

Herbal Clinical Trials-Historical Development and Application in the 21st Century

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Abstract: It is established that many more people are reverting to the use of traditional herbal medicines, especially in the US, where the practice declined partly due to the influential Flexner Report of 1910 that was critical of alternative remedies including herbal. The hope advanced by Ehrlich's chemotherapy or magic bullet in 1909, did pretty much the same to European classical herbalism. In Asia, where Traditional Medicine (TM) enjoys a long history and patronage, the practice is waxing even stronger as millions of non-Asians embrace Traditional Chinese Medicine (TCM) and Indian Ayurvedic Medicine (IAM). However, in most of the Third World, where TM patronage is up to 80% of the population, a more complex situation exists, because: (1) while increasing use of TMs in the West resulted from changing preferences, the endemic high patronage in the Third World resulted from chronic poverty and (2) drug regulators in the Third World (where innovative laws are most needed but least well articulated) lack the resources to properly address the nuances of phytotherapy, the way the US and Europe did in 1994 and 2004, respectively. In particular, the literature revealed the sore need for a fresh global look at the whole subject of herbal clinical trials. When are herbal clinical trials (HCTs) required? When are HCTs probably uncalled for? Clear answers are needed, because: many herbal remedies patronized in the West originate from the Third World, where drug regulators, in their zeal for Western Medicine, have not quite seen why the US and Europe opted to fine-tune their laws on herbal products in 1994 and 2004. This review attempts to bring to the open for discussion and resolution the lingering misunderstanding of the place of clinical trials in herbal drug development, especially among bioprospectors/sponsors of drug development, researchers and regulators in the Third World.

Key words: Current phytotherapy, herbal clinical trials (HCTs), drug regulator, traditional medicine (TM), Indian ayurvedic medicine (IAM), African traditional medicine (ATM), traditional chinese medicine (TCM), historical development, bioprospecting

INTRODUCTION

Since the Alma-ata Declaration in 1978, interest in TM had been growing, reaching critical points in 1994 and 2004 in the US and EU, respectively (DSHEA, 1994; De Smet, 2005; Ann Godsell Regulatory, 2008). There, innovative laws were enacted that ultimately changed the hitherto rigid outlook of controlled clinical trials to meet realities arbitrated by time-tested traditions. Paradoxically, the legal engineering that informed the subtle moves of 1994 and 2004 which resolved the argy-bargy in the West over clinical trials of traditional remedies, was lost to most of the Third World which had been the main advocate of the Alma-ata Declaration (Ameh *et al.*, 2010a, b). Owing to the critical role played by clinical trials in pharmaceutical

medicine and medical thinking generally in the last 50-60 years, there had been a tendency to overstretch that role to treatments and practices that had stood the test of time. For example, clinical trial, as an issue, is figured to be critical to the fate of any interesting ethnobotanical remedy. This is because; the following questions are invariably asked in developing such a remedy for conventional medicine: Is a clinical trial required to evaluate safety and/or efficacy? If required, at what stage and for what purpose? When would a clinical trial not be required and why? This review is necessitated by the fact that a great deal of anxiety and uncertainties still dog the events and the decisions that must take place to assure sponsors, researchers and regulators of the safety and efficacy of herbal remedies. To start with: What are

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the immediate laboratory tests that need to be conducted on an interesting ethnobotanical remedy? What exactly is a clinical trial? What are the probable origins, or rather the historical roots, of herbal clinical trials and what constitutes such a trial in TM? These questions are tackled one at a time, to create the background for clear thinking in developing herbal remedies. The importance of the review stems from the fact a decade into the 21st Century, mankind's hope for fresh drug discoveries still lies in bioprospecting.

CLINICAL TRIALS

An overview: The basics of clinical trials were first propounded by Avicenna in the 11th Century (Brater and Daly, 2000) and were applied in the trial treatment of scurvy with citrus fruits (<http://www.faqs.org/health/bios/33/James-Lind.html>). Sikorski and Peters (2009) stated the following:

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.

An immediate import of the two positions is that clinical trials refers strictly to controlled research or 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 therefore 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. For example: None of the 113 plant materials, including the seeds of *Piper guineense* (Ameh *et al.*, 2011a) described in Nuts and Seeds in Health and Disease Prevention, was introduced to health practice through controlled clinical trials. Each material had data on: historical cultivation and usage, present-day cultivation and usage and applications to health promotion and disease prevention. Thus, as will be seen in the next subsection, not all clinical studies strictly fall under the rather rigid definition of controlled clinical trial rendered

above. In general, many or most observational or epidemiological studies, or naturalistic experiments are not classifiable as controlled clinical trial.

Scope, study protocol and classification of clinical studies: Normally, a clinical study can only take place when satisfactory preclinical data have been gathered on a drug or intervention and the relevant Health Authority/Ethics Committee has approved the study protocol and scope of the tests to be conducted. Over the past 50-60 years, clinical research as a biomedical methodology has evolved into a complex enterprise with an array of insightful terminologies that need to be defined. The technical scope and cost implications of most 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 1.

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 protocol and interpretation of results. Since aim is a determining factor in the classification of clinical studies, it follows that aim is critical to the formulation of study protocols. Figure 1 shows a classification of clinical study while Table 2 describes in more detail some of the terms associated with the different types of clinical research.

Table 1: Key working terminologies of clinical research

Term	Meaning
Study protocol	A document prepared 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 remedies) 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 fuller list of terms associated with clinical research is found in (<http://clinicaltrials.gov/ct2/info/glossary>)

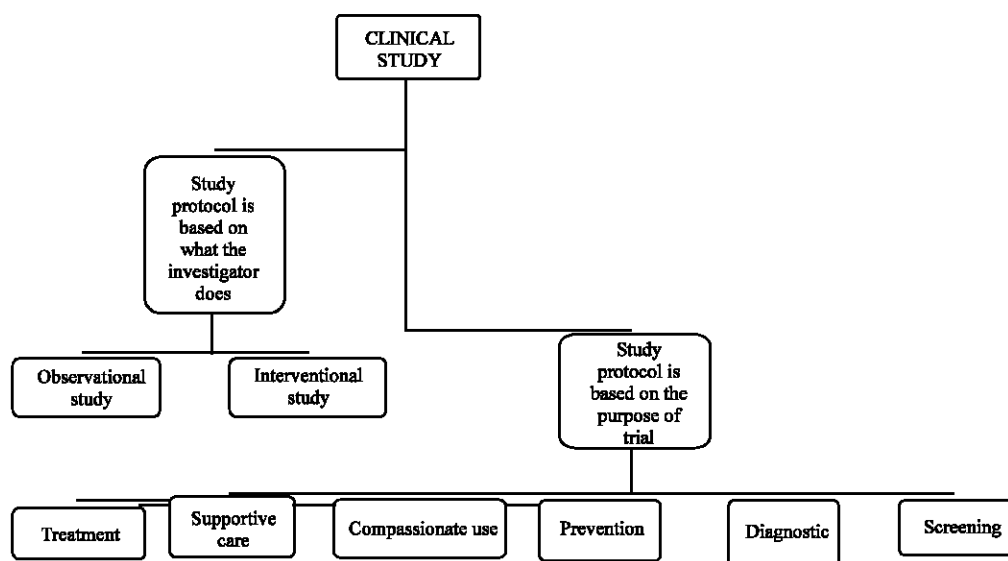


Fig. 1: A classification of clinical study

In an observational or epidemiological study (or natural experiment) 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

Phased clinical research: A four-phased clinical study is usually called into play when a new and promising treatment is in the offing. As a rule, phased trials are nearly always costly-in the region of a billion US dollars

some years ago. Phase-I studies of a new compound or formulation are carried out with a small number of healthy volunteers or patients suffering from the disease for which the medicine is intended. The main purpose is to

Table 2: Classification/ types of clinical study

1. Classification of clinical studies in terms of what 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. Classification of clinical studies in terms of their general purposes	
I. Trials seeking to identify better preventive measures, screening, or diagnostic techniques	II. Trials seeking to identify better curative, or management measures.
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.	a. Treatment trials: these test new doses or a particular disease or condition. combinations of drugs, or new approaches such as surgery or radiation therapy
b. Screening trials: test the best way to detect certain diseases or health conditions	b. Quality of life trials (or supportive care): explore ways to improve comfort/ quality of life for persons with a chronic illness
c. Diagnostic trials: discover better procedures for diagnosing a particular disease or conditions	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. Clinical studies designed to answer very specific health issues	
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 of a new intervention with that of an already approved intervention in patients with a particular type disease.	
The aim of an herbal clinical trial may be to validate safety and efficacy as claim in TM practice; to develop new herbal medicines; to examine a new indication for an existing herbal medicine; to change 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	

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 are also carried out on a limited number of patients to determine clinical efficacy and to further confirm safety. Studies in Phase-II 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 studies are most often large studies involving larger patient groups 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 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.

PROBABLE HISTORICAL ROOTS OF HERBAL CLINICAL RESEARCH

Zoopharmacognosy-a prelude to safety and efficacy studies in animal?: Most drugs in use today in conventional medicine 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 still remain unknown. More recently however, a body of educated conjectures 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 about 457 BC (Scofield Study Bible, 1996). The term literally means animal drug 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 (Unpublished observations by S.J. Ameh). 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 is said to have 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).

Probable instances of animal self-medication and related observations:

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 *et al.*, 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 obochi which literally means wisdom personified.

Biochemical teleology of herbs and spices used in food:

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 and Sherman, 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 and Hash, 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.

Doctrine of Signatures—a probable signal/ impetus for human experimentation?:

Doctrine of Signatures refers to the idea that the shape, colour and other features of parts of a plant may suggest its medicinal purpose. For example, during the European Renaissance, many physicians or physiomedical herbalists followed this idea in prescribing. They noted, for instance, 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 (Redmond, 2008). 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, 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 roles played in human health by culture, belief, psychology and placebo effect.

HISTORICAL LANDMARKS IN THE USE OF BIOACTIVE PLANTS FOR HEALTH PURPOSES

Mandrake: Known botanically as *Atropa mandragora* or *Mandragora officinarum*, mandrake is the object of many tales and superstitions. 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).

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 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 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 (<http://answers.google.com/answers/threadview/id/263405.html>). 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" (<http://www.coffeebargains.com/>).

It may be taken that this Kaldi story provides a link between zoopharmacognosy and human clinical trial.

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. It is known that the wealth of India, especially spices, notably black pepper, were the main attraction for Vasco Dagama'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 (Parveen *et al.*, 2010), 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).

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 TCM, *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 Dispensary 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. African Traditional Medicine (ATM) among the Yoruba of West Africa in the Diaspora (Green, 2006) utilizes a wide variety of spices in preparing medicines. For instance, Niprisan, based on Yoruba medicine contains as spices, *P. guineense* and *Eugenia caryophyllata*-clove (Ameh *et al.*, 2009).

HERBAL CLINICAL STUDY AT A GLANCE

Application of the principles of pharmacodynamics to herbal remedies: Application of the principles of pharmacodynamics to an herbal remedy may uncover or lead to one of the following: 1) a drug whose efficacy has been demonstrated, that is-the active principle is known and its dose is more-or-less established; 2) drug whose efficacy is probable, but has not been clearly demonstrated, that is-the active agent may be used to standardize it and 3) drug with uncertain efficacy but a long history of traditional usage-such drug can be used for treating common disorders, but should be used exactly as in the traditional practice.

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.

Approval: An herbal clinical trial can only take place when the respective national regulatory authority is satisfied

with the quality of data provided on: 1) the safety and efficacy of the drug; 2) the necessity for the trial; 3) how the trial is to be carried out, that is-the availability a detailed study protocol and 4) the capability of investigators/sponsor.

Scope, methodologies and examples of herbal clinical studies: An herbal clinical study may consist of: 1) administration of the drug to selected subjects; 2) 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; 3) the data collected are subjected to statistical analysis. Some examples of herbal clinical research are described in Table 3.

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 *et al.*, 1999) and cover such specific issues as: 1) Interactions between herb and commonly prescribed conventional drugs (Izzo and Ernst, 2001); 2) Adverse effects vis-à-vis herb-drug interactions (Cupp, 1999; Abebe, 2002); 3) Risk-benefit profile of commonly used herbal therapies (Ernst, 2002) and 4) Herb-herb interactions (Houghton, 1988; Wheatley, 2001; Cropley *et al.*, 2002).

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 of the 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. 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

Table 3: Examples of publications on herbal clinical studies 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 <i>et al.</i> , 1998; Leung <i>et al.</i> , 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 (McCord <i>et al.</i> , 1998).
Niprisan herbal trial in patients with sickle cell disease (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. (Wambele, 2008; (http://sec.gov/Archives/edgar/data/919611/000114420406015544/v040579_10ksb.txt))
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)
Trends and Current Status of Clinical Trials of Herbal Medicine in the United States.	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	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).
A systematic review of randomized clinical trials of individualised herbal medicine in any indication.	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	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 <i>et al.</i> , 2007)
Trial of Chinese Herbal Medicine in the Treatment of Upper Respiratory Tract Infections (URTIs)	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	The study is sponsored by the University of Hong Kong (UHK), supported by the Government of the Hong Kong. The principal investigator is Lam, C. L. K. The study location is UHK. The results/ conclusion of the study were being expected as at February 2011

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.

POLITICAL AND SOCIOECONOMIC FACTORS IN HERBALISM AND CLINICAL RESEARCH

As mentioned elsewhere (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 by key members of the West. Wahlberg of London School of Economic and Political Science, had; for instance, argued that the current integration of Vietnamese Traditional Medicine in to the National Health Care System, owed largely to Ho Chi Minh's ideology in his 1955's appeal to Vietnamese scientists: 'to study means of uniting the effects of oriental remedies with those of Europe' (Wahlberg, 2006). The world's most advanced economy, the US, only began to embrace alternative approaches (Holland, 2000) including 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). A fairly detailed account of the origin of interregional differences in herbal drug policy, research and development and what developing countries need to do to take full advantage of their comparative advantage is presented elsewhere (Ameh *et al.*, 2010b).

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.*, 2001). 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 as many more government lend their support for TM practice and with the coming on stream of new Asian, African and European journals committed to herbal remedies. First, as an example, in 2007, after much prodding by academic and traditional institutions, Nigeria finally enacted a TM policy in collaboration with WHO (Lambo, 2007). Secondly, a look at the authors list and the lists of references in the chapters of Nuts and Seeds in Health and Disease Prevention (1st edition) amply demonstrate the huge scope, depth and variety of interest in herbal remedies worldwide.

However, there is, of course, the unending debate 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 and the debates on the status of traditional herbal remedies are not as acrimonious as in the past.

CONCLUSION AND PROSPECTS

It is clearly evident that the popularity of phytotherapy is still on the increase worldwide and that this calls for sound bases for its regulation. But while most of what needs to be done to ensure adequate regulation and patronage is simple enough, there is still a need for sustained advocacy to institute that fact firmly, especially in the developing countries of Africa where traditional knowledge and technology is rapidly fading away. 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 for development to the stage of clinical trials. These agencies should nurture promising TMs the way the US-FDA 2006 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 and D base. Clearly, what is needed is progressive-partnership not adversary-partnership as in a Cold War, whereby TM remedies stand the risk of being hounded into extinction by misguided regulation. It is evident that early clinical trials of promising traditional herbs could become be a powerful bioprospecting strategy if researchers work hand-in-hand with regulators to fine-tune the modus operandi. Also evident is the fact that the underlying issue in most herbal clinical trials is not so much about whether the traditional remedy works but how much of it is suitable for the condition for which it is traditionally prescribed.

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