Natural Product-Based Medicine: A Historical Perspective and Future Outlook

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Abstract- The present review article has been envisaged at the evaluation of indigenous medicinal plants aimed at traditional knowledge-driven drug development. Firmly entrenched in the past, the practice of using plants in the treatment of various ailments had been going on for thousands of years, and still continuing to address the basic health care requirements of a large section of population all over the world. The majority of contemporary medicinal agents have originated from plant sources recognized through time-honoured ethnomedical cultures. Of late, the phenomenal progress in physico-chemical analysis and assay techniques, fueled by the advancement in biochemical perception at the molecular level, revolutionised the development of drugs from herbal origin. In this context, the role of indigenous plants, its safety and efficacy is increasingly becoming important for India, with a rich heritage of traditional medicinal practices which continue to thrive to this day, despite a waning inventory of endemic plant species.

Key Words: Medicinal plants; Traditional Medicinal System; Herbal therapies; Complementary and alternative medicine

I. INTRODUCTION: MEDICINE FROM NATURE & HISTORICAL OVERVIEW

At the dawn of civilization, the challenge to thrive in an extremely hostile environment had taught mankind how to exploit Nature through co-existence with natural flora and fauna. Thus, since prehistoric times, the medicinal as well as the toxic properties of plants were recognized as remedies for various ailments. Fossil records documented the medicinal use of plants by people in the Middle Paleolithic age, some 60,000 years ago. Evidences of this early association have been found in an ancient grave of a Neanderthal man through the pollen analysis of numerous plants buried along with the corpse [1].

In 2600 B.C., it was the Mesopotamians who first used the oils of cypress, liquorice, and poppy juice for treating different ailments, followed by Indian Buddhist system of medicine that dates back to 2500 B.C. Then came the Egyptians (1500B.C.) who documented, in Ebers Papyrus, about 700 drugs and formulae, such as, gurgles, snuffs, poultices, infusions, pills, and ointments, followed by the Chinese compendium, viz. Wu Shi Er Bing Fang (1100 B.C.), which contained 52 prescriptions, and the Indian Ayurveda (Charaka and Sushruta Samhita, 1000B.C.) describing the medicinal application of numerous indigenous plants and herbal formulations. From these ancient cultures some of the knowledge reached Mediterranean countries, and it was in Hippocrates's time (460-377 B.C.) when pharmacognosy reached a summit in Greece. The philosopher and naturalist, Theophrastus (ca. 300-322 B.C.), was the first to deal with the history of plants. Pedanius Dioscorides, the Greek physician, produced De Materia Medica, in 78 A.D. which described more than 500 plants and their medicinal uses in detail. Galen (129-199 A.D.) founded 'Galenics' and taught Pharmacy and Medicine in Rome. Avicenna (980-1037 A.D.), the Persian pharmacist, physician, and philosopher, described 1400 drugs and medicinal plants through his works, such as 'Canon Medicinae', which greatly contributed to the formation of Graeco-Romanian Medicinal system in 5th Century A.D. Paracelsus (1524) wrote his "Archidoxa" of the "Arcanum" where, he was referring to the need to discover the essential active component, the "secret" of a treatment, whether it was animal, mineral or vegetable. The Unani system owes its origin in Greece and it was Hippocrates, and other Greek and Arab scholars like Galen, Raazes and Avicenna, who had enriched the system considerably. Bhutanese medicinal systems (gSo-ba Rig-pa), and Tibetan medicine (Gyu-zhi) containing

more than 300 herbal recipes, took shape in 7th-8th Century with the advent of Mahayana Buddhism. Even Homeopathy, founded by German physician Samuel Hahnemann, which became popular in USA in 1830s, included extracts from medicinal plants [2] Thus, the art of discovering plant-derived drugs could be viewed as one of the historical achievements of mankind in the archives of science.

More recently, a separate field of ethno-medicine has emerged as an academic specialization focusing on traditional healing systems. Thus, encouraging trials with a Tibetan formula, viz., the Padma Products in Switzerland, and Japanese Kampo medicine [3], proved to be successful in the treatment of various diseases. In this way, the traditional medicinal practices, based on the enormous reservoir of knowledge accumulated through the ages, persist to thrive even to this day, serving the primary health care requirements of people in different cultures [4].

II. TRADITIONAL MEDICINAL SYSTEMS : CURRENT TRENDS OF USAGE

Traditional medicinal system is often described as holistic approaches that consist of a total body of knowledge, techniques, skills and practices, recognized and accepted for its role in the diagnosis, prevention or elimination of imbalances in the physical or mental well-being. It is primarily based on the socio-cultural and religious bedrock of indigenous theories, observations, and experiences that are handed down from generation to generation. Although traditional medicine is now practiced in many countries throughout the world, but it is not always included as part of the scheme accepted by the government, and is often categorized as one of the many non-standard approaches which involve varying levels of training and efficacy. The umbrella term complementary and alternative medicine (CAM) is now widely accepted, which includes both traditional and more recent forms of non-conventional health care systems [5].

Throughout the world, the popularity of CAM is growing at a remarkable, and perhaps disquieting, speed. Problems associated with the emergence of drug-resistant microorganisms, side effects of modern drugs, and manifestation of new diseases where no medications have been available, stimulated renewed interest in plants as a significant source of new therapeutic agents. Moreover, high costs of modern medicines also compelled people of the developing countries to rely on traditional natural formulations for their primary health care management. Although herbal drugs were used extensively in many regions in Africa, Asia and the developing world, including India and China, it is only recently that there has been resurgence in their popularity even in the most developed parts of the United States and Europe.

The World Health Organization (WHO) estimated that ~ 4 billion people, i.e., around 80% of the world population, continue to use alternative medicine for primary health care. According to the WHO survey, the percentage of population which has used CAM for at least once, is 48% in Australia, 70% in Canada, 42% in USA, 38% in Belgium, and 75% in France. In terms of economic value, expenditure on CAM therapies were not only significant, but growing rapidly, e.g. Malaysia spent about US$ 500 million annually, while in Australia, Canada and the United Kingdom, annual CAM expenses were estimated at US$ 80, 2400, and 2300 million, respectively [6]. This is particularly true in the United States, where the market for herbal supplements is now approaching US$ 4 billion a year [7]. A 1997 survey estimated that 12.1 percent of adults in the United States had used herbal medicine in the previous 12 months (as compared with 2.5 percent in 1990), resulting in out-of-pocket payments of $5.1 billion [8]. The top-selling herbal products in United States such as ginseng (e.g., *Panax ginseng* and related species; total 1998 retail sales of $96 million), ginkgo (*Ginkgo biloba*; $151 million), and St. John's wort (*Hypericum perforatum*; $140 million) can be traced back to the ancient traditional systems, whereas others, such as echinacea (*Echinacea angustifolia*; $70 million), saw palmetto (*Serenoa repens*; $32 million), and kava ($17 million) are of more recent origin [2,9]. On the face of this statistical estimate of the burgeoning market, we should now be inclined to ask "Are there sufficient trials which can confirm that modern herbal therapies do really work, and if these are safe enough to be sold as 'over-the-counter' merchandise?"

III. HERBAL THERAPIES: SAFETY ISSUE

The escalating popularity of CAM (Complementary and alternative medicine), as evident from the booming sales figures of herbal drugs quoted above,

would probably make us sceptic about one of the important principles of imparting health care, which is 'to do no harm' ('Oath of Maimonides')! In fact, the marked revival of complementary and alternative medicine during the last three decades was driven by the common belief that 'anything natural is safe'. However, the safety issues associated with the indiscriminate use of herbal drugs need to be considered critically. Thus, an increasing body of evidences from systematic reviews and meta-analyses of randomized clinical trials suggested that some of the herbal medicines are effective indeed [7]. Yet, thorough scientific study have shown that many of these formulations are often not free from deleterious side-effects [10,8]. There lies the enormous importance of 'quality control' of the plant products marketed as 'phytotherapeuticals', which is typically suboptimal, or non-existent, in many countries. For example, herbal products have been frequently found to be contaminated with heavy metals (viz., selenium, lead, cadmium, mercury and arsenic coming from the environment), micro-organisms, fumigation agents (viz., ethylene oxide, methyl bromide, phosphine, etc.), and pesticides. Even adulteration with powerful prescription drugs (viz., aminophenazone, phenylbutazone, indomethacin, corticosteroids, etc.) have been noted [8]. Besides, herb-drug interactions have also become a significant area of concern, owing to the notoriously poor documentation of the interaction between herbal products and conventional medicine, or stuffs like, alcohol, caffeine, nicotine / tobacco, etc. [10].

Nevertheless, many individuals are of the opinion that carrying out clinical research on traditional formulations need not be a priority, since they believe that the ethnic knowledge and "test of time" would provide adequate support for the efficacy as well as safety of these complementary and alternative therapies [9]. However, most herbal products in the United States are considered as dietary supplements; hence, those are neither regulated as medicines, nor required to measure up for drugs specified in the Federal Food, Drug, and Cosmetic Act, and would just meet the standards set forth in the Dietary Supplement and Health Education Act [11]. Moreover, consumers would be unaware of this 'double standard'. Unfortunately, the 'herbal companies' are not concerned about conducting systematic examinations, as it would be difficult for them to recover the high research costs, apparently because of the complications faced in patenting these products as compared to newly synthesized drugs [12]. Hence, enthusiastic commercial thrust for scientific explorations is rarely forthcoming. In fact, hardly a small fraction of the plethora of medicinal plants used worldwide has been tested rigorously in randomized controlled trials. As a result, much of the available evidences are built upon either purely experimental results, or inadequate clinical trials, leading to a major lag in the 'hard' data to explain the potential hazards of using herbal medicines. Consequently, verification of the nature and occurrence of adverse effects/contra-indications, caused by most of the indiscriminately formulated herbal preparations, is not satisfactory, and this would compromise the safety of the consumers in the long run [10]. Thus, the standardization and quality control of traditional herbal drugs would continue to be a major public health concern, worldwide, focusing on the unequivocal need to undertake medicinal plant study, particularly from the viewpoint of safe use of such products.

Table 1: Popular Herbal medicines and associated risk factors:

Common Herbs	Used In	Adverse Effects	Potential Interactions with Drugs
Aloe (internal / latex)	Laxative (short-term)[17]	Diarrhea, hypokalemia, pseudomelanosis coli, kidney failure, as well as phototoxicity and hypersensitive reactions [17]	Long-term usage of aloe latex could contribute to a deficiency of potassium such that a risk of electrolyte imbalances might result from laxatives containing anthraquinone glycosides not consistently used for longer than 1 to 2 weeks. [18]
Ashwagandha (*Withania somnifera*)	Stress, anxiety, sleep [19]	Chronic liver disease [20]	The bioactive compounds of *ashwagandha* is known to elicit immunomodulatory activity and possess plausible anti-viral properties.[21]
Chamomile (*Matricaria chamomilla L.*)	Used as antiseptic, anti-inflammatory and antispasmodic.[22]	Allergic reactions [22]	An ethanolic extract of *M. chamomilla* extract (MCE) with two NSAIDs, diclofenac and indomethacin on carrageenan-induced paw inflammation and gastric injury in rats. [22]

Dong quai (*Angelica sinensis*)	Traditional gynecologic uses[23]	Adverse effect on the prognosis of breast cancer [20] Darmatological effects, Carcinogenicity, Estrogenic effects, Gastrointestinal effects [24]	The use of Dong quai with other blood thinning herbs may increase the risk of bleeding in certain individuals. [24]
Echinacea spp.	Common cold (short-term use)[26]	Stomach pain, diarrhea, rash, and dizziness[27]	*Echinacea purpurea* herbal extracts have little potential for CYP450 drug interaction, especially against cytochrome P450 (CYP)1A2 and/or 3A4 isoforms.[27]
Fenugreek (*Trigonella foenum-graecum*)	Glycemic support, lactation[28]	Many teratogenic effects of fenugreek, from congenital malformations to death, antifertility effect[30]	Strong inhibitor of CYP2C11 expression, which can lead to an undesirable pharmacological effect of clinically used CYP2C11 substrate drugs with a low therapeutic index. [30]
Garlic bulb	Raised blood Cholesterol [10,11]	Allergic reactions, nausea, heartburn [10,11]	Anticoagulants ; antidiabetics ; antiretroviral [ritonavir, saquinavir, warfarin] [10,11]
Ginger (*Zingiber officinale*)	Nausea, dyspepsia [31]	gastrointestinal discomfort, heartburn, and allergic reactions [31]	Ginger increases the anticoagulant effect of warfarin which leads to warfarin toxicity and causes bleeding. [31]
Ginkgo leaf	Dementia, peripheral and vascular disease [10,11]	Gastrointestinal symptoms, diarrhoea, vomiting, allergic reactions [10,11]	Anticoagulants [acetylsalicylic acid, rofecoxib, warfarin, trazodone] [10,11]
Ginseng	CNS stimulation, fatigue, diabetes, inflammation, cancer, immune disorder [10,11]	Diarrhea, euphoria, headache, mastalgia, nausea, vaginal bleeding [10,11]	Monoamine oxidase inhibitors; hypoglycemic agents [warfarin] [10,11]
Green tea (*Camellia sinensis*)	Alertness, metabolic health [32]	Nausea, vomiting, dehydration, lethargy, central nervous system stimulation such as dizziness, insomnia, tremors, restlessness, confusion, diuresis, heart rate irregularities and psychomotor agitation [33]	Warfarin is an anticoagulant used for the prevention and treatment of thromboembolism patients with atrial fibrillation, prosthetics heart valves, or deep-vein thrombosis. [34]
Hawthorn	Heart failure [10,11]	Nausea, dizziness, Fatigue [10,11]	Antihypertensives; cardiac glycosides [nitrates, digoxin] [10,11]
Holy basil / Tulsi (*Ocimum tenuiflorum*)	Stress, traditional glycemic support [35]	Increase in levels of superoxide dismutase, reduced glutathione and total thiols, but marked reduction in peroxiodised lipid levels as compared to untreated control group. The leaves were found to possess both superoxide and hydroxyl free radical scavenging action [35]	Basil may have a sedating effect that could be amplified with certain sedatives, and there's a possibility it could interact with medications metabolized by enzymes like CYP2B6 and CYP3A4 [36]
Kava rhizome	Anxiety [10,11]	Liver damage [10,11]	Drugs acting on CNS [alprazolam, cimetidine, terazosin] [10,11]
Kinnikinnick (*Arctostaphylos uva-ursi*)	Treatment of lower urinary tract infections [37]	Gastrointestinal problems [37]	The in-vitro inhibition of UGT1A1 by uva-ursi happens due to its constituents gallotannin and TeGG. [37]
Licorice (*Glycyrrhiza glabra*)	Cough, traditional GI uses [38]	Throat infections, tuberculosis, respiratory, liver diseases, antibacterial, anti-inflammatory, and immunodeficiency [39]	Affect the metabolism and clearance of certain drugs that are substrates of CYP3A4 and CYP1A2[40]
Moringa (*Moringa oleifera*)	Nutrition, traditional glycaemic control [42]	Anti-reproducibility effects [41]	Rutin-it is observed to have maximum affinity and interaction towards BRAC-1 gene. [42]
Neem (*Azadirachta indica*)	Traditional uses (skin, parasitic) [43]	Rare liver injury reports; hypoglycaemia [44]	Herb-drug interactions between *A. indica* and two second generation sulfonylureas-glibenclamide and glimepiride in

			streptozotocin induced diabetic animal model [43]
Saw palmetto	Benign prostate hyperplasia, inflammation [10,11]	Gastrointestinal complaints, dysuria, decreased libido [10,11]	Hormonal drugs [10,11]
St John's wort (*Hypericum perforatum*)	Mild-moderate depression [45]	Gastrointestinal symptoms, allergic reactions, dizziness/confusion, tiredness/sedation and dry mouth [45]	St. John's wort (SJW) itself interacts with a variety of drugs, which it activates CYP450 enzymes (particularly CYP3A4) and P-glycoprotein, thus lowering concentrations and activities of medications such as warfarin,digoxin,cyclosporine, oral contraceptives and some HIV medications. [45]
Turmeric / Curcumin	Osteoarthritis, inflammation [46]	Toxic and carcinogenic effects in normal cells for prolonged uncontrolled use [47]	Curcumin reduces the activity of CYP1A2 and CYP3A when it is conjugated with warfarin. [46]
Warmwood (*Artemesia absinthium*)	Used as febrifuge, anthelmintic, stomachic antiseptic, cardiac stimulant, antispasmodic, improving nervous and liver functions [48]	Results hallucinations, mental disturbances, pyschosis, digestive disorders, delirium, vertigo, thirst, dyspepsia, biliary dyskinesia and paralysis etc. [48]	Thujone in *A. absinthium* oil is neurotoxic which act as a $GABA_A$ receptor causes convulsions in mice, which can be blocked by diazepam or phenobarbital. [48]
Yohimbe / yohimbine	Erectile dysfunction (traditional) therapeutic agent for sexual difficulties, beneficial in erectile dysfunction, myocardial dysfunction, inflammatory disorders, and cancer [49]	Hypertension, perspiration, chest pain, sleeplessness, anxiety, and palpitations. [49]	Yohimbine stimulates the sympathetic nerve by antagonizing the presynaptic α2-adrenergic receptors (ARs). [49]

Most of the time we do not fully understand how the medicines prepared out of the common herbs described above in Table 1 would really work. Nor do we always know which component of these products is pharmacologically active. For example, in the case of St. John's wort, hypericin has always been considered to be the active principle, although current evidences would indicate that hyperforin may be equally significant [13]. Again, its mode of action was presumed to be that of a monoamine oxidase inhibitor, until recent data showed that inhibition of serotonin uptake might also be partly responsible for its actions [14],[7].

Again, the question still remains that even though herbal remedies may be effective, do their benefits outweigh the risks? Currently, these issues have been addressed by many international authorities, including World Health Organization, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine, European Pharmacopoeia Commission, National Center for Complementary and Alternative Medicine (NCCAM), US Agency for Health Care Policy and Research, Department of Indian System of Medicine, etc., who are working with the standardisation and testing of clinical efficacy of some of the commonly used herbal products. It is thus expected that a rigorous surveillance mechanism would take shape in coming years through extensive scientific investigation, whereupon some of the therapeutic and preventative modalities currently deemed complementary and alternative, might prove to be clinically effective[15],[2].

IV. CONCLUSION

Thus, persistent scientific enterprise would herald the fruitful culmination of the ethnomedical knowledge garnered over the centuries, which had already contributed to our primary health care systems. However, with the rapid industrialization, and the consequent loss of ethnic cultures and customs, the awareness in this area is gradually disappearing. Should we not strive to give our efforts to recover the ethnomedical reservoir, so that the plant-derived drug discovery process may keep going? Let us not forget that "*those who cannot*

remember the past are condemned to repeat it" [16]. It is high time that ethno-directed bio-rational approach should be adopted to systematically explore the plants, and the herbal formulations, not only to rationalise ethnomedical claims, but also to identify the valuable active constituent(s) with a vision to discover 'lead molecules' for designing novel 'single agent drugs' in future.

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