & D as well as commercial production and application of ethno-pharmacological agents for therapies to help meet the ever increasing health care needs of the world's population, particularly in the developing world, as it has limited the procedural burden of drug development that is time consuming, costly and often futile. This does not however negate the need for the application of innovative and more efficient technologies as expertise and financial resources permit. Distinguished researchers in the field of ethnopharmacology have recommended that for the developing countries, the approval as drugs of standardized and formulated plant extracts might be the starting point of an innovative and successful local pharmaceutical industry, which can compete with the western pharmaceutical companies, not only for the treatment of minor diseases, but also for severe and life-threatening diseases (Pieters and Vlietinck, 2005).

Natural Medicinal Products Research, Development and Commercialization: The Malaysian Experience

Malaysia is one of the South East Asian nations with an estimated population of twenty six million. It is a tropical rain forest zone, a rich source of medicinal herbs and plants and is the world's oldest forest and the fourth most bio-diverse in Asia after India, China and Indonesia. Malaysia is predominantly (59%) under forest cover in spite of the loss of some forest areas to agricultural development and unmanaged timber exploitation (Guan, www.fao.org/documents/show_cdr.htm) and is also rated as one of the 12 countries in the world with wide mega diversity of plants (Herbal Medicine Research Group, 2002). There are an estimated 15,000 known plant species of which 3,700 have medicinal values and have been in use for generations as foods, food additives and traditional therapies (Azlan, 1999). As in many developing nations, the use of herbal medicines in Malaysia is also widespread especially among the rural populace, but the concerns and skepticisms similarly exist about the safety, efficacy and quality of presentations of locally manufactured products due to lack of good manufacturing practices. The apparent shortcomings of modern synthetic drugs especially the lack of success in solving health problems such as cancer and heart diseases have in part contributed to creating the demands for natural products and have resulted in good sales of herbal remedies and dietary supplements in Malaysia.

The Malaysian Government has recognized the great potential of the herbal /natural medicinal products industry in providing competitive advantage to Malaysia towards the attainment of a developed status by the year 2020. The industry is therefore recognized under the Third National Agricultural Policy (1998-2010) as one of the new growth areas to be developed and strategies are put in place for the achievement of these objectives. Among the steps taken was the establishment of the Malaysian Industry-Government Group for High Technology (MIGHT) Interest Group (MIG) in herbal products in December, 1998. MIGHT itself was a government created non-profit organization earlier, under the office of the Science Advisor, Prime Minister's Department, whose initiative is to create smart partnership between the government and industry for the purpose of prospecting and harnessing technology for the domestic and global markets. This partnership, it is hoped would create new business

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opportunities for Malaysia towards the attainment of vision 2020 objectives. For the development of this sector, the MIG in herbal products steering committee was formed with 3 sub-working groups for herbal medicines, herbal cosmetics and toiletries/herbal food and drink respectively. Major issues being dealt with by these committees were: incentives and facilitation of financial assistance for herbal industries, enhancing awareness programs for herbal industries, enforcement of good manufacturing practices (GMP) to meet international standards, long and short term plans on human resource development for the industry, commercial plantations and cultivation of raw materials and enhancing collaboration between research institutions, universities and NGOs in order to increase the level of R & D and technology organization. To improve product development, companies were required to comply with GMP that marches the global market and to use the rich resources available in the country, the implementation of new and improved processing and packaging technologies to produce higher quality products and the use of biotechnology to improve raw materials genetically in the development of new and improved products. The Malaysian Pharmaceutical Industry now consists of manufacturers actively engaged in drug research and development and is capable of producing about 80% of the various categories in the Malaysian Essential Drug List. There are currently 72 licensed drug manufacturers of which 40 are producers of OTC medications including health and food supplements. There are also another 140 manufacturers licensed to produce traditional medicines. All licensed manufacturers have to be in full compliance with the code of good manufacturing practice based on the WHO code. The industry also adopted the PIC code of good manufacturing practice for medicinal products, Malaysia having joined the European Pharmaceutical Inspection Cooperation Scheme (PIC/S) in January, 2002 (14th Asia Pharmaceutical Conference). The establishment of the Malaysian Herbal Corporation (MHC) to assume a catalytic role in promoting and coordinating industry members was a booster to the development of the industry.

A major factor in the push for the development of natural medicinal products industry is the National Pharmaceutical Control Bureau (NPCB), formerly, National Pharmaceutical Control Laboratory, set up in October 1978 under the quality control activity of Pharmacy and Supply Programme. In 1985, the board was empowered to undertake the task of ensuring the quality, efficacy and safety of pharmaceuticals (including natural medicinal products) through the registration and licensing scheme which requires the evaluation of scientific data and laboratory tests on all products before they are marketed. The board receives between 1000 to 2000 drug applications for registration a year and has so far received about 20,000 applications for traditional medicinal products. The Center for Quality Control, a division of the NPCB, consists of two sections namely, the Pharmaceutical Biology and Pharmaceutical Chemistry Testing respectively. The two sections have laboratory units that are well equipped with modern facilities for research in biotechnology, pharmacology, toxicology and pharmaceutical analysis among others. The Ministry of Health through the office of the Director of Traditional and Complementary Medicine oversees the activities of the traditional healers and undertake the regulation and enforcement of laws against the sales of unregistered products.

The establishment of a National Committee for Research and Development in Herbal Medicine (NRDHM) under the auspices of the Ministry of Health in April 2002 by the Malaysian government is another milestone in the planned development of herbal medicine industry. The purpose of the NRDHM is to set directions, coordinate and integrate all clinical trials using herbal products in Malaysia. NRDHM will play an important role in facilitating the government's vision of traditional/complementary medicine (T/CM) coexisting alongside modern medicine in Malaysia (NRDHM, 2002). Since its inception, the NRDHM has published various guidelines on good clinical practice in T/CM research and development. In order to complement and execute the strategy of NRDHM and to bring potential herbal medicinal products to market, the Ministry of Health (MOH) set up the Biovalley initiative with the government investing (in the initial phase), RM100 million (about ₦4 billion) on infrastructural facilities. The initiative consists of a concentration of biotechnology research institutions, universities and companies within the Multimedia Super Corridor (MSC), brought together in a network of collaborations to accelerate the research and commercialization of technologies critical to the development of Malaysia's regional and global competitiveness. Among the first commissioned centers of excellence was the National Institute for Natural Products & Vaccinology (NINPV). NINPV itself along with six other institutes; Institute for Medical Research (IMR), Institute of Public Health (IPH), Institute of Health Management (IHM), Institute of Health Promotion (IHP), Network of Clinical Research Centers (CRC), and Institute of Health Systems Research (IHSR), are part of an umbrella organization, the National Institute of Health (NIH). The NIH, officially opened on August 12, 2003, was expected to focus on clinical trials and commercialization of potentially useful natural products (NINPV), biomedical research (IMR), public health research (IPH), health management research (IHM), behavioral research (IHP), clinical research (CRC) and health systems research (IHSR) respectively. IMR, in conjunction with NINVP have an active collaborative research link in traditional and complementary medicine in the area of High throughput screening, combinatorial chemistry, metabolomics and bioinformatics.

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An important issue in the development of herbal medicine industry is the need for conservation of the country's biodiversity. The Malaysian government's policy on biological diversity launched in April 1998 stressed the need to develop the economic potential of medicinal plant resources through its management in a sustainable manner for the benefit of the society. Fulfilling such a demand would require undertaking concerted initiatives and research efforts to promote conservation and sustainable production of quality herbal plants and products by government agencies, research institutes, universities, private enterprises and local herbal industries (Anak, 2002). Among the principal actors in the conservation efforts is the Department of Forestry charged with the responsibility to give permit/license to enter forest reserves and collect plant species, formation of protected areas, inclusion of medicinal plants in the national forest inventory, management of medicinal plants' park (in Perlis, Pahang, Langkawi etc), as well as Forest Research Centers and Ethnobotanic gardens (in Sabah and Sarawak). Others are the Malaysian Agricultural Research and Development Institute (MARDI), Institute of Development Studies (Sabah and Sarawak Biodiversity Centres) and the Malaysian Department of Agriculture that regulates plants under customs prohibition of exports order of 1998. The Malaysian universities, notably Universities of Malaya (UM), Sains Malaysia (USM), Kebangsaan Malaysia (UKM), Putra Malaysia (UPM) and Malaysia in Sabah & Sarawak (UMS) through the relevant Faculties and multi-disciplinary approaches involving agricultural specialists, botanists, taxonomists, curators etc, are also actively engaged in research and conservation efforts for medicinal herbs and plants. The Forest Research Institute of Malaysia (FRIM) established by the British colonial forest scientist in 1929 and now a statutory body governed under the Ministry of Natural Environment effective from 2004, was also making a significant contribution to the development of herbal drug industry in Malaysia. FRIM in general, promotes sustainable management and optimal use of forest resources by generating knowledge and technology through research, development and application. With effect from 1995, the institute was given the mandate to conduct research on medicinal plants and has established 5 functional units for bioresources, chemistry, bioactivity, formulation and herbal technology. The institute also undertakes collaborative projects in R & D with industries and government agencies including universities on plant conservation and cultivation, processing, ethnobotanical information and chemical analysis. One notable activity of these establishments is the emphasis placed on knowledge sharing and dissemination through regular conduct of national and international seminars, conferences and workshops.

Perhaps the most commendable and far reaching action of the Malaysian government in its resolve for the development of natural product medicine industry is the funding for R & D and the strategies adopted to ensure proper utilization. The funding made available by the government through the Ministry of Science, Technology and Innovation (MOSTI) are: The Science fund, the Technofund and the Innovation fund (The Ninth Malaysia Plan, 2006-2010). The science fund is aimed at supporting basic and fundamental research particularly in universities and institutions of higher technologies. However, collaborations with private sectors are encouraged. Under this, individual researchers can obtain up to RM 200,000=00 (about ₪ 8 million) to cover direct expenses for a period of 2-3 years. The Technofund which is of two types [Pre-commercialization and Intellectual Property (IP) Acquisition funds], is designed for collaboration between researchers in government research institutes or institutions of higher learning with one or more industry partners (Medium/Large Malaysian Companies, Government Linked Companies & Malaysian Public Listed Companies) who should contribute financial or non-financial resources equivalent to 50% of the total project cost, while the government contributes the other 50%. The IP fund comprises acquisition of IP (laboratory scale prototype) from overseas or local sources for further development up to pre-commercialization stage, while the pre-commercialization fund is for the development of commercial ready prototypes/pilot plants/clinical trials/ upscaling for demonstration and testing purposes but not commercial exploitation. Applicants can apply for up to RM 15 Million (equivalent to about ₪ 600 Million) for pre-commercialization and IP fund or RM 5 Million (equivalent to about ₪ 200 Million) for pre-commercialization only. The Innovation fund which comprises of the Enterprise and Community innovation funds respectively is designed (1) to assist individuals/ sole proprietors, micro and small enterprises to develop new or improve existing products, processes or services with elements of innovation for commercialization, and (2) to assist groups to convert knowledge/ideas into products/processes/services that would improve the quality of life of communities. Application for either of the two can attract a funding of up to RM 1 Million (about ₪ 40 Million). Conditions and eligibility and the necessary steps for application and utilization of the funds have been clearly outlined (MOSTI).

Nigeria and the Challenges of Natural Medicinal Products Research and Development

The use of natural medicinal products as a major socio-cultural heritage in Nigeria as in other parts of the world can be traced to the beginning of civilization. It is interesting that the discovery and isolation of the Calabar

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bean's alkaloid, physostigmine in Southeastern Nigeria dates back to 1800s. Hence, drug development and discovery from natural products is certainly not new. According to WHO facts sheets, in Ghana, Mali, Nigeria, and Zambia, the first line of treatment for 60% of children with high fever resulting from malaria is the use of herbal medicines at home (W.H.O., 2006). One classical example is R&D work by some Nigerian researchers from Obafemi Awolowo University on the use of *Zanthoxylum zanthoxyloides* – Fagara in the management of sickle cell anemia, which has shown a great therapeutic promise.

The reemergence of natural products use has rekindled active research and development in many developed and developing nations alike. Unfortunately, however, the current trend of natural medicinal products R&D, use and commercialization in Nigeria is no much different from the primitive age. Although traditional medicine in Africa has come a long way from the times of our ancestors, not much significant progress on its development and utilization had taken place due to colonial suppression on one hand, foreign religions in particular, absolute lack of patriotism and political will of our governments, and then the carefree attitudes of most African medical scientists of all categories on the other hand (Elujoba 2005). This is evident from the trend of research activities in this challenging era, records of unregulated use and commercialization of herbal products, and lack of government commitments. The case in point is the ₦1.9 Billion earmarked in the National Policy on Traditional Medicine Development to be used for scientific, physicochemical and medical researches (including characterization and purification, toxicological studies, clinical trials of herbal preparations, and manpower development) (Nigeria's Policy on R&D, 2002) in the whole of a country like Nigeria with a population of over 140 million and where a large proportion of the African biodiversity is found. Whereas in a country of about 26 million people, a single researcher can obtain up to ₦600 Million equivalent from government for the development of a single natural product to a pre-commercialization stage (MOSTI: <http://www.mosti.gov.my>). It is more surprising to note that the fund estimated for the overall scheduled activities for the R&D of traditional medicine and its integration into the nation's healthcare delivery system is ₦ 4.1 Billion Naira (Nigeria's Policy on R&D, 2002). This is presumably planned to be disbursed to numerous research institutions, universities, ministries, agencies, and professional bodies. Further, there is a reasonable doubt as to the validity of the contention and views enshrined in the National Policy on Traditional Medicine Development as well as by Elujoba and colleagues (2005) on the need for institutionalizing traditional medicine in parallel with conventional medicine as the most workable health agenda for Nigeria. While a national policy on traditional medicines is a welcome development, strategies therein must be geared towards real integration with the orthodox medical practice. Apparently, rather than integration, the policies are aimed at the eventual establishment of traditional medical system of health care that would run in parallel with the modern healthcare system. This in our view is a recipe for conflict in the future. Inevitably, traditional medical practice must succumb itself to modern scrutiny for Integration. Establishing standard regular and consulting traditional medicine clinics and hospitals nationwide will do just the opposite and such integration is beyond the banality of establishing such clinics in all the LGAs of the federation. More importantly, the current direction in medicine is practice based on evidence. In as much as we believe that the natural medicinal products have undergone the due and high-quality research processes, qualifying them to be safe, effective and qualitative alternative therapies, there is no reason not to consider them as prescription products by orthodox medical practitioners.

The major global challenge, particularly in Nigeria is that scientific evidence for the proof of safety and efficacy of traditional medicines, quality standards and regulations are not being developed at the same pace as the demands for the medicines. In spite of the renewed interest, the caveat is that R&D in natural medicinal products is not sufficiently supported and funded by governments as demonstrated *inter alia*. For this reason, the existing safety and efficacy data are grossly insufficient to support the production and commercialization of these products. Given that more than 80% of the population of the African Region uses traditional medicines for their primary health care needs, the 19th session of the African Advisory Committee for Health Research and Development (AACHRD) in 2000, recommended that the Regional Office should revitalize research on traditional medicines, particularly for common and rather pressing problems such as HIV/AIDS, tuberculosis, malaria and childhood diseases (AACHRD, 2002). Furthermore, the Organization of African Unity (OAU) Heads of States declared at the Summit Meetings in Abuja and Lusaka in 2001 that research on traditional medicine should be made a priority and that the period 2001 – 2010 as the decade for African Traditional Medicine. Are these declarations realities or myth? The allocation of financial and other resources for traditional medicine research by the Federal Government is grossly inadequate as outlined elsewhere in this article. The National Institute of Pharmaceutical Research and Development (NIPRD) has the mandates to conduct such researches on medical plants, herbs as well as drug development and formulary. This institute in Nigeria has reported two of the many herbal preparations that traditional health practitioners claim to be effective for the management of HIV/AIDS: Dopravil[®] and Conavil[®] on which phase II clinical trials are being conducted (AACHRD, 2002). Whether adequate research funds are been disbursed by government for the conduct

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of such researches or not is controversial. It is worrisome, however that even after potentially useful researches are undertaken, many come to an eventual standstill and the progress disappears without trace. For instance, a research by a team at the same institute, led to the development of herbal medicinal product called Niprisan®, which is meant for the management of sickle cell anemia (AACHRD, 2002). Reports have shown that the product has reached marketing stage, but to date the huge global market potential of this novel therapeutic agent is yet to be exploited.

Undoubtedly Nigeria has all the national policies on traditional medicine R&D as well as regulations on the control of their manufacture and distribution. Accordingly, the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria is mandated to regulate and control the manufacture, importation, exportation, distribution, advertisement, sale, and use of foods and drugs amongst other things. Has the NAFDAC been able to accomplish these roles with respect to distribution, manufacture, advertisement, sale, and use of natural medicinal products? We see herb sellers on the streets and our markets everyday; listen to radio adverts on traditional medicines; watch traditional medical practitioners aggressively claiming and parading the magical powers of their herbal remedies daily on the TV; and lots of unregulated practices including trade fair staging often with the blind support of the governments. Are these practices outside the confines and definitions of the NAFDAC's regulatory roles? The forgone clearly demonstrates that such existing policies and regulations are grossly underutilized and are not being imposed or implemented.

R&D in the area of natural medicinal products is quite diverse and need a lot of expertise and capacity building. It requires expertise from various scientific disciplines such as phytochemists, pharmacists, ethnobotanists, geneticists, pharmacologists, pharmacognosists, pharmaceutical technologists, physicians and many more. Formulation of herbal medicines, for example, represents a specialized expert area that requires training and experience. Sadly, we are deficient of systematic plans for developing research capacity in traditional medicine leading to lack of a critical mass of natural products researchers including the traditional health practitioners. Further, lack of tools for protecting indigenous knowledge and intellectual property rights (IPR) is one other remarkable challenge in natural medicinal products research and development in Nigeria. This absence of an effective and coherent policy on Intellectual Property Rights (IPR) has stunted inventiveness and creativity in science and technology, because inventors and creators of commercialisable ideas and technologies have reaped little or no direct benefit and reward commensurate to their efforts. Undue advantages of extant IRP laws are being taken by third parties to the detriment of inventors and innovators. This has often discouraged this talented group of Nigerians and/or forced them to take their inventions outside the country (Nigeria's Policy on R&D, 2002). This led to the development of the national policy on IPR a few years ago, but the implementation of this policy is still at its infancy.

The conservation and protection of medicinal plants is not a high priority on the agenda for natural resources management in Nigeria. Government programs give priority to agricultural, forestry and wildlife resources due to the identified potential of such resources in contributing to national development (Rukangira, 2001). The area of medicinal plants is left alone as a niche for traditional doctors. Hence, the challenges of and constraints to natural medicinal products research, development, and commercialization in Nigeria are numerous.

Natural Medicinal Products R&D in Nigeria: The Way Forward

Despite the various challenges enumerated in this paper, Nigeria can still excel in this virgin area if the issues of serious commitment, energy and resource mobilization as well as government's political-will are properly addressed. All Asian countries including China, India and Malaysia started several decades ago from somewhere. Therefore, there is need for rapid enhancement of research, development and commercialization of such natural medicinal products in Nigeria where similar natural forest endowments abound. Looking at the global trend and specifically the Malaysia's experience as highlighted in this paper, it is evidently clear that Nigeria is certainly left behind in natural products R&D. We therefore would use the Malaysia's example as a lesson to proffer feasible solutions. In our opinion, therefore, the followings steps and measures need to be taken with dexterity as inevitable, if any change is to be brought into the system.

Political-will and support of the government of the Federal Republic of Nigeria is of paramount importance in this giant stride. Intensive and unwavering support from government and multinationals through sufficient research grants to support natural medicinal products research, development and commercialization is highly needed. With the various declarations made by the Nigerian government on Roll Back Malaria, 2001 – 2010 as the decade for African Traditional Medicine, it is high time we followed the footsteps of other developing nations as Malaysia in order to earn self-reliance and economic liberation in healthcare supplies and financing. The existing regulations and guidelines on the control of herbal medicines by NAFDAC are not being properly enforced looking

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at the unregulated practices taking place in the country. In order to see meaningful changes, however, we must begin by admitting our shortcoming, predicament and practical realities.

Human and resource capacity building is a necessity in order to have adequate manpower and stimulate active research on natural medicinal products. Efforts have to be geared towards training scientists in research institutes and universities as well as sponsoring individuals with potentially high scholastic abilities for higher degrees and fellowships.

Establishment of a Natural Medicinal Products Research and Development Institute with annexes in some universities would be a successful intervention. The institute's focus should be solely on natural medicinal products and should be tasked with the responsibility of investigating scientific proofs of the medicinal values of all ranges of natural products, undertaking all scientific processes to develop a product. If this intervention seems to be a duplication of one of the roles of the NIPRD, then we would strongly recommend reinvigoration of this function and making the institute more active nationwide in terms of natural products R&D. Hence, research should be conducted to validate claims made on quality, safety, and efficacy of natural medicinal products used for the treatment or prevention of priority health conditions (malaria, tuberculosis, sickle cell anemia, HIV/AIDS, tobacco/drug dependence, malnutrition etc). The W.H.O. has developed a guideline on research methodologies as highlighted earlier (WHO, 2000). This should be judiciously utilized as guidance to the development of our national guidelines that would suit our local situation in Nigeria. The caveat however is that government has to be committed to providing adequate funding for such institutions to be functional. Collaboration with international donor agencies in conducting R&D would also be of utmost significance. Such international collaborations strengthen the existing local institutions and should be vigorously pursued by the Government.

Another strategy to facilitate the development of this industry is collaboration and collegiality in traditional medicine research and development. The traditional medicine practitioners should be educated on the detriment of indiscriminate sale and distribution of herbal products without due research and development processes. The demerits of their unethical and hazardous practices can be circumvented by their integration into a modern system and harnessing all the potentials of natural medicinal products available in Nigeria. Hence, there is need to collaborate with the traditional practitioners and integrate their practices into modern R&D. By so doing, the indiscriminate sale and advertisement of herbal products in all forms of media without compliance to the existing regulations would be abolished.

Large scale cultivation and conservation of medicinal plants and appropriate policy is required for continuity of research, development and commercialization of natural medicinal products. The available medicinal plant resources may be doomed to extinction by overexploitation resulting from excessive commercialization and other artificial destructive influences unless stringent conservation measures are employed. Hence, trainings on Good Agricultural Practices (GAPs) and Good Harvesting Practices (GHPs) should be provided to ensure more sustainable techniques. One important step forward is the establishment of medicinal plant gardens and conservation areas all over the country. Government has to encourage allocation of large scale of lands for ex situ cultivation of medicinal plants. Government should also create conducive environments to protect intellectual property rights and indigenous knowledge on natural medicinal products as enshrined in the W.H.O model tools for African nations. This will contribute to a fair and equitable sharing of benefits.

Finally, the private sectors particularly the indigenous drug industries should be stimulated through incentives and dialogue to invest in traditional medicine research, development and commercialization. Lasting solutions to these challenges can only be found if all stakeholders converge together and work in good faith to bring their specific expertise and experiences towards a common goal and understanding, as illustrated from the Malaysia's examples above.

Conclusion

Research and development leading up to commercialization of modern drugs is a highly expensive venture that is a privilege of few private multinational drug companies in the industrialized world having the resources, expertise and technological facilities. These companies are less inclined to venture into the research and development of natural medicines because of issues connected to patenting and intellectual property rights among others. Local pharmaceutical companies in the developing world that are largely small and medium scale manufacturers, lack the desired expertise and resources. However, for such companies, drug development from standardized plant extracts can be the starting point of a successful research, development and commercialization of natural medicinal products. The development of herbal medicine industry in developing world would provide jobs and stimulate the growth of local and national economies. It will also complement government's effort in meeting

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the health needs of its populace. Governments of the developing nations can therefore play a vital role in the development of traditional medicine industry by supporting research, development and commercialization of natural medicinal products through the execution of carefully planned and workable strategies that would involve the stakeholders, including universities, research institutions and local manufacturing industries. Commendable and potentially promising strategies have been put in place by the Malaysian government for the development of natural medicine industry in the country. These efforts are bound to produce results in not too distant future. These strategies can usefully be employed by other developing nations and in particular Nigeria, to develop this economically viable industry in view of the enormous resources available in the country and the potential this industry has in contributing to the nation's economic and social growth.

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