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Safety, Efficacy, Regulations and Bioethics in Herbal Medicines Research and Practice

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Abstract

Herbal medicines are used by about 80% of the populations in Africa. Despite being the main management strategy for a number of medical conditions, few studies have been done to suggest their toxicity and efficacy. Moreover, herbal medicines are not prescriptive. Users commonly find information from relatives, and friends. The classification of plant herbal medicines as complementary and alternative medicines also remains to be recognised as nutritional products. This therefore presents a special bioethical challenge in both research and practice for both researchers and medical physicians. Research on herbal medicines also demonstrates the lack of consistency in repeatability and reproducibility of their findings. Some studies have also established efficacy while others demonstrate otherwise. Variation in their findings has been attributed to variations in geographical locations of sources of plant materials and soil diversity. Moreover, ethical consideration in research may not have the appropriate social value, validity in research, risk benefit ratio and collaborations required for ethical sustainability. This may be as a result of the different cultures and traditions in the use of plant materials among different communities. In addition, ethical principles such as beneficence and no malfeasance may not be sustainable for all the medical physicians using plant herbal medicines in the management diseases in patients. The patient autonomy is also not valid table from the existing toxicity and safety studies. More research on bioethics is needed to bridge the gap between ethics, research and practice for herbal medicines.

Key words:

Ethics; Safety; Toxicity; Research ethics; Ethical principles; Herbal plant materials; Bioethics

Introduction

It is common practice that most of the dietary supplements are produced in mass, released to the market and sold without the need to conduct the safety and efficacy just like the common pharmaceutical drugs. FDA is charged with the responsibility of providing evidence that the dietary supplements are not fit for human consumption before they can be removed from the market. This is a contravention of the conventional practice for pharmaceutical products for which evidence of safety and efficacy is first generated for approval is granted for production, release to market and then marketing [1].

The discrepancies' in the regulation of the compounds with pharmacological activity therefore raises challenges in the consistency and safety of herbal products currently produced and marketed in mass. Research findings have been able to show that plant variation in the concentration of active compounds with pharmacological activities in products such as ginseng for gingsenosides and eleuthrosides [2]. This also raises questions on the precision and certainty of the phytonutrients components of the products released in the market as supplements. Herbal products are referred as dietary supplements [1], it is also explained as anything that has capacity to supplement the diet. They are considered to be in the form of vitamins, minerals, amino acids, enzymes, organ tissues, metabolites, and concentrates of the same [1]. In contrast to pharmacological drugs, it has been suggested that a dietary supplement cannot be purported to cure, mitigate, diagnose or prevent illness [1]. Moreover, structure activity relations and functions claims have also been widely made in the prevention of most health cases such as support for the natural defences of the body. In this case, it subjects the uses to very thin line of safety, efficacy and regulatory protection frameworks. This therefore can be suggested to go against the theory and practice of the need for ethics on matters of protecting human life.

Safety of Herbal Extracts

The discussion of safety of herbal extracts has been inconclusive in many forums. This follows the perception of herbs as natural plant products and therefore safe and fit for human consumption as supplements [3]. However, many serious reports of side effects of herbal extracts are documented and reviewed [3-5]. This follows the use of biologically active constituents from herbal and their associated side effects which may have been caused by herbs and sides effects promoted by the use of contaminants leading to drug interaction. Examples of such safety concerns in trials are widely available. In Belgium, 105 patients suffered from severe nephropathy after using a Chinese herbal extract Aristolochia fangchi meant for inducing weight loss. In the same study, about 12 patients also developed urethelial carcinoma, 43 developed end stage renal failure, and 39 patients had to have their kidney removed prophylactically [6].

Similarly, the use of a Pyrrolizidine alkaloid also turns tragic in many cases when used as an additive to herbal medicines. It is known to cause venous occlusion which also rapidly becomes fatal when used as a form of treatment [7].

Heavy metal poisoning also occurs in many cases as a result of the use of herbal medicines. A study evaluating the safety of 260 patented Asian medicines revealed that about 25% of the products contained significantly high levels of heavy metals while an addition 7% of the drugs had non recorded new compounds introduced to the drugs to generate the desired effects of the drugs [8].

The safety for most of the drugs is not established. A variety of herbal effects have also been registered. Some herbs extracts interact with pharmaceutical drugs [5]. An example of such drugs includes St Johns worts, it has been suggested to interfere with the activity of cytochrome 450, a key drug metabolic enzyme. It is also a protease inhibitor, interferes with the activity of chemotherapeutic agents, and oral contraceptives [9]. Some plants like Kava, valerian and St John's worts have been found to interfere with anaesthetic agents and many other drugs administered at the pre-operative periods [10].

Some extracts are known to induce excessive biological effects, such as ephedra. It contains ephedrine which has been widely marketed as a product for weight loss and energy regulation and enhancing. However, recent findings have suggested that most users of ephedra are 40 times more likely of reporting a side effect following its use [11]. It has been associated with more than 2 fold increase in nausea, vomiting, psychiatric symptoms and palpitations [12]. This finding is part of the reason that led to the decision by FDA to remove it from market as a toxic product in 2004 [13]. Analogues of ephedrine such as synephrine have also been marketed as products and have similar pharmacological activity [14]. This herb was extracted from the fruit herb citrus aurantium and known as the bitter orange. Complexing the herbal extracts from bitter orange with caffeine has also been recorded to increase the systolic and diastolic heart pressure to about 9mmHg and pulse of 16.7 beats per minute in healthy adult subjects [15]. This is associated with elevated pulse or blood pressure and insomnia.

It is also known that the evaluation of side effects in large clinical trials for herbal extracts are also absent, in adequate and/or fail to cover more than 1% of the events in trial [16]. Miscommunication through the use of wrong information in the marketing of the product, for instance, in a study involving the use of bitter oranges for weight loss [17], only the effect of the herb was evaluated and reported incorrectly by suggesting that it significantly promoted the benefit for weight loss among the users [18] when compared to the placebo treatment. Side effects of citrus aurantium are also rarely mentioned in many of the studies [19]. More often, internet sites marketing herbal extracts claim to treat, prevent, cure diagnose diseases [20].

Efficacy

There are several herbal drugs that have their efficacy studies done on them [21]. *Urtica dioica* has been used for the management of most of immunological, hepatic and nephron damaging diseases. It has also been found to be an effective regimen at various doses of 50 mg/kg, 100 mg/kg to a dose of 450 mg/kg [22].

Other medicines such as *Echinacea* commonly used in the management of common cold have found conflicting findings. In a randomized placebo controlled trials, 9 of the trials found positive findings while other 7 were negative. The lack of consistency in the findings led to the conclusion that there is some positive benefit in the use of the extract in the management of Common cold [23]. A similar high randomized controlled trial on induced rhinovirus did not establish any beneficial effects of *Echinacea angustifolia* [24]. It has been argued that other species of the same plant may possess beneficial effects on the management of the disease [25]. Moreover, it has been determined to safe for use and also possesses similar side effects as those possessed by the placebo groups [23].

Gingseng is a similar plant with potential herbal activity. It has been used in the management of physical and cognitive performance and in the improvement of energy [26]. It has also been used as an ingredient in many drinks and tonics. Several placebo randomized controlled trials did not establish any evidence for efficacy in the management of physical performance, psychomotor performance and, cognitive boosting, immunomodulation, diabetes mellitus and in the management of a herpes simplex type two infections [27]. There have been no issues of toxicity, and hence considered safe. It has however been associated with cases of arousal and hyperactivity [27].

Ginkgo has been used as herbal plant for ages. It is indicated to possess about 24% flavonoids and about 6% terpenoids. Findings and reviews from previous controlled trials suggests that it may be an effective herbal extract for the management of the dementia. This has also been ascertained in the management of Alzheimer's disease [28,29]. However, it was not effective in improvement of cognitive function of elderly patients in the absence of dementia [30]. In addition, was able to manage pain free walking distance [31]. However, it seems to have common side effects in all the clinical trials [32]. It has also been shown to promote spontaneous bleeding among the patient's [33].

Garlic has also been widely studied following the numerous claims of medicinal effects. It has been validated that it has significant potential in the management of cholesterol. It was able to lower cholesterol levels by about 5% on average [34]. However, this has been suggested to be modest in comparison to active FDA approved drugs such as statin which lowers about 17-32% of cholesterol [35]. However, it is associated with gastro intestinal discomfort and bad garlic breath [34]. It has also been associated with increased danger of bleeding after use of garlic [36,37].

St Johns worts have been effective in the management of mild depression [38,39]. However, it has been found not to work in the management of patients with severe depression [40,41]. The use of St John's worts and its association with drug interaction is the main challenge in its use [9].

Most people use Peppermint in the management of irritable bowel syndrome. This has also been supported by about 8 different clinical trials which show the benefit of the herbal extracts. However, no conclusive statements can be made from the research findings as a result of the limitation of the quality of the studies [42]. Few side effects are also reported [42].

Ginger is used in tea and coffee and as a drug for the management of nausea. The potential of application of ginger in the management of post-operative nausea has also been evaluated in three randomized clinical trials. While two of the trials established the beneficial aspects of ginger, all the studies combined recorded a statistically non-significant benefit [43]. It has also been found effective in the management of different sickness; morning and seasickness in addition to chemotherapy induced sickness. The evidence for toxicity is inconclusive but signs of possible efficacy have been recorded [42]. To date, there have been no recorded side effects with the use of Ginger [26].

Soy has been associated with its ability to lower the symptoms of menopause in women. This has been attributed to the presence of

phytoestrogens. It has also been identified to lower the levels of cholesterol. In the recent review of different clinical trials, it has been suggested that increased dietary soy.

Efficacy studies on the use of Soy as a source of phytoestrogens has indicated that it is a weak source of estrogenic activity. In has commonly been used in the management of symptoms of menopause women with hot flushes and in the reduction of the levels of cholesterol. However, reviews of literature from about 9 clinical trials on the effect of dietary soy and other 9 clinical trials on efficacy of soy indicate that it is not effective in the management of menopausal symptoms [44]. Other clinical trials now suggest that soy is effective in the lowering of the total LDL cholesterol by about 4-5% [45]. This effect is considered small compared to findings made on garlic [34].

Chamomile is a common plant for the management of pain, sleep disorders, anxiety, and gastro intestinal problems. Even though the plant is considered safe, there are case reports that have identified serious allergic reactions [46]. The efficacy of this plant is also not well defined as demonstrated from many of the reported research findings.

Kava is also used as a sedative in many places, but mostly in the south pacific region. It is also a relaxant and has beneficial effects in the management of anxiety [47]. Several studies have identified potential hepatotoxicity from the use of this extract [48].

The biggest challenge of relying on this results output from the above studied medicinal plants is that some studies have suggested efficacy while others do not find any efficacy. This is probably a result of poor methodology and hence lack of reproducibility and repeatability of data from similar studies. It also comes from inconsistent outcomes, use of different formulations of the extract and therefore conflicting findings from the results [49]. Limited evidence for efficacy remains a challenge for use of this extracts. Many studies however have inconclusive findings with both negative and positive findings.

Ethics

In order to understand the role of traditional medicines in public health, this required to view all the responses from an ethic perspective. It is the expectation that the traditional herbal medicines need to be subjected to similar standards as those of other drugs used for human subjects [50]. Previous ethical strategies have been well demonstrated [51]. They offer the best direction for possible formulation and adoption in the regulation of current research on traditional herbal medicine. According to the framework developed by Emanuel et al, about eight universal and comprehensive requirements are needed for adapting to the various social environments to which the research can be implemented [51].

In general the research ethics can be categorized into four lines of thoughts: social value, scientific validity, favourable risk benefit ratio and finally, collaborative partnerships. This would have the potential of evoking the specific challenges in the international herbal research communities in addressing all the shortcomings in research for proper ethical practice. The biggest challenges is in meeting the social value, scientific validity and Risk benefit ratio as a basis for international research on herbal medicines (Figure 1).

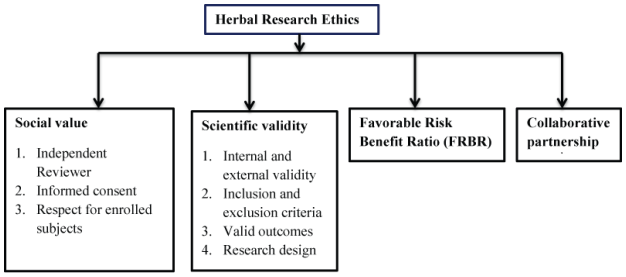

Figure 1: Ethical frameworks.

Social Value

The interest of research is to meet the expectation of the society, which is expressed as the social value. This may however vary from one place to another due to the diversity of the cultures and traditions. However, in the interest of common public health, there is need for defining the safety and efficacy of herbal medicines for the diverse medical conditions such as Malaria [52]. Wrong use of herbs may be detrimental to one's health as demonstrated by the Africa potato [53]. It is often argued that the herbal medicines have stood the tests of time since time immemorial. Recent findings however find big gaps as a result of the inconclusive nature of the data output from the clinical trials performed on some of the Herbal extracts all over the world. Hence, they pose a serious challenge to both the investigators and researchers in this field of drug discovery and development in most of the developed and developing countries. The need for standardization and complete commercial exploitation of the potential benefits from herbal and traditional medicines has called for establishment of safety research programme in developed countries like China. It has specifically focused on the use of injectable herbal remedies [54]. In Africa, South Africa has been on the forefront in identifying the need for investigating traditional medicine within the confines of national drug policy [55]. It also consumes a bigger chunk of the national health budget for several countries and companies (Figures 2 and 3).

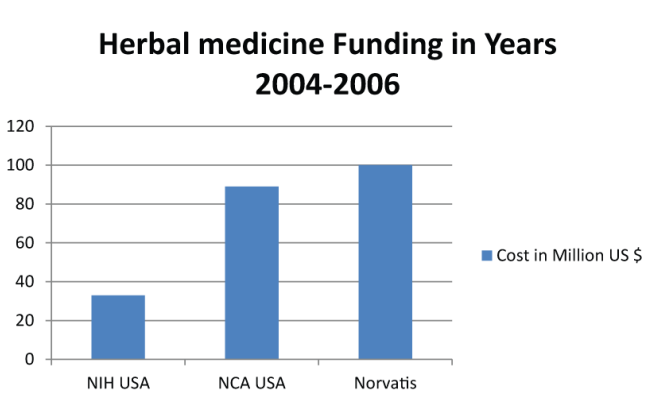

Figure 2: Investment in Herbal Medicines.

NIH, USA represents the National Institute of Health; NCA stands for National cancer Association. Norvatis is a pharmaceutical industry, 100 Million US$ was money invested in herbal medicine research in Shanghai alone in 2006 [4,5,12].

This costs are smaller than the rates in the core pharmaceutical industry and but represents the growing interests in the pharmaceutical industry. This is an indication of the growing interest by the public, private and government in the area of herbal medicines.

It is already clear that for the potential of use of herbal medicines as chemical compounds for future pharmaceutical industries. Large scale bio-screening for therapeutic pharmaceuticals or active components is now being conducted for all potential medicinal medicines with potential medicinal values.

Africa has demonstrated growing interest for promoting and preserving the traditional knowledge on the use of herbal medicines. This is active in Senegal and Dakar through the activities of Non-Governmental organizations such as the Association for the promotion of traditional medicines [56-59].

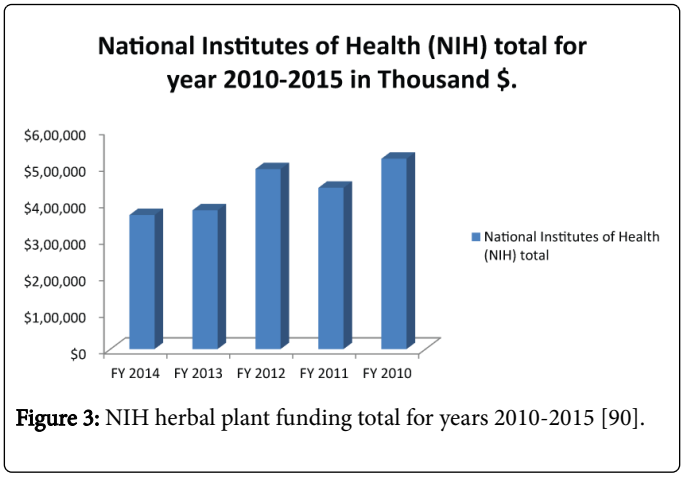

Figure 3: NIH herbal plant funding total for years 2010-2015 [90].

Countries in Africa have also taken the initiative of preserving the local culture and sharing of their knowledge to the global health as a way of increasing the countries market share. This has taken root in Nigeria [60].

However, the perception for the need of research on traditional medicines differs from country to another. In the absence of social value, the ultimate impact of the use of herbal medicines will be null and void in the near future. Involvement of the public as stakeholders in these discussions through interviews and use of questionnaires in qualitative research will be the best tool in fact finding for the relevant social value and impact. The extension of the social value beyond the borders will also offer a good basis to give room for partnership.

Scientific validity

To ensure safety and efficacy of herbal medicines, proper science needs to be applied in the research studies. Despite collaborations may be the hallmark for herbal medicines, the scientific validity is a special ethical requirement. It addresses specific scientific challenges. It is able to address the aspect of scientific validity. It also determines the strategies for inclusion and exclusion of study subjects. Moreover, it establishes how best the outcomes can be used as a measure of the findings for the study and finally, it guides the formulation of the required study design.

Internal and external validity

In any valid scientific research, there are two aspects that require consideration: Internal and external validity. Internal validity refers to the reliability of the tests that has been hypothesized and the relationship between the intervention and the outcome applied under the controlled conditions for the study [61]. External validity represents the possibility of application of the research results to another targeted population outside the experimental settings for the study. The output of external validity needs to be comparable to the internal validity research output.

The disconnection between the internal validity and external validity raises lots of questions on the value and meaning of the result findings of the output. A case in this context is the recent study on the use of *Echinacea angustifolia* extracts in the management of para-influenza virus infection [62]. It was established that the study did not give emphasis on how the herbal medicines are used. The experimental aspects needs to apply find the connection between the practice and theory in the real world application.

Some of the variations in the use of the drug are as a result of the source, preparation, dose, and indication. Moreover, generalization of findings from the various clinical trials is a challenge to the dissemination of the data collected from herbal medicines. Hence, there is need to ensure that every study meets the internal and external validity requirements.

Inclusion and exclusion criteria

In order to ensure that the results are externally valid, there is need to ensure that the inclusion and exclusion criteria for involvement in the research are in tandem with the current diagnostic practice in the target population. The lack of uniformity in medical systems across countries is the biggest challenge for standardization of herbal medicine research practice in inclusion and exclusion criteria. Several cases have been used in various countries while recruiting subjects for clinical trials involving herbal medicines (Table 1) [63-65].

Measuring valid outcomes

Emphasis on the need of using data in contributing to the new body of knowledge is very essential in any scientific study. Outcome measures that capture the general effects conferred by the herbal medicines need to be used in all herbal medicinal studies. The terms also need to be precise and specific for the effect of use of herbal medicine [66]. Valid methodologies that measure the desired effects therefore have to be applied so as to make sense in the healing tradition [66,67]. New measures also need to overlap with existing instruments and tools applied. This will significantly contribute to building on the existing body of knowledge.

Developing an appropriate research design

All human research needs to be done in accordance with the recommended study designs. The components and characteristics of a valid research design are however debatable. For instance, in medical studies, it is recommended that one should be able to use randomized double blind studies in the evaluation of efficacy of a clinical drug. Placebo controlled trials can also be done in many cases as a research design. The use of other study designs makes the science from such studies invaluable since it a deviation from the scientific validity.

It is also argued that the use or scientific methodologies on traditional medicines may fail to generate new and true knowledge since their relevance relies on the use of scientific vocabularies that

only remain relevant in biomedicine [68-70]. Some repute that experimental designs are western and imperialistic in nature [68-70].

It is advisable that randomized controlled trials should be applied in research of herbal medicines. It they have the best model for building on the knowledge on the safety and efficacy on herbal medicines despite being imperfect [50,61,71].

In the implementation of Randomized controlled trials (RCT), the treatments arms are individualized to the patients. This can be also be used for evaluation of several or dozens of herbs using the commonly used form of preparations. Double blind RCT designs have also been applied in some clinical trials. Some studies have adopted a three arm controlled trials in the evaluation of the clinical efficacy of the standard complex herbal extracts, customized therapy and a placebo [72]. The study findings were able to show comparable beneficial effects between the standard and customized therapy to the placebo group.

Case	Country	Inclusion/exclusion criteria	Short coming
SARS epidemic [17]	China	deficiency of chi and yin stagnation of pathogenic phlegm	It requires additional effort and medical flexibility to categorize subjects on the basis of nosological conditions. Not the best for maximizing external validity
Heart failure [18]	USA, new york heart association guideline	Heart yang chi deficiency Kidney yang deficiency	Limited ability to maximize external validity
TCM practictioner [19]	All communities	Pulses Tongue examination Other elements of traditional diagnosis	Has potential to maximize external validity

Table 1: Inclusion and exclusion gaps in clinical trials.

Moreover, cluster RCTs may also be used in many of the cases. This allows the researchers to be establishing the variability of the practitioners while evaluating efficacy of the therapeutic methods. In a cross cultural setting, the research questions also need to respond to aspects of the cultural contexts.

Ethical issues emanating from many of the studies on traditional medicines have attracted attention to issues revolving around financial conflicts of interests, publication bias, clinical trial registries, cross cultural variations and validity of the science. There are many of the positive studies on herbal extracts in many places such as China. This raises lots of efficacy questions and long term scientific credibility of the international herbal medicine research. All this aspects of research needs to be addressed on the outset.

Measuring favourable risk-benefit ratio

The link between theory and practice raises several accurate risk benefit queries in the international herbal medicines research. The normal procedure in pharmaceutical companies involve a step wise process which includes: isolation of compounds, testing on cultures, tests in animals, then phase 1, 2 and 3 clinical trial testing. However, it is common knowledge that the herbal medicines are commonly used despite the variations in their species, growing environments and conditions and biological constituents. It is therefore believed that their applications have always been as a result of the trial and error. Hence, the clinical basis for dosing is weak and not often given consideration in practice. Similarly, the purity, stability, quality and active constituents are therefore the biggest challenge in herbal medicine trials [73,74].

Involvement on large scale research trials hence should be able to justify the risk and benefit ration for participation in the research. Herbal studies also need to factor in the uncertainty of product variability in making a decision on the risk benefit ratio of the herbal extract. The reviewers also need to define the safety and efficacy of the extracts.

It is also a common understanding for the need to develop a rational dosing standard for biologically active compounds [75,76]. Determination of dosing greatly gives strength on the assessment of risk and benefits in the participation of large scale herbal medicines. Standardized use of procedures in reporting safety and efficacy will significantly contribute to long term effectiveness in establishing risk benefit ratio in clinical trials [77].

Culture may offer a good contribution to decision making on the risk and benefits in herbal medicine research. Familiarity of the history and culture for which the drug has been applied and considered to be applied is essential in herbal research [78]. However, this may offer a challenge when considered on the basis cultural differences on the risk benefit ratio [79]. Standardization of the protocols in the search for evidence based demonstration of the safety and efficacy before the use of the herbal medicine extracts for clinical trials is required.

Collaborations and partnership in research

It is a requirement by the international research ethics that collaborations need to be part of the scientific studies. The rationale is to provide the proper application of the ethical requirements. For this to be effected, the scientific vocabulary needs to be common on aspects of social value, scientific validity, favourable risk benefit ratio. Collaborations allow for partnerships in the implementations of the international research ethics in the use of common language and goals. These strategies enable a safe and collegial process in the making of decisions [80]. It is also positive in the generation of social values in a rigorous clinical research [81]. This will also allow sound research in international scientific investigation in international herbal medicine. Sustainable collaborations and partnerships will greatly boost the independent and adverse reporting of events in herbal systems research. This will help in the establishing of the risk benefit ratio for use of herbal medicines in research. A comprehensive framework is however needed in addressing ethical challenges in traditional and cultural medicines. Collaboration and partnership is needed in the

implementation of research designs. This will define and propel better research findings in traditional herbal medicine that will contribute positively to the global health

Ethical decisions in herbal medicine and practice

There are various guidelines that provide direction on the decisions that should be made in line with the use of conventional medicine. This includes the principles of beneficence, non-malfeasance, patient autonomy, justice and public accountability.

These principles provide a guideline on how clinicians need to interact with the patients and which serves the primary function of medicines in complementary and alternative medicine. As a result of the growing need to adopt the use of herbal medicines in Africa and Western world, ethical principle that work on this platform needs to be reaffirmed [82].

Beneficence caters for the clinician's obligation in the promotion of the good health of the patient. This requires appropriate measures so that only positive outcomes can be assured in the management of the patients as expected by the medical practice [83]. Moreover, Beauchamp and Childress [83] categorize beneficence into utility and positive: Utility refer to the efforts of the individuals in considering the advantages and hazards that may affect a patient so as to ensure the best solution is reached. On the other hand, medical professionals including the clinicians have the task of preventing others from getting harm as a way of ensuring positive beneficence. Moreover, it is expected that the safety and evidence based efficacy of the management strategy has to be determined before they can be applied on the patient [84].

Non malfeasance is the ethical principle that gives the responsibility of the medical physicians to not harm others (Beauchamp and Childress, 2009). It is described closely with beneficence. However, they represent different aspect of protecting the patient's. The duty to prevent harm is very different from the duty to always ensure the well-being of the patients [83]. Despite the plant extracts being natural products developed through metabolic processes just like in humans, they may not be safe for human consumption [85]. In case of harm, preventive strategies for management of patients need to be in place as a way of nonmalfeasence. It is important that all possible risks of use of natural herbal plants be evaluated for use as medicines.

The patient autonomy is also used in the evaluation of herbal medicines. However, the challenge with the use of herbal medicines is that is not prescription regulated, this has been the motivation behind the widespread use. The most common use has been on self-care of patients. This also raises many questions on the amount of information that the patients have to make personal informed decisions [86]. The common practice has been to collect the safety and efficacy information form relatives, magazines and online blogs through the Internet [87-89]. It is the responsibility of the clinician to search for information and share it with the patients. Hence, they are the most relevant and important source of information.

Conclusion

Herbal drugs are the most widely used form of diseases management all over the globe. Unlike herbal plants, potential pharmaceutical compounds with pharmacological effect for recruitment as drugs require complete safety and efficacy profile through clinical trials. In complementary and alternative medicine, herbal drugs with potential pharmaceutical effects remain to be recognized as nutritional products. Similarly, findings from studies show that there is absence of consistency in the safety and toxicity study findings for many potential herbal plants with indicated medicinal properties. In addition, lack of proper regulation to govern the use of plant herbal extracts may contribute to the poor ethical practice in the management of patients placing the big populations of patients using herbal drugs at risk. Therefore, there is need to establish better standards that will be able to govern the research and use of traditional drugs as complementary and alternative medicines. This will offer the link between the theory, research and practice in the management of diseases. Furthermore, it will offer long term solutions on the ethical protection of the patients all over the globe.

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