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RESEARCH ARTICLE

A PREDICTIVE MODEL FOR ETHNOMEDICINAL DISCOVERY RESEARCH- A NIGERIAN CASE STUDY

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ABSTRACT

Using a model parametrically dependent on a number of research factors we have examined the relationship between ethnomedicinal drug discovery research in Nigeria and the goal of advancing drug candidates into preclinical evaluation. Our investigation covered a 13-year period and involves several ethnomedicinally relevant plant materials. The employed qualitative model utilizes model scores in assessing research quality and the chances to attain preclinical testing. Based on the model, the research methodologies were found to focus on highly rudimentary tools involving crude extraction, which the model indicated as a vital disadvantage. The existence of foreign collaborations as well as the number of such collaborations was found to improve model score and as extension the likelihood to generate candidates for drug development.

Key words: Ethnomedicine, Drug discovery, Natural product drug discovery, Model score, Drug development.

INTRODUCTION:

The discovery of new drugs represents the basis upon which the pharmaceutical company and most clinical management of diseases rests [1]. However, the rising cost of developing a new drug together with tightening drug regulatory policies, is mounting pressure on Pharma industries to evolve cost-effective ways of bringing new drugs to the shelves [2-6;6-8]. For instance, this has led to the emergence of virtual screening and other computer-aided drug design methods [4;9-19]. In virtual screening, a rules-based physicochemical filter is used to exclude unlikely candidates from the chemical library [12-16]. This significantly reduces the cost of synthesizing the compounds and performing high through-put assays; it is typical to have the library reduced from a million compounds to a few hundreds which are then screened in wet lab[13]. Apart from virtual methods to drug discovery, pharmaceutical companies are also increasingly either outsourcing the discovery phase or buying off promising projects from smaller institutions [20-23]. In the end however and in any case, the success of a development project vitally depends on the identification of suitable lead compounds that survive the discovery pipeline into preclinical trials [22]. The continued survival of the pharmaceutical world and most of our clinical apparatus depends on the discovery of new drugs 1) for the management of incurable diseases 2) to confront the resistance development, and 3) to improve upon existing chemotherapeutic agents.

For decades, ethnomedicine has continued to constitute a viable source of new leads for drug development [23-31]. Vincristine from *Catharanthus roseus*, quinine from Cinchona, reserpine from *Rauwolfia serpentina*, artemisin from *Artemisia annua*, paclitaxel from *Taxus brevifolia* are but few examples of its substantial contribution to modern drug use. It was estimated that roughly 80 percent of existing drugs are either wholly or partly derived from plant sources [31]. These phytochemicals represent millions of years of evolutionary synthesis, which partly explains the chemical complexity that often renders them intractable for synthetic chemistry, but that also underlies their diverse pharmacological actions spectrum [24;32-38].

The use to which ethnomedicine sources are subjected often depends on the quality of effort one is willing to invest to arrive at the medicinally useful principles. In the prehistory of modern medicine, plants were used in raw forms in local formulations relying on crude extraction[39]. Developments in pharmacology and chemistry in the first half of the 20th century encouraged the isolation and synthetic modification of the active principles, as well as their pharmacological profiling[40]. By functionalizing the isolated active compounds it became possible to improve upon the isolate's

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pharmacological profile. The resulting optimized molecules can then pass through preclinical and clinical developments before being licensed for human use after sufficient proofs have been demonstrated for its safety and efficacy.

In other words, to make the most of an ethnomedically important plant, it is often helpful to have its active principles identified, isolated and characterized. While most of the world's developing countries as represented by Nigeria are richly endowed with rich flora and biodiversity, the local research communities have yet to translate this natural endowment into new drugs. In the present article we have investigated how factors surrounding the conduct of ethnomedicine-based drug research in Nigeria help to predict the possibility of advancing drug candidates to preclinical trials.

In modern day science, following the identification of the ethnomedicinal importance of a plant material, drug discovery efforts usually follow an activity guided extraction path beginning from the crude extracts to the identification of the most active and safest metabolite. Here, plant selection is either based on the widespread use in indigenous traditional medicine, or as a part of an exploratory research.

In the simplest sense, once the plant material is collected, appropriate extracting solvents especially capable of solubilizing a broad range of compounds (e.g. water and methanol) are selected to obtain the crude extract. The unstated goal of crude extraction is usually to get as many and as much present metabolites into the solvent medium. The crude extracted is then tested for biological activities which may involve testing against batteries of physiologic or pathologic model systems. The crude extracts typically contain tens and hundreds of different chemicals, with activities ranging from beneficial, to toxic, to *inert*. Drug discovery research aims at optimizing the beneficial biological properties while eliminating toxicities. Subsequent fractionation using chromatographic setup (for example) separates the components along polarity/solubility line. Structure-determination tools such as the nuclear magnetic resonance (NMR), mass-spectrometry (MS), and x-ray crystallography are then employed in determining the chemical identity of each fraction. Repeating the biological assay at each step helps to track the activity of interest from the crude extract, usually with the weakest activity, to the pure isolate which is expected to demonstrate enhanced activity devoid of pharmacologic noise from other compounds present.

Depending on prevailing factors, the active isolate can serve as a new lead. By performing limited modifications on the parent compound, a lead series results useful in generating structural-activity relationship (SAR). This can also permit patent filing. Further lead optimization may be required to render the compound of interest more drug-like, for example, to improve its oral bioavailability, central nervous system penetration and other DMPK properties. The resulting drug candidate is then ready for preclinical evaluation.

From the above a model can be designed for quality assessment of discovery research. The logic is simple and can be captured in this relationship: discovery research terminating at the crude extract stage is less likely to produce new drug candidates than one that advances to the generation of a lead series for SAR. In this work we have generated a logical model to score such implicit probabilities encapsulated in the conduct of ethnomedicinal research using data from Nigeria. Our model additionally suggests ways to improve on ethnomedicinal drug discovery research in Nigeria.

In the model represented by the scheme labeled "Stages in drug discovery from ethnomedicine" (figure 1), the discovery process begins with the identification of the ethnomedicinal value of a plant material associated with a model score (MS) 1, and ends with the achievement of at least one drug candidate (MS 8) that can progress into preclinical trials. In MS=2, 'Extracts', refers to the use of crude extraction methods which after subjection to further separation as obtained in partitioning with solvent systems attains MS 3. At stage 4 the chemical identity of the activity principle is determined, which can be chemically modified (MS 5) for SAR data. The *best* derivatives constitute the leads which may require further modifications ('Lead optimization', MS 7) to enhance druggability to qualify for preclinical evaluation (MS 8). It follows therefore that the higher the score attained, the more advanced the discovery research, and the closer the discovery research is in delivering candidates for preclinical testing. Higher model scores are secondarily an index against which one can estimate researchers' commitment to finding new drugs, or at least their success at realizing such commitment. To determine the MS for the analyzed research investigations we carefully examined the methodologies as well as the results.

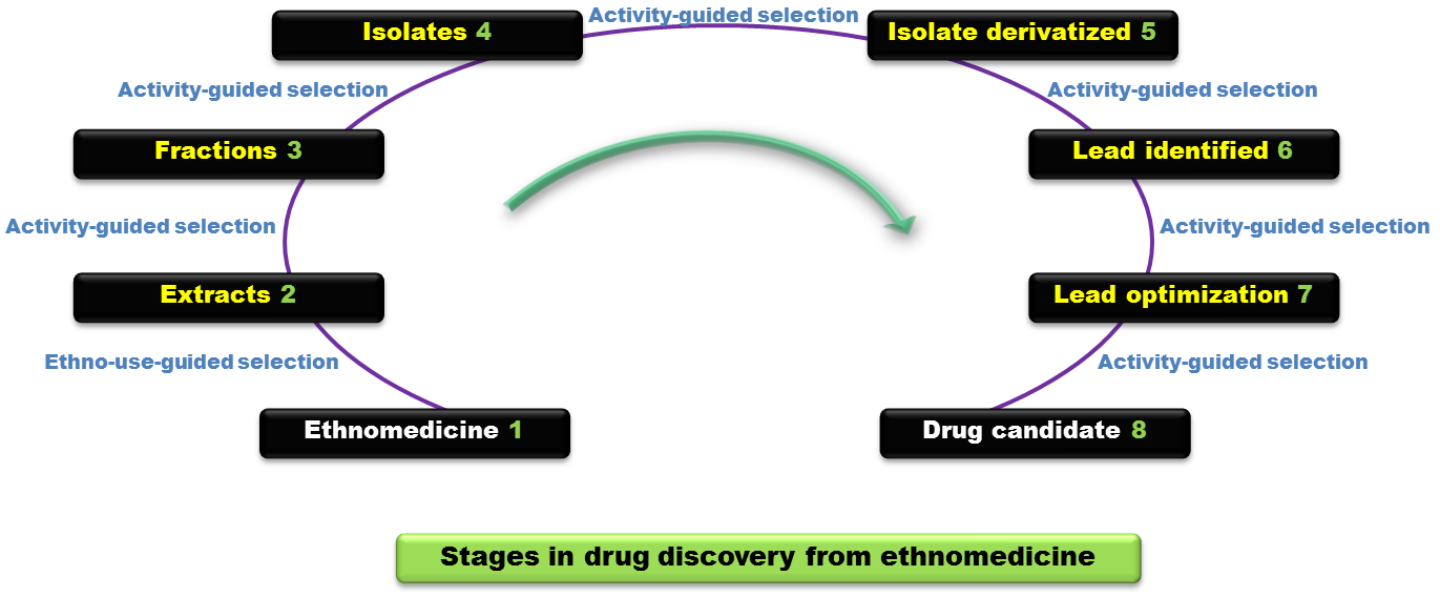

Figure 1: Stages in ethnomedicinal drug discovery research by model score.

MATERIALS AND METHODS:

Data gathering utilized the PUBMED (www.pubmed.org) as target research database which was filtered with two search terms- "Nigeria", and "Plant" applied to all fields. While no time limits were employed, the target literatures were required to have full articles available. The returned articles were downloaded and analyzed focusing on the institutional affiliations of researchers, the employed research method, and the results. Lastly, a list of investigated plant materials was generated and the recurrence rates studied.

RESULTS:

The performed PUBMED search returned a total of 110 unique research publications; the present analysis was based on 107 found to be relevant to the subject matter of ethnomedicinal drug discovery. The examined data covered a 14-year period from 2001 through 2014 fifty-percent of which was published in three years-2011, 2012, and 2007 (figures 2 and 3).

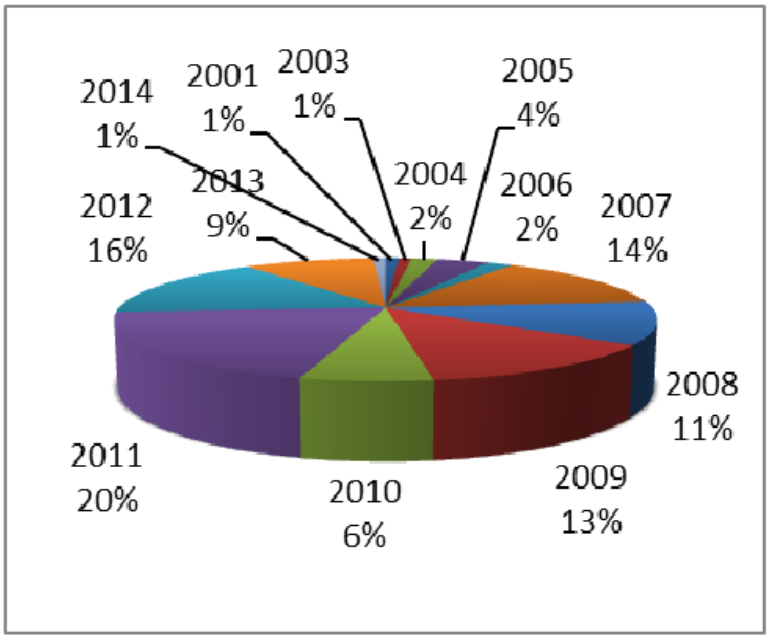

Figure 2: Data spread. Shows the distribution of ethnomedicinal drug discovery researches conducted in Nigeria as a function of publication year.

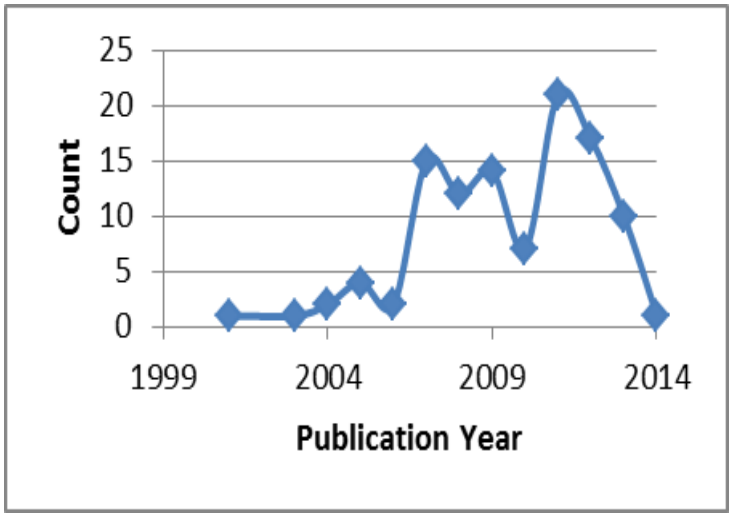

Figure 3: A representation of publications indicating yearly variations.

Analysis of how the ethnomedicinal researchers performed on the MS scale revealed that 80 (~75 %) out of the 107 examined data attained MS 2 as the highest score, while 19 (~18 %) made it to MS 3 (figure 4). Only 6 %, however, progressed to MS 4 while two publications did not progress beyond MS 1 representing mere awareness of ethnomedicinal use. Scores higher than MS 4 were not observed in the data set.

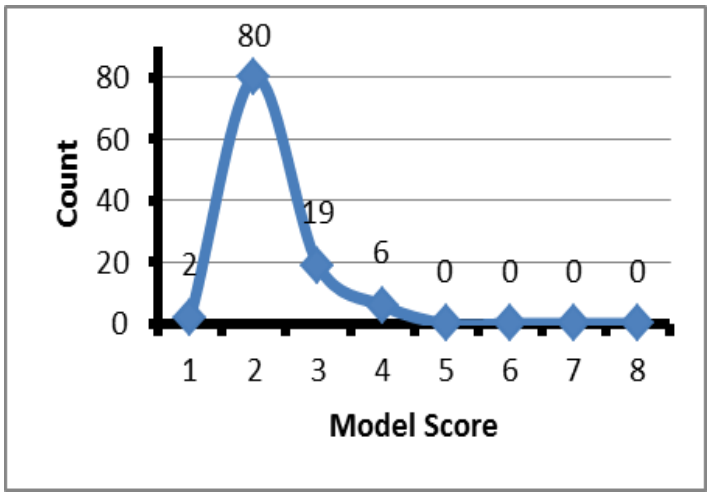

Figure 4: The distribution of model scores attained in the analyzed ethnomedicinal research data.

We next examined the influence of foreign collaboration (FC) on the attained model scores. We defined foreign collaboration institutionally rather than by the nationalities of participating researchers. For instance, research articles featuring a Nigerian researcher who was affiliated with a foreign institution was considered as representing a foreign collaboration since foreign resources were available for the discovery project. (The initial selection criteria for the 107 analyzed data had required that at least one Nigerian institution must be represented in the research effort.) The number of such FCs were analyzed and correlated with the model scores. The obtained number of foreign collaboration range from FC=0 for no foreign collaboration, to FC=4 representing the maximum number of foreign collaborators. To suitably compare the relationship between attained model score with FC, we normalized the counts by dividing with the total number of analyzed investigations under each FC grouping. Figure 5, presents the variation of model scores with the number of foreign collaborators. With no foreign collaborators (FC=0), the analysis peaked at MS 2 with normalized research count of 0.8 while only 0.13 count was recorded for MS 3 and 0.04 for MS 4. With FC=1, normalized count increased to 0.14 and 0.07 for MS 2 and MS 3, respectively. At FC=2, peak for MS 1, MS 2, and MS 3 became 0.40, 0.40 and 0.20 respectively. With FC=3, the data trend peaked at MS 4.

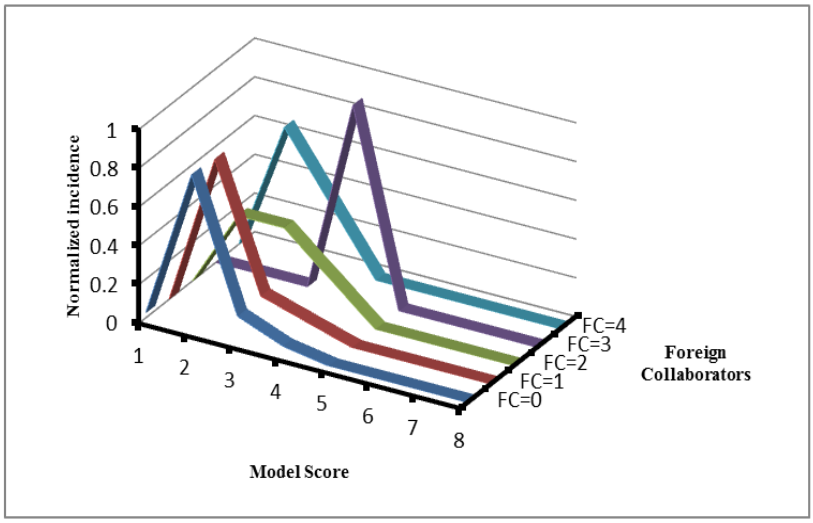

Figure 5: A 3D graph showing the influence of foreign collaborations on the overall quality of ethnomedicinal research as indicated by the attained model scores

DISCUSSION

As already mentioned, data covered a 14-year period from 2001 through 2014 (Figure 1) with the fewest number of publications recorded in 2001, 2003, and 2014. Data for 2014 understandably represent an incomplete set since data collection took place in the early part of the year. The annual growth rate revealed a general trend characterized by multiple peaks and depressions and ultimately peaking in 2011. The first peak was observed in 2005 followed by a trough in 2006. A substantial rise was seen in 2007 and 2009 with a saddle point in 2008. The next peak, the highest point, was recorded in 2011. Oddly, all the peaks were recorded in odd-numbered years… The trend of rise in the research reveals an erratic growth perhaps suggesting the absence of an organized and sustained commitment to drug discovery, as might have been suggested by a linear pattern of growth. The erratic nature could also reflect changing funding structure and the underlying policies affecting drug discovery research. Since the 2011 peak in 2011, research publications into ethnomedicine have suffered a sustained downward trend that has persisted through the end of 2013.

80 (~75 %) out of the 107 examined publications attained MS 2 as the highest score, while 19 (~18 %) attained MS 3 (figure 3). Approximately 6 % progressed to MS 4 while two publications did not progress beyond MS 1 representing mere awareness of ethnomedicinal use. Scores higher than MS 4 were not obtained in the investigated researches. The observed pattern in score distribution suggests that a disproportionately large amount of resources and attention are focused on crude extracts with the studies discontinued at MS 2 for different reasons. In the most common instance, insufficient funding and the absence of the expected activity may cause the termination of a project at MS 2. In addition, the pattern may also indicate an underlying publications-centric attitude whereby the main aim is to turn out publications. And since it is easier, cheaper and faster to attain MS 2, more publications can be published by strictly sticking to the crude extraction stage in each project. This however contrasts with a discovery-centric attitude in which the aim is to solve specific scientific problems and not merely generating research articles in quantities.

We next examined the influence of foreign collaboration (FC) on the attained model scores. We defined foreign collaboration institutionally rather than by the nationalities of participating researchers. In other words, research articles featuring a Nigerian researcher but affiliated with an institution outside Nigeria will be considered as having a foreign collaboration since foreign resources are available to such project. The number of such FCs were analyzed and correlated with the model scores. It is also worth noting that all 107 research articles investigated included at least one Nigerian institution, a criterion that qualifies them as Nigerian research in the first place.

The obtained number of foreign collaboration range from FC=0 for no foreign collaboration, to FC=4 representing the maximum number of foreign collaborators. To suitably compare the relationship between attained model score with FC, we normalized the counts by dividing with the total number of analyzed investigations under each FC grouping. Figure 4, presents the variation of model scores with the number of foreign collaborators. With no foreign collaborators (FC=0), the analysis peaked at MS 2 with normalized research count of 0.8 while only

0.13 count was recorded for MS 3 and 0.04 for MS 4. As the number of foreign collaborators increased, an interesting trend began to emerge as the distribution began tilting towards higher MS values. With FC=1, normalized count increased to 0.14 and 0.07 for MS 2 and MS 3, respectively. At FC=2, yet greater tilting towards higher MS values resulted with MS 1 reducing to 0.40 while MS 2 and MS 3 increasing to 0.40 and 0.20 respectively. At FC=2, the distribution was bimodal with peaks at MS 2 and MS 3. The tilting pattern increased and eventually peaked at MS 4 with FC=3. (With FC=4, there was a reversal in the tilt direction peaking again at MS=2). In other words, as foreign collaboration increases ethnomedicine-based drug discovery research climbs higher the discovery ladder as assessed by the model score. This may be as a result of the increased access to better experimentation resources such as structure determination tools. Collaboration may be an evidence of the existence of a stronger commitment to drug discovery in which case the attainment of more milestones in the discovery path evidenced by the tilt pattern of the distribution can be interpreted as a non-accidental outcome. In any case, based on the data set analyzed, foreign collaboration increases the quality of ethnomedicinal drug discovery research in Nigeria, and as a result the potential to birth a candidate for preclinical development.

Drug discovery research is a highly expensive further compounded by the associated high attrition rate. In order to understand the major forces affecting ethnomedicinal drug discovery research in Nigeria, we have analyzed relevant researches published over a period of 14 years. Our analysis shows an erratic trend in the growth of drug discovery research in spite of the increasing health challenges uniquely facing different African sub-regions. We suggest this to be a product of the absence of adequate research funding backed up by a definitive commitment towards ethnomedicinal drug discovery research.

Using a logical model to assess the potential of the Nigerian discovery research to deliver new drugs to the clinic, our analysis indicates that the widespread publication-centric attitude may be an important mitigating factor against successful discovery research. The leads to the premature termination of promising research projects at the level of crude extract where it is difficult to objectively capture the complete pharmacological essence of the medicinal agent. This sharply contrasts with a problem-centric attitude focusing on identified disease areas and is strictly committed to advancing each project to preclinical and clinical developmental phases.

In certain instances studied, the observed pattern causes the repetition of research efforts whereby different research groups investigated the same plant and up to the same model score stage. 24 plants were observed to have been investigated more than once (some up to five times): with MS value generally remaining at 2, such repeated efforts can hardly be suggested to have any direct impact on research quality. Our investigation additionally suggests a positive impact of foreign collaboration towards the attainment of quality in the conduct of ethnomedicinal research in Nigeria. We believe this is a result of increased access to research equipment and know-how not immediately available in Nigeria, or only available at prohibitively high cost to individual researchers.

In conclusion, in order to make good use of the abundantly diverse plant resources that richly adorn the African clime, it is important that both government and private bodies push for a clear-cut commitment towards quality ethnomedicinal research. Such commitment towards quality should necessarily consider ways of encouraging participation in researches that tackle specific health problems in the country. One way to achieve this is to dedicate grants to specific disease areas and having unambiguously defined milestones and expected research endpoints. For instance, funded postgraduate theses can be beginning to be advertised with clear-cut research objective. This has the advantage to encourage pragmatism and promote the expenditure of research resources in disease areas immediately relevant to the country's needs. This also prevents mere academic exercises having no social advantage than the conferment of the degree on the researcher. The administrators of the limited available funding should therefore associate each grant with the solving of specific research problems.

The highly complex nature of drug discovery calls for high-level collaboration between different disciplines. In particular, collaborations should be encouraged between different institutions both local and foreign. Our analysis revealed a positive influence of foreign collaboration in promoting research quality. By encouraging such interactions, for instance via travel grants and by requiring foreign collaborations as a precondition for granting of certain research funding, the quality of ethnomedicinal research in Nigeria can be improved. Lastly, to avoid re-inventing the wheel and thus the wastage of the available highly limited funding, the setting up of a national body for drug discovery research is encouraged. Such body will set up a national drug discovery data repository for research investigations, the model score attained, and recommendations for

continuance. Rather than repeating previously conducted research, an investigator will only need to inspect the repository to avoid research effort duplication and to allow the focusing of available resources on advancing each project towards preclinical research stage.

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