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Mapping Clinical Evidence of Herbal Medicine for Translation to Clinical Practice in Nigeria: The Case of Anti-Malarial Herbal Medicines

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Abstract

There has been an astronomical rise in the cost of developing drugs in the last four decades. This has had a resultant effect on public health and Nigeria is particularly negatively affected. As the world spends more money on drugs' R&D, the volume of innovative synthetic drugs dwindles. This trend points to the necessity for a paradigm shift in drug development strategy.

Although herbal medicines offer a wide diversity of medicinal properties and have proven to be a boom for therapies, its clinical evidence mapping is largely lacking and thus cannot be integrated into Nigerian public health structures. Also, there is a high incidence ranking of malaria in Nigeria, and clinical evidence mapping of herbal anti-malarias might be the innovation to improve malaria control and elimination programs.

Few or no studies have illustrated methods to engage herbal medicine clinics in Africa and perhaps none in Nigeria on ways to describe and evaluate clinical use of herbal medicines as anti-malarial in patients. Observational clinical studies could be carried out to estimate the efficacy and toxicities of herbal anti-malarias in clinical protocols and thus document any adverse effects. This should provide the needed opportunity to measure patient outcome in malaria patients exposed to the herbal drug in a clinical setting. ***This paper discuses the challenges to drug development in weak and fledgling economies, the dearth of clinical research on herbal anti-malarial therapies and the prospects of herbal clinical research to malaria control and public health in Nigeria.***

Key words: Herbal anti-malaria, Malaria, Herbal medicines' clinical evidence research, Drug development and Public health

Introduction

Works by DiMasi (2001); DiMasi *et al.*, (2003) and the 2011 publication of the Pharmaceutical Research and Manufacturers of America (PhRMA), (PhRMA. 2011) points to the astronomical rise in the cost of developing drugs for three decades (1975-2005). The Food and Drug Administration (FDA) of the United States' approved drugs in 1975 was estimated at an average cost of $140 million for their Research and Development (R&D), $320 million in 1987 and over 1.5 billion by 2005. Meanwhile many nations especially in Africa experienced serious drops in their gross domestic products as poverty increased and the capacity for research funding dwindled. All this have had resultant effects on public health in these countries and Nigeria is by no means an exception.

It has also been noted, [Booth and Zemmel, (2004); Woodcock and Woosley, (2008) and Bunnage, 2011], that while the first worlds which could afford it spent more on drugs' R&D, the volume of new molecular drugs dwindled and as pointed out by PhRMA, (PhRMA. 2011), the year 2010 registered a '20-year low with only 15 New Molecular Entities (NMEs) to receive marketing approval' This trend suggests a necessary paradigm shift in drug development strategy globally and for poor African nations to look inward and evolve new drugs based on age old indigenous health systems.

In Nigeria, this is particularly worrisome as the rapid rise in population and urban settlements is not matched with structured medical facilities to facilitate public health. As a result of this, a large percentage of public health expenditure is based on out of pocket of individuals who can afford it while an overwhelming 85% are believed to depend on traditional medicines which utilize herbal medicines as drugs. Traditional Nigerian Medicines (TNM) has thus been the bedrock of public health in the country. This is not surprising if we consider also that traditional medicine is the global source of many effective medicines. This thus provides Nigeria and indeed Africa a "competitive advantage" as it has very rich traditions of herbal medicine.

This development is not unconnected with government effort for the development of our traditional medicine sector through the establishment of the Nigeria Natural Medicine Development Agency (NNMDA) which has spearheaded advocacy, intellectual property (IP), documentation, training of practitioners on hygienic practices and quality packaging, Good Agricultural and Collection Practices and demonstrations via its pilot production technology and technical assistance.

Most traditional health systems depend on plants for drugs and general health management. Creation history as documented by the Bible suggest that herbs were created for food and healing (Genesis 1:29-30). Herbal medicines therefore abound for the management and preventions of various diseases**.** Although herbal medicines offer a wide diversity of medicinal properties and have proven to be a boom for therapies, its clinical evidence mapping is largely lacking thus cannot be integrated into Nigerian public health structures. It is therefore imperative to carry out clinical evidence mapping of herbal medicines as an aid for the formal translation of our innovative herbal therapies into public health. This requires a deliberate and determined policy to embark on herbal medicines' clinical research.

Conceptualising Clinical Evidence Research of Herbal Medicines

Maiers *et al.,* (2009), noted that healthcare consumers continue to seek-out traditional medicines which include herbal medicines 'for their health and wellness needs'. The WHO, (2013) corroborate this in its report and states that there was "an increasing global trend to incorporate traditional medicine in the healthcare systems of both developed and developing countries to combat chronic ailments for which conventional medicine has not proved efficacious."

At the same time, Maiers *et al.,* (2009), point out that "public health groups and policymakers remain steadfast in their call for quality research in this arena". They further noted that traditional medicines such as herbal medicines, "like other whole system approaches to health care, presents unique challenges to traditional research methodology". This notwithstanding, herbal medicines as compared to orthodox medicines have a comparative advantage in their clinical research as there is cost reduction for conducting clinical studies since the formulations or its components are largely already in use by people within study communities and could be considered to be relatively safe. Also, research strategies have evolved for the low cost conduct of herbal medicine clinical trials Graz, *et al.,* (2007).

Although toxic indications have been severally documented, observational clinical studies could be carried out to estimate their efficacy and toxicities in clinical protocols as the documented history of use in the community would highlight any adverse effects. In fact this is what is required for most of the herbal formulations in clinical use in Nigeria as the standard approach of Randomized Clinical Trials (RCT), may be too risky considering the wide gap in scientific data and evidence to guarantee ethical conduct of such studies. The ISOPOR group (Berger, *et al.,* 2012), noted that health policy researchers increasingly use comparative effectiveness research to guide policy decisions and prospective observational studies have been found to be effective ways of conducting such studies especially in treatment comparison and evidence development in which case the study design is aimed at testing a hypothesis which in this case is to estimate the degree of efficacy and safety of the drug or if it "does more good than harm"

As is widely noted, the peculiar environment of herbal medicines suggest the lack of the critical need to impose the rate limiting step of pre-clinical toxicology of the component constituents of the herbs. Such would be a basic prerequisite for a protocol designed towards the clinical evaluation of a New Chemical Entity (NCE) or single component drugs. However, the wholesale conduct of RCT

with no pre-existing clinical data on an herbal medicine may be pushing ethics of such studies to its limit.

As in the opinion of the United Kingdom Medical Research Council (MRC, 2000), it is a well known fact that Randomized Controlled Trials "is the optimal study design to minimize bias and provide the most accurate estimate of a complex interventions' benefits, however, there are circumstances where such a design is not possible". This appears to be the case in most herbal drugs in clinical use in Nigeria. The authors further suggested that, "If a particular intervention to be evaluated is already widely practiced, a theoretical phase may well not be essential; **the health service already has what is considered a clear understanding of the 'mechanisms of action' of an intervention that is nevertheless to be evaluated"** -(MRC, 2000). This is because, as they pointed out, "it also has to be recognized that, for pragmatic reasons or urgency of answers for public policy, it is not always possible to await clarity from theory prior to evaluation".

In the peculiar circumstance of anti-malarial herbal medicines widespread in Nigeria, clinical use outside standard clinical research protocol design may never provide the necessary clinical data to acquire a "**clear understanding of the so called mechanisms of action"** as suggested by the MRC (2000), so much as to place patients at the full risk of research**.** Also, such lack of clear understanding denies the investigator the needed opportunity to set safety nets and effectively determine exclusion and inclusion criteria. Adverse effects and serious adverse effects which might exist may not have been identified because prior use was not designed to watch out for them and thus could happen unexpectedly and constitute a major crisis for the study team.

Recognizing that the value of herbal medicines in our health system is substantial does not becloud the fact that much remains to be known about these therapies, particularly with regard to scientific studies that might convincingly demonstrate the value of individual therapies hence the need to proceed cautiously and consciously in a responsible manner. This attitude should form the background to the conceptual frameworks of clinical studies that are designed to guide public and policy decision making on herbal medicines to translate the research findings into clinical practice. In doing so, issues that mitigate translation should be addressed on the bases of clinical data as proof rather than assumptions.

Maiers, *et al.,* (2009), notes that historically less emphasis has been placed on research skills and evidence-based medicine in traditional medicine practice clinics as compared to other alternative health care practices. Few or no studies have illustrated methods to engage herbal medicine clinics in Africa and perhaps none in Nigeria on ways to describe and evaluate patients in their clinics. Works such as those published by Xing and Long (2006), on patient characteristics and outcomes carried out in an acupuncture teaching clinic are lacking in African settings and on African healing systems. This is perhaps because traditional medicines' clinics are sparse and were they exist are not structured for evidence based data collection. It is thus difficult to conduct clinical data evaluation to estimate patient characteristics and the medical outcome of various herbal medicines utilized by herbal medicine practitioners.

Xing and Long (2006), suggested that prospective observational studies will serve: "to better assess patient experience and outcome in a practice-based setting". Maiers *et al.*, (2009), pointed to the 2004 work by Osterbauer *et al.,* which: "prospectively collect demographic and outcome data to describe patients seeking care at an acupuncture and Oriental medicine teaching clinic". Conduct of evidence mapping will provide a foundation for data collection procedures by researchers and clinicians in Nigeria.

Clinical research in herbal anti-malarial therapies, its dire necessity and prospects

Prevailing communicable and non-communicable diseases in Nigeria has broken the barrier of the health system which operates by the use of synthetic orthodox drugs. This is because disease prevalence rather than dwindle has persistently outweighed the existing medical infrastructure over the decades. The consequence of this is that loss of life to communicable and non-communicable diseases in Nigeria is an all time high with WHO putting their estimates at 73 and 16 percents respectively, (WHO, 2014 -Nigeria Health profile).

At the same time, it appears that traditional medicine practice has proved efficacious on a one–on–one patient-operator relationship in terms of out of pocket cost/affordability, availability, dependability, trust and social support as Traditional Nigeria Medicine Practitioners (TNMPs) are more amenable to patients than western trained medical doctors who perceive themselves as being in a special social class hence hardly connecting with patients due to very unfriendly behaviour. In the face of this, TNMPs appears to be making effort to upgrade their practice by improving service quality in terms of hygiene and good packaging of herbal medicines for commercialization. The most welcome of this is the appearance in the last two decades of systematic herbal clinics across Nigeria specializing in various practices such as general practice, bone setting/massage therapy, birthing and mental clinics.

Although Nigeria has a heritage of prehistoric use of herbs for management of various ailments, due to the dearth of research and historical documentation on these laudable treatment strategies, there is an embarrassing lack of clinical evidence bases for their use. We lack a systematic and empirical record of the evaluation of these drugs to provide the evidence bases for use. In modern times, usage of herbs in Nigeria like in other countries including the developed world, have increased in the face of modern realities of socioeconomic downturn, resistance to synthetic drugs and advent of new diseases with no known cure (WHO, 2013).

Herbal medicines are available, affordable and accessible and could stimulate economic growth while improving public health in most communities with a further attendant outcome of improved socioeconomic quality of life which could eliminate diseases. Having a cultural origin among the people, herbal medicines are naturally preferable by Nigerians hence encouraging dosage compliance by most patients. Needless to point out that added to the fact that various other cultures globally posses their herbal medicine's heritage, herbal medicines have in recent times gained global popularity and thus in widespread use but with peculiar challenge of dearth of evidence bases for clinical use except for a few nations which have taken this challenge and made deliberate effort to carry out clinical research to generate such needed evidences allowing clinicians to confidently prescribe herbs in clinical settings aside from rural communities.

It is therefore imperative at this period of our socioeconomic and medical realities to embark on clinical research on herbal medicines in what could be termed 'Clinical Therapeutic Efficacy Studies' (CTES) and evidence mapping on herbal medicines/products used in the management of various ailments in clinical settings.

As a result of the high incidence ranking of malaria among the communicable diseases in Nigeria (WHO, 2014 –Nigeria Health profile), the clinical therapeutic efficacy studies and evidence mapping of herbal anti-malarias could be considered innovative, an urgent priority and imperative for the improvement in malaria control and elimination programs. Malaria is a national challenge in Nigeria requiring dire intervention. The WHO documents that Nigeria uses herbal medicines in 60% of cases of early febrile diseases perceived to be malaria (WHO, 2003). Also, in the few systematic herbal medicine clinics across Nigeria and the many treatment homes existing in almost every hamlet, malaria and febrile conditions are the most encountered diseases by TNMPs.

According to the WHO, (2014), malaria incidence (severe *falciparum* malaria -WHO, 2000) ranks highest among communicable diseases in Nigeria. This is worrisome as the issue of malaria drug-resistance to artemisinin-based combination therapy again appears in the horizon as indicated in the Greater Mekong Sub-region of South Asia. The WHO has indicated that drug efficacy studies have detected resistance of *Plasmodium falciparum* to artemisinin in the Greater Mekong sub-region of South-East Asia, (WHO, 2014). Although this may not be the case in Nigeria as the clinical and parasitological efficacy of artemisinin combination therapy (ACT) was earlier reported not to have been compromised (WHO, 2010). However, resistance to malaria drug by its parasite has been identified as an obstacle in the battle against this deadly disease as it threatens efforts and improvement in malaria control and elimination programs (Takala-Harrison *et al.*, 2014). Even though P. *falciparum* resistance to artemisinins is not yet a widespread phenomenon, this initial report is a sign of the things to expect in the future and the strategy to stem the spread of drug resistance includes development of novel drugs.

Due to widespread parasite resistance to Chloroquine (CQ) and subsequently, Sulphadoxine-Pyrimethamine (SP), all malaria-endemic countries in sub-Saharan Africa had adopted artemisinin-based combination therapy (ACT) as the first-line drugs for the treatment of uncomplicated *P. falciparum* (WHO, 2010). Artemisinin resistance has not yet been documented on the African continent (Taylor *et al.,* 2014), but the emergence of the reduced sensitivity to artemisinin in focal areas of South-East Asia prompts global concern (Dondrop *et al.,* 2009) and it will be appropriate to begin to look inward in a deliberate effort to evolve our own home grown solution to a home-based problem. This is more so that WHO (2015), indicate a widening of the artemisinin resistance and confirmed "Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam" as resistant. They further state that "along the Cambodia-Thailand border, *P. falciparum* has become resistant to almost all available anti-malarial medicines. There is a real risk that multidrug resistance will soon emerge in other parts of the sub-region as well"

There is a widespread practice among Nigerians to self medicate in febrile conditions. Such presumptive treatment with the current first-line drug, artemisinin-based combination therapy (ACT), for suspected rather than confirmed malaria cases may further lead to rapid development of drug resistance. Being a health indicator country, (life in sub-Saharan Africa is largely dependent on the social situation in Nigeria owing to its large population and constant movement of people in and out of the country), malaria drug resistance in Nigeria could imply an Africa-wide resistance. Since herbal medicines offer a wide diversity of medicinal properties and have proven to be a boom for malaria therapy in Nigeria, its clinical evidence mapping becomes imperative to make ready for the next treatment failures associated with drug resistance in the sub-region. Needless to point out that the central core of malarial therapy over the ages have been herbal medicines either as direct drugs (quinine and artemisinin) from *Cinchona officinal is* and *Artemisia annua* respectively or as models from which synthetic drugs (e.g. chloroquine) has been made.

The works of Willcox (1999) and Wilcox et al., (2011) is somewhat pioneering in the clinical evaluation of anti-malarial herbal medicines in Africa. These works yielded anti-malarial herbal drugs in Uganda and Mali respectively. The approach suggested and adapted for these studies is considered to be cost effective, resource conserving and time effective, (Graz, *et al.,* 2005; 2007). One of the herbal drugs, AM, was reported by Graz, *et al.,* (2009), as government-approved in Mali hence "could be tested as a first-line complement to standard modern drugs in high-transmission areas, in order to reduce the drug pressure for development of resistance to ACT, in the management of malaria". They further indicate that "AM may also constitute a first-aid treatment when access to other anti-malarials is delayed".

On the socioeconomic front, Graz *et al.,* (2010) noted that clinical data of herbal medicines aside from providing 'treatment quality index' also have 'local sustainable development implications'. The authors suggest that the gains of developing healing drugs from indigenous and local resource extends to 'improvement in population health', 'stimulus to local economy' and "create a corpus of knowledge that helps patients to make their choice among the very numerous traditional medicines".

Conclusion

Herbal anti-malarial clinical evidence mapping will provide health operators the evidence basis for utilization of the anti-malaria such as information on safety/efficacy and point in the direction of the next probable anti-malarial drug. While enriching the world's arsenal against the plasmodium parasite, it prepares nations to deliberately work for the preservation of such herbs and the ecosystem where they flourish.

The outcome of such studies would provide the needed evidence bases for prescription and use of such drugs, define their safety nets in terms of predictable adverse effects and thus enhance the acceptability and dependability, provide opportunity for a holistic development of indigenous and cost effective solutions to the menace of malaria, and provide the impetus for the incorporation of Herbal Medicines into our Primary Health Care through randomized clinical trial.

Health is a factor of the economy. This is not just because a healthy population carry out activities that build the economy but that if the resource of good health is indigenous, the population will spend less on health while at the same time exploiting the value chain of the health resource to further

improve their economy. Since herbal medicines originate from the biodiversity, dependence on it will stimulate a conscious effort towards maintaining a balance in the ecosystem which could wholly eliminate ill health. Therefore, clinical evidence mapping of herbal anti-malarials could be perceived as a strategic single action to control malaria, improve the economy and conserve our biodiversity.

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