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ABUILDING BRIDGE BETWEEN PEOPLE OF KNOWLEDGE

MODERN MEDICINE & COMPLEMENTARY ALTERNATIVE MEDICINE

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ABSTRACT

Drug resistance, the evolution of diseases around the globe especially in developing countries coerces (forces) scientists to liaise (collaborate) more efficiently with nature. An optimistic approach between the two systems (CAM & Modern medicine) has to be harnessed to establish desired health care system that effectively alleviates diseases.

Keywords: Clinical pharmacognosy; natural products; clinical significance; social implication; research implications

INTRODUCTION

First question we need to ask ourselves is, “Why we are denying the basic and the foremost source of health maintenance on this planet?”. Phytomedicine/ phytotherapy is the oldest form of treatment and is still practiced by majority of population living in different regions of the world. Rural

populations of almost every country especially in Asia prefer phytotherapy and these regions do possess unique flora whose significance is already attracting scientists. In this scientific era we have opportunity to prove their significance in our lives. Many objectives can be fulfilled through this effort

of scientists either we will be continued to practice them or we will identify the resourceful components present in them. China is the only country seriously struggling to preserve the phytomedicine (**Fatai Oladunni Balogun et al., 2019**).

Phytomedicine is the *mother* of Medical medicine. Currently, unproven quality, safety and efficacy are the main issues which need to be addressed rather than completely eliminating the centuries old knowledge. Always the preferred form of treatment is the one accessible health resource available to community. However, phytomedicine is yet to scale through clinical trials to establish their safety and efficacy profile. After their clinical trials phytomedicine will be included or integrated into the national health care system of their countries. As we all know the time taken by drug to reach clinic is more than a decade and huge investment is required to market them.

Why Phytotherapy should be considered part of healthcare?

Concept of phytotherapy is not unknown but since the birth of mankind. Ancient Egyptian used herbs for the treatment of diseases. Ayurveda and Unani systems of medicine define health as a state where physical body senses and psyche are in original or natural state with respect to body and function.

Ancient science, “Science of Mercury” and Pharmacopoeia of ‘Ayurveda’ comprises of drugs not only derived from plants but also other sources (animals, minerals, metals etc.). A very famous practice of *similasi milibus* (Homeopathy) is also not unknown to world of medicine. Much literature has already discussed the ancient sciences of healing so I am not going in detail here.

A very significant science of healing was “the Chemical therapeutics” Paracelsus, the Creator of Iatrochemistry. In this science human body was treated as a chemical system. Restoration of this chemical system is considered to be a cure of disease. This concept has dominated the modern science in the form of pharmacology/chemotherapy (Iatrochemistry/medical chemistry) (**Hosein Tajadod, 2014**).

Every system of medicine mentioned above utilized nature as a source of treatment in one form or the other. One practice which people never reported to do in the past is they never used to compare new/existing treatments with a placebo or control. They often do not include factors like family history, coincidence etc. while treating the patients. In the past people lack the complete knowledge about the physiology of body. Understanding of the body’s physiology has changed the history of medicine.

Global perspective of Phytotherapeutics:

The World Health Organization (WHO) does consider herbal medicine (HM) as medicine (herbs/herbal formulations). They are now named as “authorized medicine” in Europe, “Dietary supplements” in United States when prescribed by a herbal practitioner, a physician or a pharmacist. Population of Industrialized countries considered phytotherapy as a part of Complementary and alternative medicine with synthetic pharmaceuticals (for symptomatic relief as well as treatment). Major populations of developing countries use phytotherapy as an affordable treatment. So, the immediate step needed is to establish continuous pharmacovigilance activities to improve the safety profile of each medicinal product.

(Wegener T, 2017)

Birth of Modern Phyto pharmaceutical Industry

Phytopharmaceuticals is not a new theory for physicians but systematic clinical trials are necessary to enhance global acceptance in this scientific era.

Current phytotherapeutic market is in swing due to various reasons. Firstly, Phytotherapies are consumer’s preference because of side effects associated with modern medicine. Secondly, psychological

believes and ease of self-medication. Thirdly, cost of synthetic medicine.

Companies often invest in researches which mostly can be patented to gain profit. Why people are not investing in this is due to the major factor that plants cannot be patented so no one is willing to invest in this research. Huge investment is required to get a final approval from authorized authorities.

however, people are continuously using phytomedicine without any safety profile and if they are using then it is also a proof they must get some cure if not complete cure with this there is a possibility of experiencing some side effects too . So, considering this *real fact* we must think seriously to collaborate with traditional healers and with them solve the issues of health rather than waiting for a perfect scenario and meanwhile rejecting centuries old knowledge. One reason of even side effects reported with modern medicine also strengthen their belief on phytomedicine. Currently modern medicine is also turning towards concept of personalized medicine, Traditional healer’s physicians of the phytomedicine are already often counsel patients and they know well about patient’s environment, prescribe individual regimen. Our focus is health for all so, we should focus on establishing safety

and rejecting wrong therapies after scientific evaluation.

It is a known fact that this knowledge was not preserved and adulterated but with collective efforts we can now identify correct remedies and document them for future research (Ernst E *et al.*, 1998). For a private industry cost of conducting a clinical trial is improvident so, with collaboration with traditional healers we can analyse the effectiveness of therapies in patients under treatment and if not completely it will provide some clinical evidence.

Clinical studies of Phototherapies: Impact/significance

Safety of phytotherapies is an issue which must be addressed properly due to complex nature of phytoagents. Clinical studies of phytotherapies (phytopreparations) will establish a link a chemical signal with a biological effect with clinical relevance. Significance of clinical trials is immense as it will transform knowledge of prior human experiences to obtain reproducible clinical effects, for example, human immunodeficiency virus type 1 infection treatment with green tea (Cooper, R., 2007). Although scientific evidence received after conducting studies *in vivo* animal models, small-scale clinical tests proved effectiveness.

Although people using herbal medicine claim lower toxicities but herbs do cause interactions (drug-drug/drug-herb/drug-food). (Blondeau S *et al.*, 2010 ; Shinde V *et al.*, 2008 ; Efferth T & Kaina B, 2011; Ulbricht C *et al.* , 2008) . Clinical trials of the phytotherapies is to be considered seriously because of few toxicities (embryo toxic, genotoxicity, teratogenicity, reproductive toxicity) reported, (Chaudhary Roy *et al.*, 2001;Chan K , 2003) for example, embryotoxic effects of 'Pippalyadivati' (traditional contraceptives and Quantity-toxin effects of Radix Bupleuri Chinensis are recent reported events confirming toxicity caused by phtoagents (L. Lv, W. Huang *et al.*, 2009).

However, Processing methods too effect toxicity of phytoconstituents, excessive heat the bitter almond enzyme loose activity and then decrease the toxicity of almond which contains cyanophoric glycoside. Similarly, in aconite and monkshood alkaloid (Diesterdi terpenoid upon heating decomposed to low toxicity whereas, antagonistic effect of ginger (*Rhizoma Pinelliae*) are to be considered in support of phytmedicine. Due to complex nature of phytoconstituents their toxicities have been divided in two classes like Intrinsic toxicity (direct) i.e., at normal therapeutic range/overdose whereas external

toxicity (indirect) from contamination of products by external stimuli (toxic metals, adulteration, improper processing/storage) e.g., Akebiae substituted by Caulis Aristolochiae Manshuriensis /*Stephania tetrandra* by *Aristolochia fangchi* (nephropathy). So, toxicity studies of phytomedicine creating a need to conduct clinical trials **(Bhattaram VA et al., 2002)**.

Hurdles in piloting clinical trials

However, following are the expected inaccuracies in clinical trials of phytotherapy reported in literature,

1. Lead Toxicity
2. Designing of placebo due to aroma and color
3. Ethical concerns
4. Standardization of polyherbal nature
5. Pharmacokinetic studies (phase I) **(Bhattaram et al., 2002)**,
6. Loss of bioavailability due to improper storage conditions. **(Thatte, 2005)**
7. Effectiveness of drugs for inclusion or exclusion criteria in clinical studies (Prakriti in ayurveda called) **(Dahanukar & Thatte, 1997)**
8. Unstandardized medical procedures
9. Variations in crude raw herb material (Environmental as well as man

handling) for reproducible quality **(Bauer & Tittel, 1996)**

10. Approach of not differentiating disease from patient
11. Continued interventions at different stages of disease not possible in clinical trial
12. No toxicity data is available (unrecognized embryotoxic, foetotoxic, carcinogenic) **(Chaudhary et al., 2001, Chan, 2003)**
13. Poisonous herbs are also hindrance to be used in clinical trials **(Moore & Adler, 2000)**
14. Interactions with other medicine as
 - Bleeding- when warfarin is combined with *Ginkgo biloba*, garlic, dong quai or danshen
 - Serotonin syndrome- when St. Johns' wort is combined with serotonin- reuptake inhibitors
 - Induction of mania in depressed patients - when antidepressants are mixed with *Panax ginseng* **(Fugh-Berman, 2000)**.

Double blind randomized clinical trials needs large volunteer groups and is of long duration and requires expensive healthcare services. Moreover, one major problem that exists is that the funds for such trials, is usually not

readily available (Shukla et al., 1991; Armstrong & Ernst, 1999).

Considering the holistic (i.e. treating mind, body and soul at the same time) approach suitability of randomized clinical trials is

questioned in the CAM concept. They individually treat a patient. Same treatment cannot be tested in all participants in same manner, amount (Kristofferson, 1996) (Ashish K Sharma et al., 2010).

Table 1: Reported safe clinical trials (Ernst et al., 1998)

Natural source	Treatment	Clinical Trials
<i>Ginkgo biloba extract</i>	CNS & CVS disorders	Safe proved
<i>Hypericum perforatum</i>	St. John's wort, used as an antidepressant	
<i>Tanacetum parthenium</i> (feverfew)	migraine headache,	
<i>Panax ginseng</i> (ginseng)	Tonic	
<i>Allium sativum</i> (garlic)	lower serum low-density protein, cholesterol level and some cardiovascular disturbances	
<i>Matricaria chamomilla</i> (chamomile)	carminative, anti-inflammatory and antispasmodic	
<i>Silybum marianum</i> (milk thistle)	cirrhosis, normalizing liver function	
<i>Valeriana officinalis</i> (valerian),	sedative and sleeping aid	
<i>Piper methysticum</i> (Kava kava)	Anxiolytic	
<i>Aesculus hippocastanum</i> (horse chestnut)	chronic venous insufficiency	
<i>Cassia acutifolia</i> (Senna)	Laxatives	
<i>Rhamnus purshiana</i> (cascara sagrada)		
<i>Echinacea purpura</i> (Echinacea)	anti-inflammatory and immunostimulant	
anti-inflammatory and immunostimulant	post-traumatic and postoperative conditions	
<i>Serenoa repens</i> (saw palmetto)	benign prostatic hyperplasia	

Herbal medicines with the largest worldwide market, have been evaluated in different clinical trials, additional well-controlled and appropriate randomized clinical trials are still needed in order to prove their efficacy (Bauer & Tittel, 1996; Harrer et al. 1999; Armstrong & Ernst, 1999).

With results obtained from clinical trials we will be able to set clinical endpoints. This in future will have economic significance for the countries exporting phytoconstituents. It will increase internal trade and good returns will be generated. Currently, lack of appropriate methods of evaluation is

bottleneck in the clinical trials of phytotherapies commonly known as. "People's medicines" (Linde K et al., 2001).

Unique blend of skills and expertise for Clinical trials

Identification of active ingredients and transformation into modern medicine is not a simple approach. Plants are self-manufacturing machineries they produce phytochemicals to heal them, to protect them from environmental stresses, to grow them, and to produce varieties. Drug development from natural sources is only thinkable with the participation of many disciplines of

science. It is not a one man show a collaborative effort is much needed.

Ethnobiologist document medicinal plants to be used as pharmaceuticals. Botanist is the one who identify the passport data of the plant. Medical botanist – identifies the plant for treatment of illness, Pharmaceutical chemist reveals chemistry of phytoconstituents (active sites of the drug moiety), scientist specialized in nutrigenomics reveals facts about influence of molecular and metabolites in control of gene expression. Pharmacogenomics' scientist guide about body's response to drugs (Individual's genetic makeup). However, **Pharmacognosist does** Ethanobotanical survey, phytochemical analysis, pharmacological evaluation (biological activities). Pharmacognosist is true experimental and investigative scientist in the field of phytomedicine because he deals with the conservation of medicinal plants ,study biodiversity in search of novel drugs ,separate and identify organic natural compounds of therapeutic significance , works on biochemistry of isolated actives as well as look at biosynthetic pathways and finally study pharmacological effects. But he lacks training to prove complete clinical significance of phytotherapies.

Clinical Pharmacist –Physician Relationship

The field of clinical pharmacy is in practice (a branch of science promoting rational use of medication merging therapeutic knowledge, clinical experience, Therapeutic drug monitoring (TDM) as well as diagnosis). However, to accomplish this task clinical pharmacist collaborates with physicians (recognition of therapeutic system and patient records) (**Jenkins N, 2010; Stubbings J et al., 2011**). Clinical pharmacist is a knowledgeable person with full command on disease etiology, drug allergies, drug interactions and patient monitoring for choosing a rational drug and regimen.

Clinical Pharmacognosist-Traditional health keepers Relationship

Lack of systematic reviews and evidence-based data about the efficacies of herbs in almost every culture is a big barrier which needs some reforms. One highly appreciated effort has already done by traditional Iranian Medicine. (**Hasani-Ranjbar S et al., 2009; Hasani-Ranjbar S et al., 2010**). Wrong Indication/Inappropriate use of phyto-medicine result in undesired effects that can be life threatening. Heart attacks and strokes are reported in US with overdose of dietary supplement containing Ephedra. Interactions

are also reported between phyto-regimens (Radix Bupleuri, Fructus Gardenia, Fructus Schisandrae Chinensis, *Semen Plantaginis*) and allopathic regimens antipsychotic drugs (Quetiapine, clozapine) (Junhua Zhang, 2015). Similarly, bleeding with co-administration of Ginkgo biloba and garlic with warfarin, Serotonin syndrome with St. Johns' wort and serotonin-reuptake inhibitors, mania induction with Panax ginseng and antidepressants.

“Clinical Pharmacognosy: Contribution of pharmacognosy to clinical trials of botanicals and dietary supplements” termed coined for the first time at American Society of Pharmacognosy. (Makino T., 2011; Cooper R., 2007). This recent raised demand of the use of herbal drugs along with the large population of the world belonging to developing countries compelling scientist to establish safety (quality control (identity, purity, consistency), efficacy (therapeutic indications, clinical studies, pharmacological investigations), documentation and safety (adverse reactions, drug interactions, contraindications, precautions and toxicities), rather than denying the facts blindly. This study will bridge the gap between clinical research and botanicals knowledge which ultimately help to establish safety in rational herb use.

A clinical pharmacognosist's role is similar to a clinical pharmacist's role but he lacks veracious training. Clinical pharmacognosist will be able to deal with the population taking herbal drugs in addition to this will be able to preserve traditional knowledge. A clinical pharmacognosist will have full command on identification, analysis, standardization, control, documentation eventually form the basis of use of natural health products with scientific evidence. So, besides all sciences inclusion of traditional healing science is also mandatory to leave no gap in the flow of knowledge.

Pharmacognosy's continued and increased legitimacy depended on its ability to integrate standardisation methods, elucidation of total chemical and pharmacological profiles and clinically proven treatments into the development of phytomedicines that could be used with confidence in medical regimens, as well as laying a much more scientific basis to the claims made for “health foods”, “dietary supplements” and “complementary/alternative medicines”. (Barnes J., 2000).

Medicinal flora should be done to fulfill local demands and great revenue can be generated by exporting them.

Impact of Clinical research in Phytotherapy

This practice may help us in designing Personalized medicine: Although idea may be weird Genetic makeup of people living in one region supports the same flora as environmental factors are same for both. So treating people with the flora of the same region may be more beneficial. But hard link with clinical trials yet (Ahmad I et al., 2006) needed. Researchers are working hard some explanatory and pragmatic studies conducted will improve in the reliable data acquisition for both traditional healers as well as patients. (Fabio Firenzuoli and Luigi Gori, 2007). Currently, Modern medicine denies completely and put phytotherapies in category of belief only (magical energetics principles). But we should select and sort out effective from ineffective therapies through scientific evidence. Conflicting views by both medical systems should not affect the health of humans but by breaking barriers between both systems may find a well-defined solution.

Careful selection of phytotherapeutic agent:

Phytotherapies/ phytotherapeutic agents must be carefully and statistically selected for the clinical trials. In this way we can compile results accurately and effectively as some indigenous healers consider, “All plants curative”. Following some quantitative tools

may help, Relative frequency citation (RFC), Use value (UV), Informant consensus factor (ICF), Fidelity level (FL), Relative popularity level (RPL), Rank order priority (ROP) indices (Heinrich M., 2003). Almost in every ecological zone sufficient plants grow for common ailments (diarrhea, respiratory problems, skin infections etc). Some plants are selected on the cultural basis accepted for extended periods of time. (Weckerle et al., 2011).

Situation in Pakistan:

Highly cultivated land of Pakistan is also a source of highly diverse medicinal plants which can be a good source of new drug leads for new drug development. About 6000 flowering plant species out of which 600 species are reported to be of great medicinal value but a portion is being processed on commercial basis (Cotton, 1996). By initiating certain projects with the collaboration of pharmaceutical companies we will be able to find new recipes for the treatment of diseases but it will be only possible after success of clinical trials.

Although Pakistan is a developing country and often literature on herbal medicine use illustrated that mostly people in developing countries use phytomedicine but practically it is seen that both the developing and developed nations are using phytomedicine

for medical and nonmedical reasons. Pakistan's traditional medicine system is based on unani, ayurvedic systems of medicine. Pakistanis considered them to be safe and efficacious. In Pakistan patients self-medicate them with phytoconstituents with or without informing their physicians.

Currently in Pakistan,

1. approximately 53000 registered unani medical practitioners (public & private; urban & rural)
2. About 360 *tibb* dispensaries & clinics
3. About 95 dispensaries under provincial departments of Local Bodies and Rural Development
4. one *tibb* clinic under the Provincial Department of Auqaf.
5. 16 000 diploma-holding unani physicians of traditional medicine (the National Population Welfare Programme)

6. About 40 000 registered homeopathic physicians (National Council for Homeopathy)

Practice of alternative medicine is considered lawful in Pakistan and approved Tibbia colleges are teaching this education (Thousands students are enrolled). This alternative form of treatment/ phytotherapy is accepted and even integrated into national health system in Pakistan and is also part of the law. Although law forbids certain practices like surgical procedures entitled to registered medical practitioners and prescription of certain drugs like antibiotics/dangerous drugs (**Ordinance 65 of 7 June 1962 (165-166)**).

Essential Medicines and Health Products Information Portal A World Health Organization resource

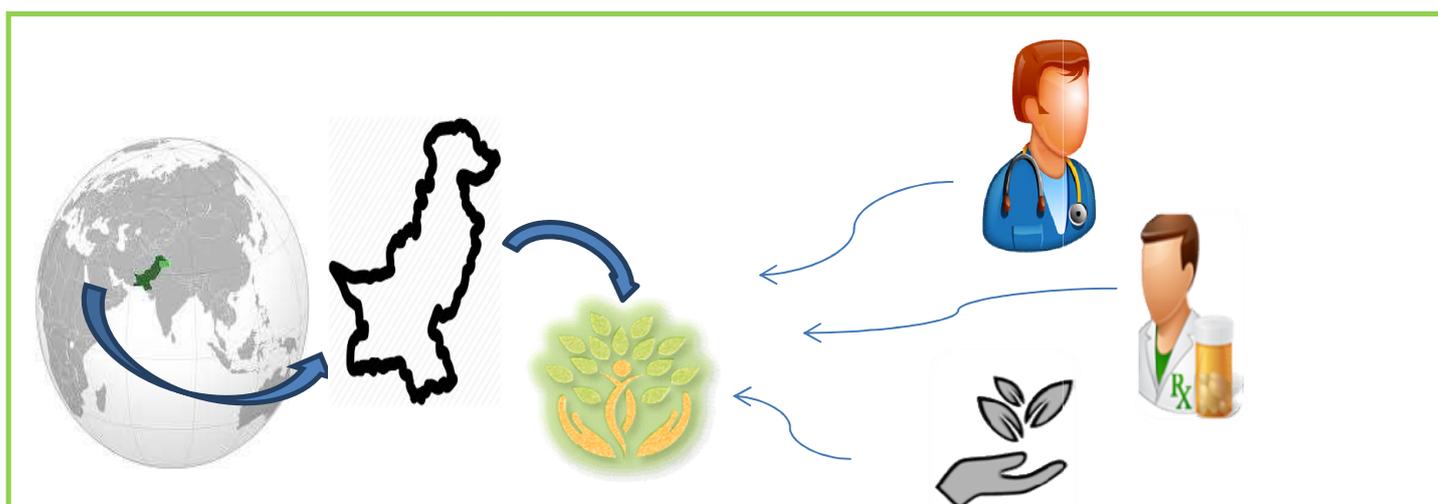


Figure: Healthcare system of Pakistan

CAM healers inclusion in Primary Healthcare

There are multiple reasons supporting inclusion of Complementary health care providers in primary healthcare. These are enlisted below,

1. CAM healers know the socio-cultural background of the people
2. They are highly respected and experienced in their work
3. Economic considerations
4. The strength of traditional beliefs
5. The shortage of modern health professionals

CAM therapies function and heal through their influence on the immune system of the human body. In pluralistic health care system of Pakistan only a balanced approach will be suitable to enhance the strength of overall healthcare system. Integration of these two systems to decrease the communication gap between public and health care providers is necessary at least in terms of evidence – based information sharing. It will be cost effective and ultimately help in reducing the disease burden. Although some CAM therapies may be rejected and some scientific evidence too through this practice. But the main objective must be accepting the truth in healing. **(Babar T. Shaikh & Juanita Hatcher, 2005)**

CONCLUSION

Respecting the traditional knowledge with appropriate evaluation will facilitate the scientific evaluation and the drug development process. By practicing the balanced approach will help global community to use medicine rationally. A uniform research policy is also required by governments **(Calixto JB, 2000; Chen et al 2016)**.

Future Perspective

In future it will interest pharmaceutical companies and researchers.

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