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Review Article

Traditional and Complementary Medicine: Historic Review and Global Nexus of Ethnopharmacology

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Abstract

The use of traditional and complementary medicines in the treatment of diseases and ailments is on the increased in both developing and industrialized countries. However, despite its long existence, popularity and widespread use, many plants used in traditional medicine systems still await scientific investigation to ascertain their claims. Safety concerns is a major drawback with the use of medicinal plants. Ethnopharmacology is directed at identifying the compounds in traditional medicines that are relevant for pharmacologic or possible therapeutic purposes. Ethnopharmacology-driven drug development is unique as it employs an epidemiological knowledge-based approach especially since these plants have been used for centuries without documented toxicities to humans. This review outlined the history of ethnomedicines and process of ethnopharmacological investigations.

Keywords: Ethnopharmacology; traditional medicine; physiological relevant; health and diseases

Introduction

The World Health Organization estimates that 80% of the world's population use some form of traditional herbal medicine for some aspect of primary care [1]. In developing countries, there is a resurgence of interest in herbal medicines for treatment of various ailments majorly due to the high cost of allopathic drugs, their unavailability in remote areas and due to popular belief, that herbal medicines are without adverse side effects. Herbal medications are thus in developing countries, an alternative way to compensate for perceived deficiencies in orthodox pharmacotherapy. In Nigeria, Ghana, Mali, and Zambia, herbal medicine constitutes the first line treatment for 60% of children with high fever due to malaria [2,3]. In India, traditional Ayurvedic medicine employs over 1200 different herbs regularly used by about 65% of the population [4]. Herbal medicinal preparations are popular in these countries because of age-long tradition in the use of medicinal plants [5]. However, in recent decades, interest in herbal medicine, has also increased in industrialized countries [6]. such as Germany, France, Italy, and the United States where appropriate guidelines for registration of such medicines exist [7].

The WHO estimates state that 50% of Canadians and 75% of people in France have tried complementary or alternative medicine, which often includes herbal remedies. And in Japan, 85% of doctors prescribe traditional herbal medicine which is covered by health insurance [8]. In no other country has the herbal medicine marketplace grown more than it has in the in USA; the US herbal medicine market reached about $3.2 billion in 1996, and $5 billion

in 1999 [9-12]. US$ 17 billion was spent by Americans on herbal medicines in 2000 [13]. About 60 million Americans over 18 years of age use herbal drugs to treat colds, burns, headaches, allergies, rashes, depression, diarrhea, and menopause, among others [14]. Traditional medicines are often multi-component remedies and need to be studied for the scientific rationale for their folkloric use so as to establish their efficacy and safety and also to develop evidence-based regulatory and public health policies for them. Such studies can and have led to the development of natural compounds for clinical use [15-17]. In this review, we present an overview of traditional and complementary medicine and focus on scientific ways to study these systems thereby relating claims in folklore with modern physiologic and pharmacologic relevance.

Traditional Medicine

The World Health Organization (WHO) defines Traditional medicine (TM) as the sum of the knowledge, skills and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses. The practices of traditional medicine are greatly influenced by level of education, culture and history and therefore vary from country to country.

Complementary and Alternative Medicine

Complementary and Alternative medicine (CAM) is defined by the FDA as a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. Some authors define CAM as modern or rejuvenated ancient practices that claim to have preventive or curative medical effects however, these practices are not recognised in medical science; they are not based on evidence or sound scientific hypotheses [18]. CAM includes various therapies such as homeopathy, massage-based therapy, naturopathy, diet therapy, and other similar practices [19]. The terms complementary/alternative/non-conventional medicine are used interchangeably with traditional medicine in some countries. We thus can view complementary medicine as TM used together with conventional medicine, while alternative medicine is TM used in place of conventional medicine. Surveys have shown significant increase in the popularity of CAM therapies in the USA and UK with some of the most popular therapies being acupuncture and naturopathy and involve concurrent use with prescription medicines [20]. People world over are increasingly opting for the therapeutic approach they consider most suited to maintain good health and to prevent or treat illness, irrespective of whether delivered through conventional medicine or CAM. Therefore, there have been proposals (even by the WHO) for TM/CAM to become fully integrated into national healthcare systems.

History of Traditional Medicine

The earliest documented proof for the use of plants/herbs in the preparation of drugs was found on a Sumerian clay slab from Nagpur; it was approximately 5000 years old. It is composed of 12 recipes for drug preparation and includes alkaloids such as poppy, henbane, and mandrake [21]. Records from Mesopotamia that dated around 2600 BC show the use of Cedrous species (Cedar) and Cupressus sempervirens (Cypress), Glycyrrhiza glabra (Licorice), Comephorid species (Myrrh) and Papaver somniferum (Poppy juice); these are still in use today for the treatment of ailments ranging from coughs and colds to parasitic infections and inflammation [22]. The Chinese "Pen Tsao" written by Emperor Shen Nung (2500 BC), contains 365 dried parts of medicinal plants [23]. Many of which are also employed today. The Ebers Papyrus (1550 BC) is made of a collection of 800 prescriptions containing 700 plant species/medicines used for therapy including pomegranate, castor oil plant, aloe, senna, garlic, onion, fig, willow, coriander, and juniper [24]. The works of Hippocrates (459–370 BC) contains 300 medicinal plants classified by physiological action: Centaurium umbellatum Gilib was applied against fever; garlic against intestine parasites; opium, deadly nightshade, and mandrake were used as narcotics; sea onion, celery, parsley, asparagus, and garlic as diuretics; oak and pomegranate as astringents [25].

Theophrast (371-287 BC), in his work, described herbal remedies such as cinnamon, iris rhizome, false hellebore, mint, pomegranate and fragrant hellebore [26]. Theophrast also underscored the importance of gradual increase of doses in his description of the plants' toxic actions. The most prominent writer on plant drugs was probably Discords, a military physician cum pharmacognosist who studied medicinal plants as he journeyed with the Roman Army. His work -De Materia Medica (AD 77) contains a plethora of data on medicinal plants [27]. About 657 drugs of plant origin, with descriptions of the appearance, locality and mode of collection, preparations, and therapeutic effect are contained in this work. Galen, a Roman physician, compiled the first identical action drugs which are interchangeable. Although, some of his proposals do not match in a pharmacological context, he however wrote of several new plant drugs in therapy that Discords had not described [28]. In the Middle Ages, the use of medicinal plants for healing grew into the monasteries. The Indian Vedas mention treatment with plants, which are abundant in the country including numerous spice plants used even today such as nutmeg, pepper, and clove [29]. The Arabs also introduced numerous new plants in pharmacotherapy, mostly from India, a country they used to have trade relations with.

The Arabs used Aloe, deadly nightshade, henbane, coffee, ginger, strychnic, saffron, curcuma, pepper, cinnamon, rheum, and senna. While the old peoples used medicinal plants primarily in their simple pharmaceutical forms—infusions, decoctions, and macerations—in the Middle Ages, and in particular between 16th and 18th centuries, the demand for compounded drugs was increased. If the drug was produced from a number of medicinal plants, rare animals, and minerals, it was highly valued and sold expensively [30]. In late 19th and early 20th centuries, there was a great danger of elimination of medicinal plants from therapy as authors pointed out their many shortcomings to include fundamental changes during the process of medicinal plants drying as it was discovered that medicinal plants' healing actions depends on the mode of drying. In 19th century, pure forms of alkaloids and glycosides were replacing

the drugs from which they had been isolated. However, it was soon ascertained that although the action of pure alkaloids was faster, the action of alkaloid drugs was full and long lasting. In early 20th century, stabilization methods for fresh medicinal plants were proposed, especially the ones with labile medicinal components. Besides, much effort was invested in study of the conditions of manufacturing and cultivation of medicinal plants [31,32].

Regional use of Traditional Medicine

Although it is not uncommon to find similarities in content, traditional medical practices vary across the world. The Chinese system of medicine is one of the oldest (believed to be more than 5000 years old) yet living traditions [33]. It is practiced in China, Singapore, Taiwan, and Japan however, in the last three decades it has been increasingly widely practiced in the West [34]. where Chinese recipes are currently being used alongside with orthodox therapy. The most complete reference to Chinese herbal prescriptions is the Modern-Day Encyclopedia of Chinese materia medica published in 1977. It lists about 6000 drugs, 80% of which are of plant derived. Examples of famous Chinese medicinal herbs are Angelica polymorpha var. sinensis, Artemisia annua, Ephedra sinical, Paeonia lactiflora, Panax ginseng and Rheum palmatum. Ayurveda (developed in North India), Siddha (established in Tamil Nadu) and Nagarjuna (established in Andhra Pradesh) are traditional systems of medicine practiced in India. Ayurveda is perhaps, the most ancient of all these medicinal traditions is probably older than the traditional Chinese medicine and is also practiced in Sri Lanka, Pakistan, and Bangladesh.

Famous Ayurvedic medicinal plants include Azadirachta indica, Centile asiatica, Cinnamomum camphora, Elettaria cardamomum, Rauwolfia serpentine, Terminalia species and Withania somnifera. The Unani (or Tibb) system of medicine was developed in the Middle Eastern Arab countries and is practiced in Northern Africa and in many countries. The earliest documented record, which presumably relates to medicinal plants, dates from 60,000 BCE in the grave of the Neanderthal man from Shnaider IV, Iraq [35]. Pollen of several species of plants, presumably used as medicines, was discovered among which are Centaurea solstitialis, Ephedra altissima, Althea sp. amongst others. Among the famous medicinal plants of the Unani system are Allium cepa, Astracantha gummifera, Carthamus tinctorius, Carum carvi, Ferula asafoetida, Lawsonia inermis, Papaver somniferum, Peganum harmala, Prunus dulcis, Punica granatum (Pomegranate), Rosa damascene (Damask Rose), Ricinus communis and Vitis vinifera. Chinese influence on the Aborigine's complex healing system is being observed but much of the traditional knowledge in Australia was lost before it could be systematically recorded. In contrast, many healing places like Malaysia, Thailand, Vietnam, New Zealand, Borneo, and the Polynesian Islands remain intact and are being developed.

Among the well-known medicinal products originating from this region are Croton tiglium, Duboisia hopwoodii, Eucalyptus globulus, Melaleuca alternifolia, Myristica fragrans, Piper methysticum, Strychnos vomica (Strychnine), Styrax benzoin and Syzygium aromaticum. The European healing system is said to have originated with Hippocrates and Aristotle. Their ideas were believed to be influenced by ancient beliefs from India and Egypt. Dioscorides, mentioned earlier, recorded the collection, storage and the use or medicinal herbs. Common African medicinal plants include Acacia Senegal, Agathosma betulina, Aloe ferox, Aloe vera, Artemisia afra, Aspalanthus linearis, Boswellia sacra, Catha edulis, Commiphora myrrha, Harpagophytum procumbens, Hibiscus sabdariffa, Hypoxis hemerocallidea and Prunus africana. Catharanthus roseus the source of anti-cancer drugs was obtained in Madagascar, a country which has the potential of contributing more to view of the diversity of the flora and fauna found there [36]. African traditional medicine is perhaps the oldest and most diverse of all TM systems. The documentation of medicinal uses of African plants is becoming increasingly urgent because of the rapid loss of the natural habitats of some of these plants because of anthropogenic activities [37].

Prospects of Traditional Medicine

In 19th century, alkaloids, and glycosides isolated in pure form were increasingly replacing the source from which they had been isolated. However, it was soon ascertained that the action of alkaloid drugs was fuller and longer lasting. In early 20th century, stabilization methods for fresh medicinal plants were proposed, especially the ones with labile medicinal components much effort was also invested in study of the conditions of manufacturing and cultivation of medicinal plants. Based on chemical, physiological, and clinical studies, numerous forgotten plants were then restored to the TM pharmacy [38]. The interest in nature as a source of potential chemotherapeutic agents is ongoing and increasing. Natural products and their derivatives represent more than 50% of all the drugs in clinical use in the world [39]. During the last 40 years, at least a dozen potent drugs have been derived from flowering plants. For examples, Dioscuri spp. from which all anovulatory contraceptive agents have been derived; reserpine and other anti-hypertensive and tranquilizing alkaloids from Rauwolfia species.

Pilocarpine to treat glaucoma and dry mouth, derived from Pilocarpus spp; anti-cancer agents from the Rosy Catharanthus roseus [40] and cardiotonic agents to treat heart failure from Digitalis species [41]; antimalarial drugs derived from inchona pubescens Vahl and Artemisia annua L [42]; narcotic analgesic drugs derived from the opium poppy (Papaver somniferum L.); three other major sources of anti-cancer drugs were derived from North American plants used medicinally by Native Americans: Asimina spp; Taxus brevifolia and the May apple Podophyllum peltatum [43,44]. Leads from traditional knowledge and experiences, are likely to provide discoveries of new remedies that will be commercialized in the future as plants from forests (particularly in tropical regions) continue to provide natural product chemists with lead compounds for the development of new drugs. The potential for finding more compounds is enormous and it has been postulated that only about 1% of tropical species have been studied for their pharmaceutical possibilities.

Ethnopharmacology

The long historical use of many practices of traditional medicine has demonstrated some degree of safety and efficacy. However, scientific research is needed to provide additional or confirmational evidence. Despite its long existence, popularity and widespread use, many plants used in ethnotherapy still await scientific investigation; traditional medicine has not been officially recognized in most countries due to arguments that derive from insufficient data on safety and efficacy. Lack of research data are often due to lack of adequate or validated research methodologies, techniques, or expertise for evaluating traditional medicine [45]. Ethnopharmacology is defined as study of indigenous medical systems that connects the ethnography of health and healing with the physiologic relevance of its medical practices [46]. Essentially, ethnopharmacology pays attention to the knowledge and experience obtained through the long history of established traditional practices in the conduct of research and evaluation of traditional medicine. Ethnopharmacology is multidisciplinary - an amalgam of perspectives, especially that of anthropologists, botanists, chemists, and pharmacologists.

Contributions made by historians of science, clinicians and agronomists are also of critical importance [47]. Consequent on the many professions contributing to ethnopharmacology, research techniques vary [48]. Plant-based remedies are a complex mix of compounds; ethnopharmacology is directed at identifying the compounds that are relevant for pharmacologic or possible therapeutic properties. Identifying these compounds is crucial for provision of evidence towards the quality control for herbal drugs or simpler galenic preparations. Also, identifying the active compounds is important because new molecules, sometimes with unique pharmacologic properties, are lead compounds for developing new drugs. It is typically a single compound in a traditional remedy that is of interest for drug development or quality control. The primary strategy for separating out that compound is bioactivity-guided isolation, in which pharmacological or biological assays are used to guide the isolation of bioactive constituents.

Ethnopharmacology involves various stages

a) Information sourcing

b) Plant Sourcing

c) Extraction

d) Pharmacological investigations

e) Chemical investigations. Information sourcing Information on the ethnomedical uses of medicinal plants (the aim being to investigate these claims) can be acquired through various approaches.

Usually there may be need to source information on the same subject using more than one approach; this may be a way of validating the information gathered. Such approaches include:

a) Ethnomedical data from the community: Going into the community and asking the residents - particularly the elderly - about the medicinal uses of plants growing in their locality is one way to source information. This may require travelling end to end within a community or even to neighboring communities [49]. Within communities, there are traditional medicine practitioners some who are specialized in certain fields. Though some may be reluctant to divulge whole information about their recipes, informing them of the intended purpose i.e., research to confirm the potency of their preparations rather than compete with them for clients may make them more obliged. A challenge encountered with this approach is the possible duplicity of information. While the same plant could have two different uses, it is also possible that the same plant will have two different names. For example, Ocimum gratissimum is known as 'efirin ajase' in Yoruba is also called 'efirin po' or 'efirin gidi' in some other Yoruba speaking communities [50]. A way this can be checked is to have a botanist on the team and the plants be sampled right where the information is being gathered if possible.

b) Ethnomedical data from herb-sellers: Markets in Africa and other developing countries usually comprise of sections where whole plants or plant parts and other ingredients of traditional medicine can be purchased. A way to get information on these ingredients is to engage the herb-sellers some who are very knowledgeable about the recipes especially for common indications such as fevers, skin ailments etc. The traditional method of preparation (e.g., hot or cold maceration, use of water or alcohol) can also be obtained [51].

c) Ethnomedical data from Scientific Publications: Scientific literature (books and journals) is abundant with reports of ethnomedical surveys that have been conducted; these publications usually contain the scientific and local names together with the medicinal usage of the plant or plant parts. Some of these publications also contain information on the mode of traditional use [52-56].

Plant Sourcing

Medicinal plants can be sourced from the wild or cultivated. Collection from the wild is preferred when the plant grows readily in the wild and produces good yield of active constituents or its cultivation requires waiting several years to maturity. When collection from the wild is difficult: too little grow in the wild or growing in area inaccessible or cultivation gives better yield, cultivating the plant may be more desirable [57]. Geographical variations that have been shown to effect distinctions in active constituents and consequently impacting differences in biological activity should be noted. An example is noted by Bamba and colleagues [58] in which Chromolaena odoratum from Cote d'Ivoire produces leaf essential oils geijerine and pregeijerine with antibacterial activity against Gram negative organisms.

The same plant in Nigeria does not produce any of those two oils and is active against mainly Gram-positive organisms. Particular note must also be given to season of collection. Active ingredi-

ents have been shown to vary across seasons even in significant proportions. Usually, a proper ethnomedical data especially from traditional knowledge within the communities corroborated with literature data will delineate the season for collection, the age of the plant and even particular time of the day for collection [59]. Storage times for plants or plant parts should be kept at a minimum unless otherwise indicated; ideally, the possibility of processing them at point of collection should be explored. When immediate processing is unachievable, fresh plant parts are usually washed in freshly prepared distilled water, air dried (or in some cases vacuum dried) with period turnings until a constant weight is achieved (usually about 2 weeks). The dried parts are then placed in zipped plastic bags and well labelled.

Extraction

The method of extraction employed usually depends on several factors, however, since the investigator seeks to establish the efficacy and safety or otherwise of the subject plant, ethnomedical information sourced earlier would be a good guide. The extract to be used for testing should be as close as possible to that obtained by traditional processes used. The general techniques of medicinal plant extraction include maceration, infusion, percolation, digestion, decoction, hot continuous extraction (Soxhlet), aqueous alcoholic extraction by fermentation, counter current extraction, microwave assisted extraction, ultrasound extraction (sonication), supercritical fluid extraction, and distillation techniques. For aromatic plants, hydrolytic maceration followed by distillation, expression, and effleurage (cold fat extraction) may be employed. Some of the latest extraction methods for aromatic plants include headspace trapping, solid phase micro extraction and protoplast extraction, micro distillation [60,61].

Pharmacological Investigations

For more than a hundred years, virtually every medical breakthrough in human and animal health has been the direct result of research using animals. Animals are good research subjects for a variety of reasons chief of which is their biological similarity to humans. For example, chimpanzees share more that 99% of DNA with humans and mice share more than 98% DNA with humans and are therefore, susceptible to many of the same health problems as humans. In addition, the environment around animals (such as diet, temperature, lighting), can be easily controlled to suit investigational requirements. In today's world though, whenever possible, the use non-animal models for research are advocated particularly in initial screens for activity or in the mechanistic studies for observed biological effects. Computer models, tissue and cell cultures, and a number of other non-animal related research methods are used today in biomedical research. Computer models can be used to screen and determine the toxic level of a substance in the beginning of an experiment and tissue and cell cultures have become valuable. These in vitro assays help not only to detect biological activity of the crude extract but also to carry out bioassay guided purification of the extracts. Several of these assays include assays for anticancer, antimicrobial and toxicity profile of crude extracts [62].

In vitro assays rely on interactions of chemical entities with drug targets (e.g., receptors or enzymes). These systems are devoid of the complex physiological environment that exists in whole animal models. Even tissue cultures can only provide isolated ex vivo conditions that may not be representative of the pharmacokinetics (e.g., drug absorption and metabolism) that interplays among systems. Animal testing thus remains a necessity as they mirror the complex living system with greatly interrelated chemistry, making it possible to explore, explain, or predict the course of diseases or the effects of possible treatments. Some of the animal models used in ethnopharmacology are detailed in journals such as the Current Protocols in Pharmacology and Fundamental and Clinical Pharmacology. These models include protocols for arthritis [63], pain [64], neuropathic pain [65], learning and memory [66], cancers [67], toxicity evaluation [68] etc. In the meantime, there are deliberate efforts in place to reduce the number of animals needed to obtain valid results through refined experimental techniques, and to replace animals with other research methods whenever feasible. Models using zebra fish, Drosophila melanogaster (fruit fly), and the nematode Caenorhabditis elegans have been developed; these recent models enable cost-effective and rapid pharmacological screening of natural products.

Chemical Investigations

Investigations into the chemical nature of traditional medicine products involve both qualitative and quantitative tests. Due to the fact that plant extracts usually occur as a combination of various bioactive compounds or phytochemicals with different polarities, their separation still remains a big challenge for the process of identification and characterization of bioactive compounds [69]. Typically, chemical constituents of the extract could be detected by chemical assays described by Harborne [70] for alkaloids, Kumar et al., [71] for Anthraquinones Van-Buren and Robinson [72] for tannins, Trease and Evans for steroids, triterpenoids and reducing sugars, Obadoni and Ochuko [73] for saponins, Sofowora, Boham and Kocipai-Abyazan [74] for flavonoids and Evans for cardiac glycosides. Phytochemical identification and quantification to determine specific chemical components in extracts from ethnomedical products involves the use of instrumentation such as thin layer chromatography (TLC), gas chromatography or high- pressure liquid chromatography linked to mass spectrometry (GC-MS/HPLC-MS). Frequently there is the need to use hyphenated techniques, such as Liquid chromatography linked ultraviolet/mass spectrometry or nuclear magnetic resonance (LC-UV/ LC-MS or LC-NMR) to accelerate the structural determination of bioactive compounds previously undocumented. Computer modelling has also been employed in the generating of chemical compounds meeting spectral properties of bioactive compounds from plants [75].

Challenges with Ethnomedicines

The safety and efficacy of ethnomedicines is a major concern. Pharmacological and toxicological studies are often used to determine the efficacy and safety profile of medicinal plants. However, scientific investigations on herbal medicines are complex with

several confounding variables. Other prominent problems associated with herbal medicines include lack of clinical trials on these products within western pharmaceutical clinical standards, dosage specifications, problems of proper packaging, appropriateness of their level of hygiene, cost of production and their level of acceptability especially among the elites in the healthcare team who continues to prescribe only orthodox/conventional medicines in hospitals and clinics. Despite the wide use of herbal medicines over many centuries, only a small number of plant species have been studied for plausible medical applications. Safety and efficacy data exist for smaller number of plants, their extracts and active ingredients and preparations containing them [76]. Herbal medicines consumption is a well-known cause of kidney, liver, cardiac and blood dysfunction, or diseases [77].

Kidney diseases demonstrated among CAM users include Acute renal failure, acute interstitial nephritis, metabolic acidosis, rhabdomyolysis, and tubular dysfunction [78-82]. Cardiac disorders described among CAM users include bradycardia, heart block, tachyarrhythmia, and hypotension [83]. Pulmonary complications which could result from use of herbs include anaphylactic reactions, asthma exacerbation, severe interstitial pneumonitis, non-cardiogenic pulmonary edema, acute eosinophilic pneumonia, and small airway disease [84]. Allergic diseases have been proven to be induced by CAM use via potentially sensitizing capacity of various herbal remedies which may lead to allergic contact dermatitis and more rarely, Ige mediated clinical symptoms. There are general assumptions that herbal medicines are generally safe because they are from natural origin. There are also conceptions that diseases may not develop resistance to herbal medicines as synthetic therapeutics, hence the value attached to the use of herbal medicines. It is now obvious that ethnomedicines can be toxic and resistance could be developed with the use of these agents.

Conclusion

Ethnopharmacology is a truly multidisciplinary task; it requires a dialogue between disciplines and between cultures. Ethnopharmacology-driven drug development is unique as it employs a knowledge-based approach especially since these plants have been widely used for centuries. However, plants with questionable safety profile must be discouraged as ethnomedicines.

Declaration of Conflict of Interest

None.

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