



Medical Herbalism and Herbal Clinical Research: A Global Perspective

Sunday J. Ameh^{1*}, Obiageri O. Obodozie¹, Peace C. Babalola² and Karnius S. Gamaniel³

¹*Department of Medicinal Chemistry and Quality Control, National Institute for Pharmaceutical Research and Development (NIPRD), P. M. B. 21, Garki, Idu Industrial Area, Abuja, Nigeria.*

²*Department of Pharmaceutical Chemistry, University of Ibadan, Ibadan, Nigeria.*

³*Office of the Director General, NIPRD, Abuja, Nigeria.*

Review Article

Received 23rd May 2011
Accepted 6th June 2011
Online Ready 23rd June 2011

ABSTRACT

This review aims to sensitize researchers, regulators and other stakeholders to the centrality of clinical research to drug development from herbs used in Traditional Medicine (TM). The review uncovered and dwelt on the fact that: While clinical trials of chemical medicines (pharmaceuticals) tend to come late in the drug development chain, the reverse is often the case with herbal medicines (phytomedicines). Once the decision is made to develop a single phytochemical entity (phytopharmaceutical, example: artemisinin) from a plant, the need for such sensitization is particularly desirable, given their huge socioeconomic implications. The review emphasized that drug development from a traditional herb can: i) take the route of standardization of the herb or its extract for immediate use without further chemical manipulations; or ii) proceed along the line of isolation and other manipulations aimed at optimising bioactivity. By the first route, development proceeds directly from confirming that the pharmacological property of the herb tallies with its traditional indication, leading instantly to value addition to traditional knowledge accumulated over years. This is because herbal medicines based on time tested traditions need not undergo phased trials as would a novel pharmaceutical (or an old herb for a new indication), since their long histories often offer evidence of their safety and efficacy. In the second route, clinical studies usually come later in the chain. This is because, unlike the traditional therapeutic, the new phytopharmaceutical, taken out of its natural microenvironment and subjected to various chemical manipulations, including purification, is no longer the equivalent of the ancient remedy with predicable effects. Moreover, in this later case, interest in the new entity (an artificially concentrate

*Corresponding author: Email: sjtodo@yahoo.com;

isolate) may shift completely from the traditional indication of the herb, hence the need for phased trials of phytopharmaceuticals (or an old herb for a new indication), despite their natural origin.

Keywords: Medical herbalism; Traditional Medicine; drug development chain; phytochemical entity; pharmaceutical medicine; phytopharmaceutical; traditional indication; clinical research.

1. AIM OF THE ARTICLE

An earlier article on “current phytotherapy” dealt with the global history, science and regulation of herbal medicine (Ameh et al., 2010a). Another on the same subject accounted for interregional differences in policy, research and development of herbal medicine (Ameh et al., 2010b). The present review concentrated on what is, or should be, the proper sequence of events, starting from the discovery of an interesting ethnobotanical remedy, right up to its commissioning for use in modern clinical practice. The review is necessitated by the fact that a great deal of anxiety and questions still surround the events that should take place to assure the safety and efficacy of herbal medicines. To start with: What is an interesting ethnobotanical remedy? What are the immediate laboratory tests that need to be conducted on such a remedy? What is a clinical trial, and what constitutes such a trial in TM? When is such a trial needed, or when is it probably uncalled for? Given the growing worldwide popularity of herbalism, are the strategies currently in place for regulating the practice adequate? In the US, deliberations over the legal status of herbal products led to the Dietary Supplements and Health Education Act (DSHEA) of 1994. Similar deliberations in the EU, led to the Traditional Herbal Medicinal Products (THMP) directive of 2004, which stipulated that with effect from April, 2011, all herbal products making medicinal claims must be registered in accordance with that directive. Similar moves had been made in many industrialized economies, where herbal medicine, though growing rapidly in popularity, is less widely patronized than in the poorly industrialized. In these later countries, where herbalism is the dominant mode of clinical medicine, but where the skill and the will for herbal drug regulation are weak or non-existent, what needs to be done? Although reports on herbal clinical trials are not lacking in the literature, most of what is on record merely sketch the periphery of some of the issues raised and addressed in this article. It is noted that the various herbal traditions have their roots in diverse cultures that have not all been fully studied, and that some aspects of traditional technologies are still perpetuated only in anecdotes rather than in formal scientific media. It is further noted that while many original research articles on herbal remedies may not (or need not) meet publication criteria in mainstream medical journals, such studies may still provide useful data and ideas for further study. The review reemphasized the fact that a thorough literature survey, as attempted here, should always be the starting point for any serious plan to embark on medicinal plant research and herbal clinical trials. This approach will help to save time and cut the cost of needless effort at reinventing the wheel – the major obstacle to drug development from TM remedies.

2. INTRODUCTION

2.1 What is Medical Herbalism?

Medical herbalism, or simply, herbalism or herbology, is “the study of herbs and their medicinal uses”. This definition can be extended to include the cultivation, collection, or dispensing of aromatic plants, especially those considered to have medicinal properties. Other terms substituted for medical herbalism, include: herbal or botanical medicine, or phytotherapy, previously defined as “the use of plant materials to prevent and treat ill health or promote wellness” (Ameh et al., 2010a). It had been noted that the practice dates to antiquity, and that the primacy of herbalism in medicine is evident from the large number of modern drugs that owe their origin to ethnobotanical remedies. It was further noted that while plants synthesize a large variety of secondary metabolites in response to various ecophysiological stimuli, most of such metabolites originate from a relatively few biosynthetic pathways that include the pathways for alkaloids; terpenes/ terpenoids/ steroids; shikimic acid/ aromatics; and polyketides. These secondary metabolites, better called phytochemicals, affect humans in ways (useful and hurtful) that require that their production, quality, distribution and use be regulated. It is, indeed, the paradoxical nature of phytochemicals that has informed the intervention of the World Health Organisation in their regulation (WHO, 1998a). The manual on quality control of medicinal plant materials (WHO, 1998b) and the guidelines on research and evaluation of traditional medicine (WHO, 2000) had been instrumental in setting the tone for global regulation of herbal medicine. It had been noted (Ameh et al., 2010b) that the most pressing issues that answers must be provided for in a TM plant recipe are: (i) Does the recipe conform to the WHO limits for heavy metals, aflatoxins, microbial load and specific microorganisms? (ii) Are there dependable criteria for identifying the herbal substance, such as by TLC or HPLC fingerprints? (iii) Are there dependable criteria of consistency, such as loss on drying, ash values and water extractability for the herbal substance? (iv) Are there threats from toxic phytochemicals like cardiac and cyanogenic glycosides? (v) Is the recipe safe (and perhaps efficacious) in laboratory animals? Once there are satisfactory answers to these questions; and there is compliance with the WHO guidelines on documentation of safety of TMs based on experience, a *prima facie* case can be made for clinical trials (Ameh et al., 2010b).

2.2 Current Regulatory Status of Herbal Drugs Worldwide

Whereas up to 80 % (WHO, 2008) or even 90% (BBC, 2006) of some populations depend almost entirely on TM for most of their primary healthcare needs, the dramatic irony is that among these same populations, TMs, including herbal drugs, are hardly regulated by the State. It had been noted earlier “that about 80% of people in developing countries depended on herbs, but contributed only 7.2% to the trade in 1999. By contrast, the developed nations, where people relied less on herbs, contributed 55.2%. Asia, less Japan and South Korea, contributed 37.6%” (Ameh et al., 2010b). The reason for this deepening paradox is that in the developed countries, herbal drugs are better regulated – that is: herbal drugs are produced according good manufacturing practice (GMP); and utilized in accordance with good clinical practice (GCP). Thus, although herbal drugs are not “pharmaceuticals” (precise chemical entities or combinations thereof), they are nevertheless treated with about the same degree of diligence. In china, India and Korea, where TM systems have been integrated into the national health scheme, TMs are treated with the same degree of respect as synthetic “pharmaceuticals”. In 2001, a total of 1249 traditional Chinese medicines (TCMs) were listed in China’s national essential drugs list, with sales of US\$ 9.8 billion. Under the 1985 State

Drug Administration law, marketing authorization was mandatory for all drugs, including herbal remedies. With effect from 1986, the process for approving new TCMs was dichotomized into: approval for clinical trial and approval for marketing. In an application for drug registration, general product data; pharmaceutical data; pharmacological/ toxicological data; and clinical data have to be submitted, as shown in Table 1 for the EU. With effect from 1995, all TCMs manufacturers and marketers had to be certified by the local drug regulatory authorities. GMP and Good Supplies Practices (GSP) were basic requirements for registration and certification. In fact, we had noted earlier that “the EU and US’ Acts of 2004 and 1994, “borrowed a leaf from this Chinese legal provision and foresight” (Ameh et al., 2010b). Old “European herbalism” or “classical herbalism”, as it is sometimes called, is still practiced in many parts of Europe (Green, 2006), and was well entrenched in the US before the Flexner Report (Pelletier, 2009). However, Vickers and Zollman (1999) wrote that: “Chinese herbalism is the most prevalent of the ancient herbal traditions currently practised in Britain”. The presence and impact of TCM and Ayurvedic Medicine in the US are well documented (Holland, 2000; Ninivagi, 2008). Yoruba Medicine from Africa is also known in the Americas (Grotte, 2008); and Chinese herbal teas are everywhere including African city supermarkets and international airports. Notably, Niprisan, the sickle cell drug, granted orphan drug status by the US-FDA and EMEA in 2003 had been developed from Yoruba Medicine. Niprisan is also known and patented in India. Indeed, a fair and graphic illustration of the importance and international status of herbal medicine was given by the World Wildlife Fund (2010), stating that: “In many developed countries, traditional herbal remedies are making a comeback as alternatives to conventional medicine. In the United States, the number of people using herbal medicines has increased from 2.5 percent in 1990 to 37 percent in 2000”.

In contrast to the enlightened regulatory status of herbal drugs in the OECD countries, these drugs in most of the developing countries in Africa are in a poor state of regulation owing to obsolete policies and lack of confidence in local know-how. A good illustration of this paradox is afforded by the situation in Nigeria. During a recent retreat (January, 2011) to discuss the Nigerian National Strategic Health Plan at the National Institute for Pharmaceutical Research and Development (NIPRD), it was revealed that NAFDAC had not “fully registered a single herbal drug since it was created in 1992/3 to regulate food and drugs in Nigeria”. This is most alarming since up to 80% of the population is thought to rely on TM remedies for most of their healthcare needs (WHO, 2008). Furthermore, it is on record that Niprisan was not recognized by NAFDAC until the US-FDA and the EMEA accorded it orphan drug status (Pandey, 2003). Thus, while the decline in North America’s use of herbal medicines, incidented partly by the Flexner Report of 1910, had been reversed by the 1990s; and the lull in European herbal use, incidented by the “magic bullet” idea sparked off by Erhlich’s introduction “chemotherapy” in 1909, had also been reversed, many postcolonial societies and their institutions in Africa especially, are yet to see the light of day in the American DSHEA (1994) and the European THMP directive of 2004 (Ann Godsell Regulatory, 2008). The said institutions in Africa remain inclined to negative notions about African and Oriental Medicine; and have not realized that even in Japan and South Korea, where TCM is called Kampo Medicine, TMs are not only highly regarded but are well patronized and integrated into their national healthcare schemes. Incidentally and disturbingly, the “Traditional Medicine Policy for Nigeria-2007”, zealously midwived by the WHO and the Nigerian Federal Ministry of Health (Lambo, 2007), hardly made any reference to the nation’s drug regulatory agency – National Agency for Food and Drug Administration and Control (NAFDAC), neither has the Agency produced a response based on that Policy. It is disturbing for obvious reasons - Nigeria may not be alone.

Table 1. Categories of data required for herbal registration in Europe by EMEA

Type of data	Details of data
Product information: Summary of product characteristics	These are: 1. Name of the product. 2. Strength. 3. Dosage form. 4. Quantity of active ingredient. 5. List of excipients. 6. Shelf life. 7. Posology/ method of administration. 8. Indications. 9. Contraindications/ special warnings. 10. Precautions for use. These are used as the basis for any insert, package information, or advertisement. Insert must undergo a process called “readability” (or “user”) testing, to ensure clarity.
Quality control data: Refer to GMP requirements for production.	The requirements apply to raw material and finished product, and include: 1. Production must be in a GMP compliant facility. 2. The medicine must be produced with a validated formula. 3. There must be a finished product specification. 4. The product must be manufactured at least on pilot scale and three batches used for stability studies. 5. Stability studies should be carried out on the product packaged in the container proposed for marketing. 6. A summary of the stability studies undertaken must be provided. 7. From the stability data shelf life and storage precautions should be proposed. 8. A quality dossier must be provided for both starting materials and finished product. 9. The product must be produced from herbs that have been cultivated and harvested in accordance with Good Agricultural and Collection Practice (GACP). 10. The raw material must be evaluated for risk of any environmental contamination.
Safety data requirements: Refers to safety pharmacology, including animal and human studies.	The data may be assembled from: 1. Published animal or human studies. 2. Review of any potential interactions with other drugs, side effects, and any proposed contraindications/ precautions. 3. Recognized monographs on the material or product with information on safety. 4. Any information concerning special groups such as children, the elderly or pregnant women.
Traditional use evidence: Refers to history and prevalence.	There is no requirement to prove efficacy (De Smet, 2005). Instead data must provide reference that the product has been in use as medicine for 30 years or more, of which the last 15 must be in Europe. The data must be presented specially - in a Common Technical Document Format.

The above was drawn based on data gathered from references including (DSHEA 1994; Goldman, 2001; De Smet, 2005; Ann Godsell Regulatory, 2008). EMEA is European Medicines Evaluation Agency.

2.3 The Place of Medical Herbalism in TM and in the Drug Development Chain

Herbal medicines are generally regarded “as the major remedy in traditional medical systems” (WHO, 1993). A clear indication of their importance is evident from the following: “About one-quarter of all U.S. prescription drugs are derived from herbs. The pharmaceutical industry uses around 120 different compounds derived from plants in the drugs it manufactures, and it discovered nearly three-quarters of these compounds by studying folk remedies. Examples of drugs from plants include quinine, from the bark of the South American cinchona tree, used to treat some strains of malaria; digitalis, a widely prescribed heart medication, derived from the foxglove plant; salicylic acid, the source of aspirin, from willow bark; and taxol, for treating ovarian cancer, from the yew tree” (Pelletier, 2009). The general trend in the literature on the place of TM in the drug development chain appears to be as described by Wambebe (2008), namely that: a simplified drug development chain encompasses discovery phase, pre-clinical/ non-clinical phase, clinical phase, regulatory phase, marketing phase, post-marketing phase and policy practice; and that TM belongs to the discovery phase. Therefore, if a proper ethnomedical survey is conducted, accompanied by clinical observational study, following WHO guidelines, it is possible to save substantial funds and drastically reduce the time needed to obtain credible data. This means that “clinical trials”, especially phased trials, are not always necessary for traditional remedies. However, whenever such trials are deemed necessary, the principles applied in the case of pharmaceuticals equally apply to herbs (Wambebe, 2008).

3. CLINICAL RESEARCH

3.1 Scope of the Ensuing Discourse

Although the basis of clinical research was first advanced in Avicenna's *The Canon of Medicine* (Brater and Daly, 2000), and had been applied in James Lind's famous clinical trials of citrus fruits in the cure scurvy (Lind, 1754); a somewhat modified, viewpoint on “clinical trial” has emerged lately:

“One of the greatest advances in medicine was the introduction of a new research technique in the mid-1950s called the *controlled clinical trial*, which is used to determine if new drugs and other treatments are safe and effective. In the controlled clinical trial, one group of patients, the treatment group, receives the new drug or new treatment. Another group, the control group, is given an inactive pill (a placebo) or the best standard treatment. Researchers then compare the two groups over a period of time. The data collected is put through rigorous statistical techniques to determine whether the new treatment is safer and more effective than standard therapy or no treatment” (Sikorski and Peters, 2009).

An immediate import of this position is that “clinical trials” refers strictly to “controlled clinical trials” –described as “a new research technique” introduced “in the mid-1950s”. Another import is that: Since traditional herbal medicine is thousands of years old, long before Avicenna and Lind, it follows that “controlled clinical trial”, which was only introduced in the “mid-1950s”, cannot be the basis of traditional medicine. It seems that, while some forms of clinical study may be required to introduce a TM herb into conventional medicine, it is unlikely that such an herb *ab initio* was introduced to TM via the instrumentality of “controlled clinical trial”. The recent book: *Nuts & Seeds in Health and Disease Prevention*, which contains “historical cultivation and usage”, “present-day cultivation and usage” and

“applications to health promotion and disease prevention” for over 113 plant materials, suggests “serendipity” rather than “controlled clinical trials” as the basis for the health applications of these items. The 40th chapter (Ameh, 2011a) of the said book is dedicated to the seeds of *Piper guineense* that had been in use among the Yoruba of Nigeria for treating sickle cell anemia for centuries, but Niprisan (formulated with *Piper guineense* and three other herbs) was subjected to clinical trials only recently (Wambebe, et al., 2001). We may conclude therefore, that “controlled clinical trials” is a useful adjunct to modern medicine but not the basis of modern medicine.

3.2 A More Pragmatic Definition of Clinical Research

Kumar (2005) in a lecture at Abuja, Nigeria, defined “clinical trial” as “a carefully designed and controlled research, in which humans receive a drug (or some other intervention), usually for the purpose of determining safety or efficacy, and the study may be divided into phases”. A clinical research can only take place when satisfactory preclinical data have been gathered on the intervention, and the relevant Health Authority/Ethics Committee has approved the study design and scope of the tests to be conducted. It may be noted that the insertion of the phrase “controlled research” emphasizes that “clinical trials” strictly means “controlled clinical trials”. Over the past 60 years, clinical research as a biomedical methodology has evolved into a rather complex enterprise with an array of insightful terminologies that helped to make the concept less rigid and more inclusive. Mostly, the technical scope and cost implications of clinical trials are of such a nature and dimensions that specialized outfits - contract research organizations (CROs) and institutional review boards (IRBs) - and wealthy stakeholders are required to initiate and sustain the project. The term “clinical trials” or “controlled clinical trials” is most often associated with the large, randomized studies typical of Phase III clinical trials. However, many trials are small and designed to answer specific questions such as whether the dose for an adult should be 5 or 10 mg. A few of the terms commonly associated with clinical trials are mentioned and briefly described in Table 2. A few more are mentioned and defined under classification/ types of clinical trials in Table 3.

3.3 Study Design and Classification of Clinical Research

In planning a trial, the sponsor or investigator may first conduct a trial run to gain insight into the most appropriate design. It is important to stress that in clinical research parlance; efficacy refers to how well a treatment works in a clinical trial, while effectiveness refers to how well the same treatment works in practice (Pocock, 2004). This may mean, for example, that an effective, well reputed traditional remedy may not do so well in terms of efficacy as determined in a clinical trial. This can happen if the trial environment failed to replicate the cultural, social or psychological settings for the treatment. If a “placebo effect” is “a sense of benefit felt by a patient that arises solely from knowing that a treatment has been given”, it follows that the environment of a clinical trial can deny an otherwise effective traditional remedy such effects as might significantly alter the outcome of that trial. Thus, if “placebo effect” works by faith, and is important even in conventional medicine, it follows that it might even be more so in TM, since TM tends to be more faith-based than conventional medicine. This explains why considerations for “placebo effect” must be factored into study design (research protocol) and interpretation of results. Since aim is a key determining factor in the classification of a clinical research, it follows that aim is critical to the formulation of study protocols. Figure 1 is a schematic rendering of clinical research, while Table 4 shows the relationship between study aims and the descriptions of various types of clinical research.

Table 2: Terms associated with clinical research

Term	Meaning
Study protocol	A document put together by a panel of experts. It describes the aim, rationale, design, methodology, statistical considerations, and organization of the research; and is used in gaining approval for the trial. It contains the precise plan for conducting the research, assuring the safety of the trial subjects, and providing an exact template for investigators at multiple sites to perform the study in exactly the same way.
Phased studies	Clinical trials involving new drug (not typical of traditional herbal medicine) are usually classified into four phases. Each phase of the process is treated as a separate clinical trial. The drug development process normally proceeds through all four phases over years. If the drug successfully passes through Phases I - III, it will usually be approved by the relevant Health Authority. Phase IV essential covers post-approval studies.
Epidemiology	Scientific and medical study of the incidence, origin, distribution and control of a disease in a given population.
Prospective	In a prospective study, trial subjects are recruited before the treatment is initiated.
Retrospective	In a retrospective study, trial subjects are recruited after treatment has been initiated. It is also called 'naturalistic study' or 'observational study'
Controlled	This is a study where the 'test' is compared with a 'control'. In a "placebo-controlled study" a placebo is used as control.
Uncontrolled	This is a study where the 'test' treatment is not compared with a 'control' treatment.
Stratified	This is a study where subjects are divided into groups based on specific criteria (example: age, sex, race, prognostic considerations and so on).
Parallel group	This is a study where each subject receives only one of the alternative treatments.
Open label	This is a study where both the investigator and subject are aware of the type of treatment given.
Single blind	This is a study where either the investigator or the subject is unaware of the type of treatment given.
Double blind	This is a study where neither the investigator nor the subject is aware of the type of treatment given.
Blind observer	This is a study where a third party clinical assessor is unaware of the treatment given.
Randomized	This is a study where treatments are given sequentially to different subjects according to a predetermined roster.
Crossover	This is a study where each subject sequentially receives each of the treatments under trial.
Statistical power	The number of patients enrolled in a study is critical to its ability to detect the effect of the trial intervention. This ability is called the "statistical power" of the trial. The larger the number of participants in the trial, the greater the statistical power.

A more complete list of terms associated with clinical research is found in Kumar (2005) and NIH Glossary of Clinical Trial Terms (2011).

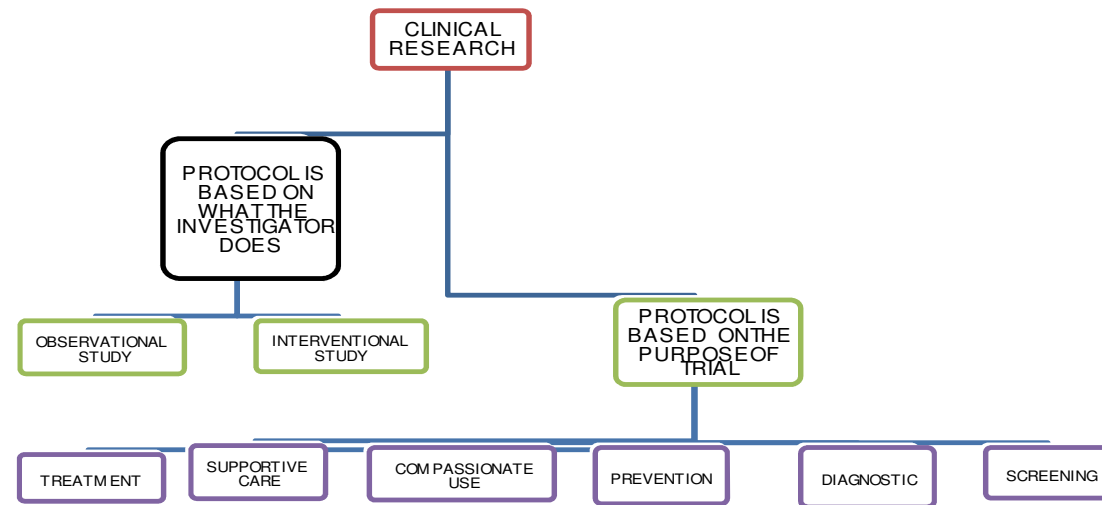


Fig. 1. A depiction of types of clinical research

Footnote to Figure 1: In an observational study (or natural experiment or epidemiological study) the investigator does not actively manage the experiment, but observes the subjects and measures the natural outcomes/ any treatment given. In an interventional study, the investigator gives the subjects the trial drug or intervention, and compares the treated subjects with subjects who receive no treatment (or a placebo) or standard treatment (or the best available intervention). Most studies whose protocols are based on aim or purpose are interventional, but they can also be observational depending on what the investigator does. The Figure is drawn based on data gathered from Pocock (2004), Kumar (2005) and NIH Glossary of Clinical Trial Terms (2011).

Table 4. Classification/ types of clinical trials

1. One way of classifying clinical trials is by what the investigator does or how s/he behaves

Observational study

This is an epidemiological study where the investigator does not actively manage the experiment, but observes the subjects and measures the natural outcomes/ any treatment given. It is also called a natural experiment.

Interventional study

In an interventional study, the investigator gives the subjects the trial drug or intervention, and compares the treated subjects with subjects who receive no treatment (or a placebo) or standard treatment (or the best available intervention).

2. Another way of classifying trials is by their purpose

- I. Trials seeking to identify better preventive measures, screening, or diagnostic techniques
- a. *Prevention trials*: look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning.
 - b. *Screening trials*: test the best way to detect certain diseases or health conditions.
 - c. *Diagnostic trials*: discover better procedures for diagnosing a particular disease or condition.

- II. Trials seeking to identify better curative, or management measures.
- a. *Treatment trials*: these test new doses or combinations of drugs, or new approaches such as surgery or radiation therapy.
 - b. *Quality of life trials (or supportive care)*: explore ways to improve comfort/ quality of life for persons with a chronic illness.
 - c. *Compassionate use trials (or expanded access)* provide, prior regulatory approval, partially tested, unapproved drugs to a small number of patients that have no other realistic options, on a case-by-case basis.
-

3. Others include tests designed to answer specific health issues, such as tests designed to:

- a. Evaluate the safety and efficacy of a new medication for a specific kind of patient (example: patients who have been diagnosed with sickle cell anemia).
- b. Evaluate the safety and efficacy of a different dose of a medication than is commonly used (e.g., 10 mg dose instead of 5 mg dose)
- c. Evaluate the safety and efficacy of an already marketed medication for a new indication, that is: a disease for which the drug is not specifically approved.
- d. Assess whether the new medication is more effective for the patient's condition than the already used, standard medication ("the gold standard" or "standard therapy")
- e. Compare the efficacy a new intervention with that of an already approved intervention in patients with a particular type disease.

Clinical trials of herbal medicines may have two types of objectives. One is to validate the safety and efficacy that is claimed for a traditional herbal medicine. The other is to develop new herbal medicines or examine a new indication for an existing herbal medicine or a change of dose formulation, or route of administration. In some cases, trials may be designed to test the clinical activity of a purified or semi-purified compound derived from herbal medicines.

3.4 Phased Clinical Research

A phased clinical trial is what is mostly thought of when the term “clinical trials” is called up, but it is only a part, albeit a big part of an elaborate methodology. A four-phased clinical trial is usually, but not always, called into play when a new and promising treatment is in the offing. As a rule, phased trials are nearly always a costly enterprise, estimated at a billion US dollars a few years ago (Kumar, 2005).

Phase I: The first phase of a phased clinical trial of a new compound or formulation is carried out with a small number of healthy volunteers or patients suffering from the disease for which the medicine is intended. The main purpose of a phase I trial is to observe tolerance to the medicine and therefore to get an indication of the dose that might be used safely in subsequent studies.

Phase II: Studies in the second phase are also carried out on a limited number of patients to determine clinical efficacy and to further confirm safety. Such trials are preferably designed as randomized, double-blind, controlled studies, using for control groups either an existing alternative treatment or a placebo. The dosage schedules established in such studies are to be used for the next, more extensive, clinical study.

Phase III: In the third phase of a clinical trial, a larger patient group is usually studied at several centers using a randomized double-blind design to validate preliminary evidence of efficacy obtained in earlier studies. Ordinarily, such trials are conducted under conditions that are as close as possible to the anticipated conditions of normal use.

Phase IV: Phase 4 studies are performed after the dosage form is fully ready and available for general use. The main purpose of such studies is to detect untoward events or toxicities that may occur so rarely that they are not easily detected earlier in the general population.

In summary, the aims of the phases are: 1st phase - to ensure general safety; 2nd phase - to determine efficacy; 3rd phase - to validate preliminary evidences of safety and efficacy; and 4th phase - to detect any rare but serious side-effects and to confirm the long-term toxicity and efficacy.

4. WHAT CONSTITUTES AN HERBAL CLINICAL RESEARCH

4.1 Doctrine of Signatures

During the European Renaissance, many physicians or “physiomedical herbalists” in prescribing followed what was termed, the “Doctrine of Signatures”- the idea that the shape, colour and other features of a plant may suggest its medicinal purpose. For example, they noted the red and puffy bladder-shaped covering of *Physalis alkekengi* fruit, and experimented with various parts of the plant in treating kidney and bladder disorders, since the papery, bladder-like structure is reminiscent of the urogenital system. Although the Doctrine was most propagated during the Renaissance, the idea that appearances of natural objects had medical significance was much older in most cultures worldwide. For example, long before the Renaissance, many cultures alluded to the use of liverwort and snakeroot, as antidotes for snake bite; and to the use of lungwort, bloodroot, toothwort and wormwood, as potent worm expellers. As will be seen later in this review, the occasional resemblance of mandrake root to human body parts led to the great significance attached to mandrake since

ancient times (Herb Magic Catalogue, 2011). William Coles (a 17th Century botanist, herbalist and author of *The Art of Sampling* and *Adam in Eden*), stated that walnuts were good for curing head conditions because "they have the perfect signatures of the head". Of *Hypericum*, he wrote, "The little holes whereof the leaves of St. Johns wort are full, doe resemble all the pores of the skin and therefore it is profitable for all hurts and wounds that can happen thereunto" (Pearce, 2008). In spite of the foregoing however, the general impression today is that there is "no scientific evidence that plant shapes and colours help in the discovery of medical uses of plants" (Bennett, 2007). But the idea cannot be discarded because, we cannot, for instance, deny the inexplicable role played in human health by culture, belief, psychology and "placebo effect".

4.2 Zoopharmacognosy – Animal Self-Medication

Most conventional drugs in use today were not decided by phased trials as we now know them, since they originated from long traditions in folk medicine. Moreover, the histories of how individual plants became associated with human health remain largely unknown. More recently however, a large body of educated guesses backed by contemporary observations is beginning to explain the involvement of plants in human health and disease. Ages before the penning of "the fruit thereof shall be for meat, and the leaf thereof for medicine" in Ezekiel 47:12, in ~ 457 BC (Scofield Study Bible, 1996), mankind had begun the practice of herbalism, as is well attested by Chinese records that date back by many millennia. But the question still remains - How did it all begin?

It is said that Rodriguez, a biochemist at Cornell University, coined the term "zoopharmacognosy" to describe the phenomenon whereby "animals self-medicate, by selecting and using plants, soils, and insects to treat and prevent disease" (Gerber, 1998). The term literally means animal drug knowledge, coined from *zoo* ("animal"), *pharma* ("drug"), and *gnosy* ("knowledge"). Indeed, observers have noticed that some animals ingest non-nutrients and toxic plants to ward off parasitic infestation (Biser, 1998). Scientists have witnessed chimpanzees ingesting certain weeds that make them sick, and evidence indicates that they swallow whole the leaves of certain rough-leaved plants, such as *Aneilema aequinoctiale*, in order to remove intestinal worms (Reynolds, 2005). In July 17th 2010 it was found that a sick dog that eventually died, had consumed a sizable quantity of the bitter Ayurvedic plant – *Andrographis paniculata* grown in a garden at 167 Cadastral Layout, Kubwa, Abuja (S. J. Ameh: Unpublished observations). Scientists in Japan (Koshimizu et al., 1994) reported sick chimpanzee in East Africa nibbling parts of *Vernonia amygdalina*, another bitter herb from which NIPRD had developed an antidiabetic - "Etidot", launched in 2009, at Abuja Sheraton. Apes have been observed selecting the stem a medicinal plant by taking off leaves, then breaking it to suck out the sap (Campbell, 1996). Indeed, Rodriguez described this phenomenon and its importance in these words: "Some of the compounds we've identified by zoopharmacognosy kill parasitic worms, and some of these chemicals may be useful against tumors. There is no question that the templates for most drugs are in the natural world" (Campbell, 1996).

In East Africa, pregnant elephants self-medicate by chewing the leaves of a tree (Family: Boraginaceae) that induces labor. Incidentally, Kenyan women also use this tree for the same purpose (Linden, 2002). People, the world over, have used hundreds of indigenous plants to treat ailments since prehistoric times, as is hypothesized in the case of the *Ötzi the Iceman*, whose body was frozen with herbs on him for over 5,300 years. Indigenous healers often claim to have learned by observing that sick animals change their food preferences to nibble at bitter herbs they would normally reject (Huffman, 2003). Ecologists have furnished

corroborating evidence based on observations of diverse species, including chimpanzees, chickens and sheep. Lowland gorillas take quite a bit of their diet from the fruits of *Aframomum melegueta*, a relative of the ginger plant - a potent antimicrobial that keeps enteric infections in check (Engel, 2002). Sick animals tend to forage plants rich in secondary metabolites, such as tannins and alkaloids (Hutchings, 2003). Since these phytochemicals often have antibacterial, antifungal, antihelminthic and antiviral properties, a plausible case can be made for self-medication (Engel, 2002). It is well known that some animals like the Australian koala have a digestive system specially adapted to cope with certain phytochemicals in the leaves of eucalyptus that is harmful to most animals, including humans. Therefore, a reasonable conjecture is that findings of this nature were traditionally collected by traditional healers - regarded in their communities as doctors and sages. For example, among the Idoma of Benue State, traditional healers are not only called "oho-onyeta" (which means doctor or saviour), but are also called "obochoi", which literally means "wisdom personified".

It is well documented that the use of herbs and spices in kitchens worldwide developed partly in response to threats of food-borne pathogens. Studies show that in the tropics where pathogens are most prevalent, recipes are wont to be most highly spiced, and spices with the most potent antimicrobials tend to be most often selected (Billing et al., 1998). Again, among the Idoma and the Igala of Kogi State, the corms of a species of *Gladiolus*, which is antimicrobial, is added to "kunu" - a non-alcoholic beverage made from cereals, to prevent it from fermenting (Ameh et al., 2011b). By contrast, among the Hausa-Fulani of the Northern States, where *Gladiolus* is less popular for this purpose, cloves and various species of *Piper* and *Capsicum* are used instead, not only for flavour, but to retard fermentation. All over the world, vegetables are spiced far less than meat or cooked legumes that are rich in protein, presumably because vegetables are less liable to microbial spoilage (Sherman et al., 2001). From the foregoing, it would appear that herbalism developed from necessity, trial-and-error, and serendipity, rather than from phased trials as we know them today. Still the term "herbal clinical trials" is not a misnomer since a certain amount of human experimentation must have taken place at some stage in the long history of herbal medicine. The histories of mandrake, coffee, among others, are briefly related in the following subsection to substantiate this view of historical herbalism.

4.3 Historical Landmarks in the Use of Pharmacologically Plants for Medicinal Purposes

4.3.1 Mandrake

Known botanically as *Atropa mandragora* or *Mandragora officinarum*, mandrake is the object of many tales and superstition. It has a large, brown root, somewhat like a parsnip. The fresh root operates powerfully as an emetic and purgative, and contains hallucinogenic tropane alkaloids like atropine, scopolamine, apoatropine, hyoscyamine (Heiser, 1969). Mandrake was much used by the ancients, who considered it an anodyne and soporific. In large doses it is said to excite delirium and madness. They used it for procuring rest and sleep, and also in melancholy, convulsions, rheumatic pain and in the treatment of warts. Mandrake was used in Pliny's days as an anaesthetic for operations. Among the old Anglo-Saxon, both Mandrake and periwinkle are said to be endowed with mysterious powers against demoniacal possession (Grieve, 1995). Mandrake, called "Satan's Apple" by the Arabs, is also reputed to be a reproductive stimulant among the Hebrews, as Genesis 30 suggests in two cases of mandrake-assisted pregnancies in Jacob's wives (Scofield Study Bible, 1996).

4.3.2 Coffee

Coffee, of which *Coffea arabica* is the preeminent species, is originally indigenous to Ethiopia, Sudan and Yemen, but popularized by Arabs, hence its name. *C. arabica* is believed to be the first species to be cultivated, and is said to produce better coffee than other major commercially grown species, such as, *Coffea canephora (robusta)*. The coffee fruit is actually a drupe, not a berry; hence the term “coffee berries” is a misnomer. Typically, the coffee drupe measures ~12.5 mm in diameter, maturing bright red to purple, and containing two seeds, called the coffee “beans”. The plant was first described by Antoine de Jussieu, who named it *Jasminum arabicum*, but Linnaeus placed it in its own genus *Coffea* in 1737 (Charrier and Berthaud, 1985). The pharmacologically active principle of coffee is “caffeine” - discovered in the late 17th Century by Dr. Sylvestre Dufour (Google Answers, 2011a). The first documented reference to coffee was in 10th Century AD by an Arabian doctor named Rhazes. Ethiopia is generally held to be the epicenter for the spread of coffee throughout Africa and Arabia. However, it was in Yemen that the practice of roasting coffee beans first began in 1200 AD. Coffee drinking throughout the Islamic world, including Spain, was spread by Muslims. “The first coffee houses in Europe opened in 1643 in Paris and in 1650 in England” (Google Answers, 2011b). The popular “Kaldi Legend” about the discovery of coffee is as follows: “Coffee was first discovered when Kaldi, a goat-herd in present day Ethiopia, observed his goats dancing on their hind legs, and acting unusually frisky after eating berries from a bush. Curious about this phenomenon, Kaldi ate the berries himself, and found they gave him a renewed energy. The news of this energy laden fruit quickly spread throughout the region. Hearing about this amazing fruit, monks dried the berries so that they could be transported to distant monasteries. Typically, they reconstituted the berries in water, ate the fruit, and drank the liquid to provide stimulation for a more awakened time for prayer” (Google Answers, 2011c). It may be taken that this “Kaldi story” provides a link between zoopharmacognosy and human clinical trial.

4.3.3 Aframomum melagueta and other historically important “herbs and spices”

“Herbs and spices” stand out as herbal remedies that have a long history of application in TM, being deeply rooted in culture and tradition the world over. For example, *Aframomum melagueta* (alligator pepper) and *Piper guineense* are often eaten with kola nut (*Kola acuminata* or *Kola nitida*) among many ethnic groups in Southern Nigeria especially during formal occasions and rituals. Notably, Chinua Achebe’s books on Igbo culture and way of life - “Things fall apart” and “Arrow of God”- spoke of “he who brings kola brings life”, in reference to *Kola acuminata*, the species mostly eaten by the Igbo of Southeast Nigeria. *Kola nitida* is the species mostly eaten by the Hausa-Fulani of the Northern Nigeria, where it plays a substitute role in settings where alcoholic beverages are forbidden. As is well known both kolas are rich in caffeine – a CNS stimulant that also stimulates the heart. Peppers play a strong role not only in cultural settings, but are indispensable in the appreciation of some types of food, and are especially linked to wellness in many cultures (Tapsell, 2005). It is known that the “wealth of India”, especially spices, notably black pepper, were the main attraction for Vasco Dagma’s epic voyage to India in 1497. The Portuguese and other Europeans having tasted what was termed “tropical delights” came up with such coinages as: “grains of paradise” in reference to the aromatic, peppery-tasting seeds of *Aframomum melagueta*; and such sayings, like “variety is the spice of life” became prevalent. Incidentally, *A. melagueta*, like *P. guineense*, is considered to have several medicinal applications (Ameh et al., 2010c), as are the Asian *Piper* species, namely *P. nigrum* and *P. cubeba* described elsewhere (Ameh, et al., 2011a). Among some ethnic groups in Nigeria, *A. melagueta* is used in preparing love potions and for casting spells. Indeed, among the Idoma, *A.*

melagueta is called “otuta”, meaning charm or magical. Among the Efiks of Southern Nigeria, *A. melagueta* is used in divination and in trial by ordeal (Simmons, 1956)

4.3.4 More on *Piper* species

In the Old World, including Europe and the UK, *Piper* species, including *P. guineense*, had been in use for centuries in various official and anecdotal remedies, including applications in mouthwash, dental diseases, halitosis, loss of voice, sore throat, fever, and cough, and as a counter-irritant (Schmidt, 2009). In traditional Chinese medicine, *Piper* is used for its alleged warming effect. In Tibetan medicine, *Piper* is one of the six herbs claimed to benefit specific organs, being assigned to the spleen. Sir Richard Burton’s book, *The Book of One Thousand and One Nights*, mentioned cubeb as the main ingredient of an aphrodisiac remedy for infertility. Similarly, the 1827 edition of the London Dispensatory informed that cubeb “stir[s] up venery, very profitable for cold grief of the womb” (Katzer, 1998). Furthermore, in England, a small amount of *Piper* was often included in lozenges designed to alleviate bronchitis, owing to its antiseptic and expectorant properties. Indeed, *P. guineense* is one of the four herbal ingredients present in a popular brand of tooth-paste marketed in Nigeria.

4.4 Herbal Clinical Research at a Glance

4.4.1 Application of the principles of pharmacodynamics to herbal drugs

Applications of the principles of pharmacodynamics to herbal drugs invariably lead one of the following three scenarios: i) herbal drugs whose efficacies have been demonstrated - their active principles are known and their doses are more-or-less established; ii) herbal drugs whose efficacies are probable, but have not been clearly demonstrated - their active agents may be used to standardize them; and iii) herbal drugs with uncertain efficacies, but a long history of traditional usage – such drugs can be used for treating common disorders, but should be used exactly as in the traditional practice.

4.4.2 General purpose

The general purpose of an herbal clinical trial is to generate safety and efficacy data needed to guide the use of an herbal medicine.

4.4.3 Approval

The trial can only take place when the respective national regulatory authority is satisfied with the quality of data provided on: i) the safety and efficacy of the drug; ii) the necessity for the trial; iii) how the trial is to be carried out – that is: a detailed study protocol; and iv) the capability of investigators/ sponsor.

4.4.4 Scope, methodologies and examples of herbal clinical studies

The research consists of: i) administration of the drug to selected subjects; ii) collection of data on the subjects’ conditions, such as: measurements of vital signs, concentration of the drug in the blood or other fluids, whether the patient’s health improved or not, and so on; and iii) the data collected are subjected to statistical analysis. Some examples of herbal clinical research are described in Table 5.

Table 5. Examples of publications on herbal clinical research excluding herb-drug interactions

Example	Purpose/ Methodology/ Results	Conclusion/ Reference
Herbal treatment of irritable bowel syndrome (IBS)	A double blind RCT study conducted to determine whether Chinese herbal medicine was safe and efficacious in IBS.	An example of a study demonstrating both safety and efficacy of an herbal TM (Bensoussan et al., 1998; Leung et al., 2006).
Garlic therapy in children with hypercholesterolemia.	A double-blind RCT to determine whether garlic extract therapy is safe and efficacious in children with hypercholesterolemia.	An example of a trial in which “efficacy” was not been demonstrated despite widespread claims of “effectiveness” in actual practice (McCrinkle et al., 1998).
Niprisan herbal trial in patients with SCD	A double-blind, controlled, randomized cross-over trial to evaluation safety and efficacy of Niprisan (US Patent No. 5,800,819 - September 1, 1998).	Niprisan is a safe and “effective” in managing SCD. (Wambebe et al., 2001; Xechem International Annual Report, 2005).
Clinical Trials of Traditional Herbal Medicines In India	A review of types of herbal clinical trials likely to be approved by the Indian drug regulatory agency (DCGI). The DCGI stipulates that the procedures for allopathic drugs be followed for TM products; Phase I studies may not be necessary; toxicity testing in animals may be reduced to the necessary minimum; and toxicity study may not be needed for Phase II trial unless herb will be used for more than 3 months or has toxicity.	In India, a clinical trial of an herbal drug may be: i) to evaluate the herbal substance for the same indication for which it is being used traditionally; ii) to evaluate an extract or a compound isolated from a plant for a non-traditional indication; iii) to a material that has never been in use before and has not been mentioned in any TM system; and iv) evaluation of an herb for possible herb-drug interactions. (Gupta, 2011).

<p>Trends and Current Status of Clinical Trials of Herbal Medicine in the United States.</p>	<p>A survey of herbal products use in the US. It looked at design features of herbal RCTs; examples of positive and negative trials; and provided comments/ advice on: strategies for future herbal RCTs and handling of challenges associated with herbal RCTs.</p>	<p>Authors stressed/ advised that: i) Phases I and II are unnecessary for herbal food supplements, and that Phase III should concentrate on long term follow-up of safety; ii) RCTs of single herb medications should follow same protocol as for conventional drug (Azen and Cen, 2011).</p>
<p>A systematic review of randomized clinical trials of individualised herbal medicine in any indication.</p>	<p>To evaluate the status of randomized clinical trials (RCTs) in assessing the effectiveness of individualized herbal medicine in any indication. Only 3 out of 1, 345 references were of sufficient interest in the study.</p>	<p>The study showed that there was a general scarcity of herbal RCTs, and suggested that: "In view of the long history of many herbal remedies the scarcity may imply that such trials are largely uncalled for if the practitioners and patients already have confidence in them. Guo et al. (2007).</p>
<p>Trial of Chinese Herbal Medicine in the Treatment of Upper Respiratory Tract Infections (URTIs)</p>	<p>An example of a Phase IV herbal RCT, and is assigned the following features: Study type – interventional; Study design: allocation – randomized, control – placebo, endpoint classification – safety/ efficacy study, intervention model – parallel assignment, masking – double blind, and primary purpose – treatment.</p>	<p>The study is sponsored by the University of Hong Kong (UHK), supported by the Government of the Hong Kong. The principal investigator is C. L. K. Lam. The study location is UHK. The results/ conclusion of the study were being expected as at February 2011.</p>

4.4.5 Examples of herbal clinical research devoted to herb-drug interactions and related issues

Herb-drug interactions are concerned with stimulation or inhibition of bioactivity by co-administration of an herbal remedy and other bioactive agents. The nature of the herb-drug interaction is a key factor in deciding whether the herbal remedy in question can be used concomitantly with other drugs. Many herbal clinical studies come under herb-drug interactions. Generally these studies usually involve a relatively small number subjects, and some are typical RCTs with over 100 subjects (Kuhlmann, 1999), and cover such specific issues as: i) Interactions between herb and commonly prescribed conventional drugs (Izzo and Ernst, 2001); ii) Adverse effects vis-à-vis herb-drug interactions (Cupp, 1999; Abebe, 2002); iii) Risk-benefit profile of commonly used herbal therapies (Ernst, 2002); and iv) Herb-herb interactions (Houghton, 1988; Wheatley, 2001; Cropley, et al., 2002)

5. TRADITIONAL HERBAL REMEDIES IN THE CONTEXT OF PHASED CLINICAL TRIALS

Once the decision is made that a clinical trial is required for a named remedy and indication, a step-by-step approach is usually followed in the development of that remedy. Usually, the point of entry to the trial phases is determined by the history and nature remedy under study. It is to be reiterated that herbal clinical trials can be designated in terms of “phases”, although study designs appropriate for a given herbal clinical evaluation may, strictly speaking, fall on the borderline between any two of the four phases described in Section 3.4. Only the following additional comments need now be taken into account:

Phase I: First trial of an herbal remedy or formulation is carried out with a small number of healthy volunteers or patients suffering from the disease for which the remedy is intended. The main purpose is to observe tolerance to the remedy and therefore to get an indication of the dose that might be used safely in subsequent studies.

Phase II: Although phase II studies are often preferably designed as randomized, double-blind, controlled studies, using for control groups either an existing alternative treatment or a placebo; such is uncommon with long standing herbal remedies. The dosage schedules established in phase II studies are used for the phase III study.

Phase III: Whenever it is practicable, a phase III trial of an herbal drug involves a large patient group studied at several centers using a randomized double-blind design to validate preliminary evidence of efficacy obtained in phase II. As in the case of conventional drugs, herbal phase III trials are conducted under conditions that are as close as possible to the anticipated conditions of normal use.

Phase IV: If phase IV studies are desired for an herbal remedy, they may be performed after the dosage form is made fully available for general use. The main purpose of such studies is to detect toxicities and idiosyncrasies that may occur so rarely that they are not detected earlier. Owing to racial or pharmacogenomic differences in drug metabolism, distribution and disposition, phase IV may be desired in situations where an endemic remedy is being introduced to a new region or population.

6. POLITICAL AND SOCIOECONOMIC FACTORS IN HERBALISM AND CLINICAL RESEARCH

As mentioned by Ameh et al. (2010a,b), herbal medicine worldwide received a boost from the Alma-ata Declaration of 1978 which took place in the Soviet block at the peak of the Cold War, and had been boycotted key members of the West. The world's most advanced economy, the US, only began to embrace herbal remedies (strategically called dietary supplements in the US) in the 1990s, by which time the Iron Curtain had already fallen. In 1992, recognition of the rising use of herbal medicines and other alternative remedies led to the establishment of the Office of Alternative Medicine by the US National Institutes of Health with a budget of \$2 million. Ten years later, the Office became the National Center for Complementary and Alternative Medicine (NACCAM) with a budget of \$73 million in 2000 (Azen and Cen, 2011). In 2002 the US National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH) began funding clinical trials into the efficacy of herbal medicine (Herbal Medicine-NIH-NCCAM, 2011). In a survey conducted in 2010, 356 of 1000 herbal products available in Europe and North America had published trial results on "pharmacological activities and therapeutic applications" (Cravotto et al., 2010).

Although many herbs show positive preclinical and small-scale clinical results (Srinivasan, 2005), many costly herbal clinical studies have produced negative results (Pittler et al., 2000). The quality of trials on herbal remedies is highly variable and many trials have been found to be of doubtful quality (Linde et al., 2005). The relatively few randomized, double-blind tests that receive attention in mainstream medical journals are often bashed on methodological grounds or interpretation. Paradoxically, studies published in journals like the *Journal of the American Medical Association* and *New England Journal of Medicine* that are less likely to be supportive of herbal remedies tend to command more attention than those published in specialized herbal journals like the *Journal of Medicinal Plants Research* and *International Journal of Phytomedicine* that are more supportive of herbal remedies. But the situation is changing rapidly with the coming on stream of new Asian, African and European journals committed to herbal remedies. A look at the authors list and the lists of references in the chapters of *Nuts & Seeds in Health and Disease Prevention* (1st edition) amply confirms this position.

Then, of course, is the unending argy-bargy between herbalists and pharmacists or between naturopaths and physicians over what should be the status of herbal remedies in the scheme of things. Herbalists and naturopaths criticize mainstream studies and conventional practitioners on the grounds that the latter do not make sufficient use of history and traditional experience, which have been shown to be the major driving force behind drug discovery and development in the past and present (Fabricant and Farnsworth, 2001). They maintain that tradition can guide the selection of factors such as optimal dose, species, time of harvesting and target population (Yarnell and Abascal, 2002). But, again the situation is changing rapidly as many more conventional practitioners are beginning to "see the light".

7. CONCLUSION

The growing popularity of herbal remedies worldwide calls for sound rules for their regulation. But while most of what should be done to ensure adequate control and informed patronage is simple enough, there is still a need for sustained advocacy to institute that fact firmly, especially in the Third World where traditional knowledge and technology are under

threats of extinction. It is strongly considered that the drug regulatory agencies in these countries have a crucial role to play in helping to identify promising TM remedies and to facilitate their development to clinical trial stages. These agencies should nurture promising TMs the way the US-FDA nurtured the US pharmaceutical industry during the 20th Century. Indeed, history suggests that the US pharmaceutical Industry is what it is today, partly because of the progressive-partnership role of FDA; and the Carnegie sponsored Flexner Report that actually paved the way for such a role. One of the best ways to accomplish this goal is for the national drug regulatory agencies in these countries to work more closely with pharmacy faculties, research institutes, teaching hospitals and research clinics. These regulatory agencies need to encourage such collaborations because the few pharmaceutical firms that exist in these countries have little or no R&D base. Clearly, what is needed is progressive-partnership not adversary-partnership as in a Cold War, in which TM remedies stand the risk of being hounded into extinction by misguided regulation. Above all, it seems that the underlying issue in herbal clinical trials is not so much about whether traditional herbal remedies work but how much is suitable for the condition for which the remedy in question is traditionally prescribed.

REFERENCES

- Abebe, W. (2002). Herbal medication: potential for adverse interactions with analgesic drugs. *J. Clin. Pharm. Ther.*, 27(6), 391-401.
- Ameh, S.J., Obodozie, O.O., Inyang, U.S., Abubakar, M.S., Garba, M. (2010a). Current phytotherapy - a perspective on the science and regulation of herbal medicine. *J. Med. Plants Res.*, 4(2), 072-081.
- Ameh, S.J., Obodozie, O.O., Abubakar, M.S., Garba, M. (2010b). Current phytotherapy – an inter-regional perspective on policy, research and development of herbal medicine. *J. Med. Plants Res.*, 4(15), 1508-1516.
- Ameh, S.J., Tarfa, F., Abdulkareem, T., Ibe, M., Onanuga, C., Obodozie, O. (2010c). Physicochemical Analysis of the Aqueous Extracts of Six Nigerian Medicinal Plants. *Trop. J. Pharm. Res.*, 9(2), 119-125.
- Ameh, S.J., Obodozie, O.O., Inyang, U.S., Abubakar, M.S., Garba, M. (2011a). Climbing black pepper (*Piper guineense*) seeds as an antisickling remedy. In V. R. Preedy, R. R. Watson, V. B. Patel (Editors), *Nuts & Seeds in Health and Disease Prevention* (1st ed.) (pp 333-343). Academic Press (Elsevier), London, Burlington, San Diego. ISBN: 9780123756886
- Ameh, S.J., Obodozie, O.O., Olorunfemi, P.O., Okoliko, I.E., Ochekepe, N.A. (2011b). Potentials of *Gladiolus Corms* as an Antimicrobial Agent in Food Processing and Traditional Medicine. *J. Microbiol. Antimicrob.*, 3(1), 8-12.
- Ann Godsell Regulatory (2008). *Pharmaceutical Good Manufacturing Practice for Herbal Drug Substances 2008*. <http://www.pharmaceutical-int.com/article/category/treatment-herbal-medicines> Accessed 2011 April 16.
- Azen, S.P., Cen, S. (2011). Trends and Current Status of Clinical Trials of Herbal Medicine in the United States (pdf). <http://www.Trends-and-Current-Status-of-Clinical-Trials-of-Herbal-Medicine-in-the-United-States-pdf> Accessed 2011 April 16.
- BBC News (2006). Can herbal medicine combat Aids? Wednesday, 15 March, 13:10 GMT. <http://newsvote.bbc.co.uk/mpapps/pagetools/print/news.bbc.co.uk/2/hi/Africa/4793106.stm> Accessed 2011 April 16.
- Bennett, B.C. (2007). Doctrine of Signatures: An Explanation of Medicinal Plant Discovery or Dissemination of Knowledge?. *Economic Botany*, 61(3), 246–255. Accessed 2011 April 16.

- Bensoussan, A., Talley, N.J., Hing, M., Menzies, R., Guo, A., Ngu, M. (1998). Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *J. Am. Med. Assoc.* 280(18), 1585-9.
- Billing, J., Sherman, P.W. (1998). Antimicrobial functions of spices: why some like it hot. *Qtr. Rev. Biol.*, 73(1), 3–49. doi:10.1086/420058. PMID 9586227: 9586227. Accessed 2011 April 16.
- Biser, J. A. (1998). "Really Wild Remedies — Medicinal Plant Use by Animals." Smithsonian National Zoological Park website. Accessed 2011 April 16.
- Brater, D.C., Daly, W.J. (2000), "Clinical pharmacology in the Middle Ages: Principles that presage the 21st century", *Clin. Pharmacol. Ther.*, 67(5), 447-450.
- Campbell, N.A. (1996). *Biology* (4th edition). 'An Interview with Eloy Rodriguez' (Benjamin Cummings NY, 1996) ISBN 0-8053-1957-3 p.23. Accessed 2011 April 16.
- Charrier, A., Berthaud, J. (1985). "Botanical Classification of Coffee". In Clifford MH, Wilson KC. *Coffee: Botany, Biochemistry and Production of Beans and Beverage*. Westport, Connecticut: AVI Publishing. pp. 14. ISBN 0-7099-0787-7.
- Cravotto, G., Boffa, L., Genzini, L., Garella, D. (February 2010). "Phytotherapeutics: an evaluation of the potential of 1000 plants". *J. Clin. Pharm. Ther.* 35(1), 11–48.
- Cropley, M., Cave, Z., Ellis, J., Middleton, R.W. (2002). Effect of Kava and Valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. *Phytother. Res.*, 16(1), 23-27.
- Cupp, M.J. (1999). Herbal remedies: adverse effects and drug interactions. *Am. Family Physician*, 59(5), 1239-1245.
- De Smet, P.N. (2005). Herbal medicine in Europe – relaxing regulatory standards. *N. Eng. J. Med.*, 352(12):1176-1178.
- Engel, C. (2002). *Wild Health: How Animals Keep Themselves Well and What We Can Learn From Them*. Houghton Mifflin. ISBN 0618071784. Accessed 2011 April 16.
- Ernst, E. (2002). The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Ann. Int. Med.* 136(1), 42-53.
- Fabricant D.S, Farnsworth N.R. (March 2001). "The value of plants used in traditional medicine for drug discovery". *Environ. Health Perspect.*, 109(1), 69–75. PMID 11250806. Accessed 2011 April 16.
- Gerber, S. (1998). "Not just monkeying around", *Vegetarian Times*, Accessed 2011 April 16.
- Google Answers. (2011b): How was coffee discovered? <http://www.nycbuzz.com/history.htm>
- Google Answers. (2011c). How was coffee discovered? <http://www.coffeebargains.com/history.html> Accessed 2011 April 16.
- Google Answers, 2011a. http://www.rio-pak.hr/pg_5.htm Accessed 2011 April 16.
- Green, H. (2006). *The History of Herbal Medicine*. Available from: www.herbal-supplement-resources.com Accessed 2009 June 2.
- Grieve, M. (1995). *Mandrake. A Modern Botanical – by Mrs. M. Grieve*. <http://botanical.com/> Accessed 2011 April 16.
- Grotte, L.B. (2008). "African Medicine". *Acupuncture Associates*. Available from: <http://www.drgrotte.com/AfricanMedicine.shtml> Accessed 2009 June 2.
- Gupta, Y.K. (2011). *Clinical Trials of Traditional Herbal Medicines in India*. <http://www.Clinical-Trials-of-Traditional-Herbal-Medicines-in-India-YKGupta.pdf> Accessed 2011 April 16
- Heiser, C.B. (1969). *Nightshades, The Paradoxical Plant*, 131-136. W. H. Freeman & Co. SBN 7167 0672-5.
- Herb Magic Catalogue. (2011). *Mandrake Root in Hoodoo Folk Magic, Spell-Craft, and Occultism*. Accessed 2011 April 16.

- Herbal Medicine-NIH-NCCAM (2011). Herbal Medicine, NIH Institute and Center Resources, National Center for Complementary and Alternative Medicine, National Institutes of Health. Accessed 2011 April 16.
- Holland, A. (2000). *Voices of Qi: An Introductory Guide to Traditional Chinese Medicine*; North Atlantic Books, 2000; ISBN 1-55643-326-3. pp. 112.
- Houghton, P.J. (1988). The biological activity of Valerian and related plants. *J. Ethnopharmacol.*, 22(2), 121-42 .
- Huffman, M.A. (2003). "Animal self-medication and ethno-medicine: exploration and exploitation of the medicinal properties of plants" (in Hindi). *Proc. Nutr. Soc.*, 62(2), 371–81.
- Hutchings, M., Athanasiadou, S., Kyriazakis, I., Gordon, I. (2003). "Can animals use foraging behavior to combat parasites?" *Proc. Nutr. Soc.*, 62(2), 361–370.
- ICH Guideline for GCP (2011) ICH Guideline for Good Clinical Practice: Consolidated Guidance Accessed 2011 April 16.
- Izzo, A.A., Ernst, E. (2001). Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs*, 61(15), 2163-75.
- Katzer, G. (1998). Cubebs pepper (Cubebs, Piper cubeba). Gernot Katzer's Spice Pages. Available at: http://www.unigratz.at/~katzer/engl/Pipe_cub.html. Accessed 2009 October 10.
- Koshimizu, K., Ohigashi, H., Huffman, M.A., (1994). Use of *Vernonia amygdalina* by wild chimpanzee: Possible roles of its bitter and related constituents. *Physiology & Behavior*, 56(6), 1209-1216.
- Kuhlmann, J., Berger, W., Podzuweit, H., Schmidt, U. (1999). The influence of valerian treatment on "reaction time, alertness and concentration" in volunteers. *Pharmacopsychiatry*, 32(6), 235-241
- Kumar, K. (2005). *Fundamentals of Clinical Trials*. Howard University, USA in collaboration with NIPRD, Abuja, Nigeria, and Xechem International Inc. USA. 14-16 July, 2005, Sheraton Hotels and Towers, Abuja, Nigeria. pp. 178.
- Lambo, E. (2007). *Traditional medicine policy for Nigeria –2007*. Federal Ministry of Health, Abuja, in collaboration with WHO, Geneva.
- Leung, W.K., Wu, J.C., Liang, S.M., Chan, L.S., Chan, F.K., Xie, H., Fung, S.S., Hui, A.J., Wong, V.W., Che, C.T., et al. (2006). Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. *Am. J. Gastroenterology*, 101(7), 1574-1580.
- Lind, J. (1754). James Lind Biography (1716-1794). <http://www.faqs.org/health/bio/33/James-Lind.html> Accessed 2011 April 3.
- Linde, K., Jonas, W.B., Melchart, D., Willich, S. (2005): The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int. J. Epidemiology*, 30(3), 526–531.
- Linden, E. (2002). *The Octopus and the Orangutan: More Tales of Animal Intrigue, Intelligence and Ingenuity*. New York City: Plume. pp. 16–17, 104–105, 191. ISBN 0452284112.
- McCrinkle, B.W., Helden, E., Conner, W.T. (1998). Garlic extract therapy in children with hypercholesterolemia. *Archives of Pediatrics and Adolescent. Medicine*, 152, 1089-1094.
- NIH. Glossary of Clinical Trial Terms (2011). <http://www.glossaryofclinicaltrialterms.nih.gov> Accessed 2011 April 16.
- Ninivaggi, F.J. (2008). *Ayurveda: A Comprehensive Guide to Traditional Indian Medicine for the West*. Westport, CT: Praeger Press. ISBN 0-313-34837-5. pp. 349.
- Pandey, R.C. 2003. Xechem's Sickle Cell Drug, NIPRISAN -HEMOXIN- Granted Orphan Drug Status by the FDA NEW BRUNSWICK, N.J.--(BUSINESS WIRE)--Sept. 2, 2003-

- Xechem International, Inc. (OTC BB: XKEM). Xechem's Sickle Cell Drug, NIPRISAN -HEMOXIN- Granted Orphan Drug Status by... Accessed November 20, 2009.
- Pearce, J.M.S. (2008). "The Doctrine of Signatures" (PDF). *European Neurology* (karger.com), 60(1), 51–52. Accessed 2011 April 16.
- Pelletier, K.R. (2009). *Guide to Herbal Medicine*. Available from: http://www.ca.encarta.msn.com/sidebar_701509401/Guide_to_Herbal_Medicine.html. Accessed 2009 June 2
- Pittler, M., Abbot, N., Harkness, E., Ernst, E. (2000) Location bias in controlled clinical trials of complementary/alternative therapies. *Inter. J. Epidemiology*, 53(5), 485–489.
- Pocock, S.J. (2004), *Clinical Trials: A Practical Approach*, John Wiley & Sons, ISBN 0-471-90155-5 pp. 278 1983 Chichester, UK:
- Redmond, W.A. (2008) "Chinese Lantern Plant." Microsoft® Encarta® 2009 [DVD]. Microsoft Corporation, 2008.
- Reynolds, Vernon. (2005). *The chimpanzees of the Budongo Forest: ecology, behaviour, and conservation*. Oxford University Press. pp. 41–43. Accessed 2011 April 16.
- RSV. (2005). *The Bible, Revised Standard Version*, The British and Foreign Bible Society, Stonehill Green, Westlea, Swindon SN5 7DG, UK. Printed at Amity Printing, China.
- Schmidt, R.J. (2009). BoDD (Botanical Dermatology Data Base) e PIPERACEAE. <http://bodd.cf.ac.uk/BotDermFolder/PIPE.html>. Accessed 2009 October 10.
- Scofield Study Bible (1996). *The Holy Bible*, Oxford University Press, Printed in New York, USA.
- Sherman, P.W., Hash, G.A. (2001). Why vegetable recipes are not very spicy". *Evolutionary Human Behavior*, 22(3), 147–163. doi:10.1016/S1090-5138(00)00068-4. PMID 11384883 : 11384883. Accessed 2011 April 16.
- Sikorski, R., Peters, R. (2009) "Medicine." Microsoft® Encarta® 2009 [DVD]. Redmond, WA: Microsoft Corporation, 2008.
- Simmons, D.C. (1956). Efik Divination, Ordeals, and Omens. *Southwestern J. Anthropology*, 12(2), 223–228.
- Srinivasan, K. (2005). "Spices as influencers of body metabolism: an overview of three decades of research". *Food Res. Int.*, 38(1), 77–86.
- US-FDA (2006) "Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies". Food and Drug Administration. January 2006. <http://www.fda.gov/cder/guidance/7086fnl.htm>. Accessed 4 April 2011.
- Vickers, A., Zollman, C. (1999). ABC of Complementary Medicine *BMJ* 1999, 319: 1050 (Published October 1999)
- Wambebe, C. (2008). From plants to medicines: challenges and prospects. The Nigerian Academy of Sciences. Public Lecture. Reiz Continental Hotel, Abuja. May 22, 2008. pp 1-17.
- Wheatley, D. (2001). Kava and valerian in the treatment of stress-induced insomnia. *Phytother. Res.* 15(6), 549-51.
- WHO. (1993). *Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines*. WHO, Geneva, Switzerland, 94 p.
- WHO. (1998a). *REGULATORY SITUATION OF HERBAL MEDICINES: A Worldwide Review*. World Health Organization, Geneva. 1998. p. 49.
- WHO. (1998b). *Quality Control Methods for Medicinal Plant Materials*. World Health Organization, Geneva, 128pp. <http://aps.who.int/medicinedocs/collect/medicinedocs/pdf/h1791e.pdf> Accessed 2006 Oct 2
- WHO. (2000). *General guidelines for methodologies on research and evaluation of traditional medicine* (Document WHO/EDM/ TRM/2000.1). 2000. World Health Organization, Geneva. 184pp.
- WHO. (2008). *Traditional Medicine*. WHO Fact sheet No.134. Revised. December 2008.

- World Wildlife Fund (2010). <http://www.worldlifefund> Accessed 2010 March 26).
- Xechem International Annual Report (2005). A submission to U.S. Securities and Exchange Commission. December 31 2005."Xechem International - Annual Report". http://sec.gov/Archives/edgar/data/919611/000114420406015544/v040579_10ksb.txt. Accessed 2011 April 16.
- Yarnell, E., Abascal, K. (2002). "Dilemmas of Traditional Botanical Research". *HerbalGram*, 55, 46–54.

© 2011 Ameh et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.