Traditional Medical System (TMS) for Sustainable Healthcare in India

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1.1 Introduction to Global Trends in Traditional Medical System (TMS)

Traditional medicine has a long history. The World Health Organization (WHO) recognizes that traditional medicine (TM) is a vital part of the global health care system. As per WHO recommendation, TM should be a part of health and wellness and promote safe and effective use. It can be done by proper regulation, research and integrate products, practitioners and practice into TM health systems. This can be assigned that the sum total 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 terms complementary/alternative/nonconventional medicine are used interchangeably with traditional medicine in some countries (Anon 2004).

Popularity of TM is rapidly spreading in industrialized and developing countries. Thirty percent to 50% of the total herbal medicinal consumption is done by Chinese traditional herbal medicine. Sixty percent of children with high fever resulting from malaria use herbal medicines in Ghana, Mali, Nigeria, and Zambia, as the first-line of treatment. Over 50% of the population have used complementary or alternative medicine in Europe, North America, and other industrialized regions. Seventy-five percent of people living with HIV/AIDS use TM in San Francisco, London, and

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M. Dikshit (ed.), *Drug Discovery and Drug Development*,
https://doi.org/10.1007/978-981-15-8002-4_1

South Africa. Seventy percent of the population in Canada, and 90% of the population in Germany have used a natural remedy at some point in their life (WHO traditional medicine strategy: 2014–2023). Annual expenditure on alternative medicine is US$ 230 million in the UK. Annually over US$ 60 billion is the global market for herbal medicines currently and is growing steadily.

Randomized clinical trials have been satisfactorily carried out for many uses of acupuncture, some herbal medicines, and therapies. However, there is an urgent need to validate the safety and efficacy of herbal therapies at clinical level. The growing herbal market and its great commercial benefit can project a threat to biodiversity through the uncontrolled harvesting of the raw material for herbal medicines and natural products used in healthcare which may lead to the destruction of their natural habitats and resources and extinction of endangered herbal plant species. The international and by most national patent laws are also inadequate to protect traditional knowledge and biodiversity (Ubale 2011).

Twenty-five percent of modern medicines are made from plants. Postoperative pain, nausea during pregnancy, chemotherapy, dental pain along with anxiety, panic disorders, and insomnia can be relieved using marginal side effects with the use of acupuncture. While *Tai Ji* techniques can help the elderly reduce their fear of falls and Yoga can reduce asthma attacks (Burton et al. 2015).

Artemisia annua is a good example used in traditional medicine of China has been found to be effective against resistant malaria. This has made a breakthrough in prevent of millions of deaths annually, especially among children. The Medical Research Council in South Africa is conducting studies on the efficacy of the plant *Sutherlandia microphylla* in treating AIDS which is used as a tonic that increase energy, appetite and body mass in people with HIV. The World Health Organization (WHO) launched its first comprehensive traditional medicine strategy in 2002 to promote safe, effective, and affordable traditional medicine. The strategy is designed to assist countries to develop national policies on the evaluation and regulation of TM practices; ensure availability and affordability of TM including essential herbal medicines; and promote therapeutically sound use of TM by providers and consumers.

WHO supported clinical studies on antimalarial medicines in three African countries. The studies revealed efficacy of herbal antimalarial treatment. Collaborations with Ghana, Mali, Kenya, Uganda, Nigeria, Burkina Faso, the Democratic Republic of the Congo, and Zimbabwe in the research and evaluation of herbal treatments for HIV/AIDS, malaria, sickle cell anemia and diabetes mellitus, are underway. WHO is providing technical support to the government of Tanzania for the production of antimalarial medicines derived from the Chinese herb *Artemisia annua*. Local production of the medicine is expected to bring the price of a single dose down from US $6 or $7 to a more affordable $2. In the Philippines, WHO has facilitated the development and introduction of traditional and alternative health care curricula. In China, Mongolia, and Vietnam, training workshops have been organized on the use of traditional medicines for selected diseases and disorders. It is promoting the use of traditional medicines over one-third of the population in developing countries which lack access to essential medicines. The provision of safe

and effective TM therapies could become a critical tool to increase access to health care (2013). Several countries have a national regulation on herbal medicines. The legislative control of medicinal plants different countries and diverse approaches have been adopted with regard to licensing, dispensing, manufacturing, and trading.

The limited scientific evidence on the safety and efficacy of TM as well as other considerations make it imperative for governments to, formulate national policies and regulations for a proper use of TM, integration into national health care systems. It should also establish regulatory mechanisms to control the safety and quality of products and practice of TM. Apart from these awareness about safe and effective TM therapies among the public and consumers should be promoted to, cultivate and conserve medicinal plants to ensure their sustainable use (Burton et al. 2015).

In India, Ayurveda developed by day-to-day life experiences is a part of its cultural heritage. Besides *Ayurveda*, the Indian Systems of medicine has several other complementary and alternative systems of medicine such as Homeopathy, *Siddha,* and *Unani* systems. These have been developed using plants and plant-based formulations for health care and disease treatments. About 2000 drugs of natural origin included in the Indian *Materia medica* where almost all of which are derived from different traditional systems and folklore practices (Mukherjee et al. 2010).

1.2 Impact of TMS on Sustainable Healthcare

The increasing global population is engulfing forests and other resources around the world. They are being rapidly and often irreversibly depleted for energy, food, shelter, material goods, and drugs to meet the immediate needs of population. Plants are being used in TMS all over the world, which is either in crude or extract form, and represent the basis of primary health care for the foreseeable future (Cordell 2011). The end of twentieth century marked a renewed interest in TM. The resurgence of natural therapies was mainly due to the limitations of modern drugs to cure complex disorders and also the observation of their increasing side effects. Contemporary harvesting methods for medicinal plants are severely depleting these critical indigenous resources.

Maintenance of the availability of quality herbal raw materials on a sustainable basis is an as yet unappreciated aspect of public health care. In order to achieve these goals for prospective health care, and refurbish the well-being of the Earth, a change in idea is necessary. Irrespective of their source, traditional medicine may be regarded as a sustainable commodity. Several approaches toward enhancing the accessibility of safe and efficacious plant-based medicinal agents include integrated strategies to get information on botany, chemistry, and biology for medicinal plant along with its quality control. Such integrated include information systems involving metabolomics, DNA barcoding, nanotechnology, biotechnology, the application of new detection techniques for in-field analysis of medicinal plants for better quality of safe and reproducible biological agents.

1.2.1 Sustainability in Traditional Medical Practice

Sustainability in TM is found in different sociological domains with different notions. Bioprospecting in general and a practiced in Ayurveda with respect to the usage of animal or plants could be the ultimate key, which can ensure a sustainable biodiversity for our future generations. Bioprospecting, which is defined as sector of pharmacological breakthroughs meant for human utilization conceives and include, (1) cultivation (2) the production of secondary metabolites in bioreactors, and (3) chemical synthesis of the compounds as the method to deal with the sustainability issue in regards to the substrates derived from living beings. Sustainability in traditional medical practice of ancient periods is relevant to current practice despite the absence of historical evidences. Theoretical assumption may be regarded as the ascendants of novel researches in science. With this in mind and with empirical evidence of its efficacy existing information base should be relied upon to take the science of TM further. Natural resources for TM are limited and are not rapidly renewable. Any unfamiliarity of this condition will be injurious to both TM and the global environment. Ideas regarding sustainability is not an assumption and is based upon perception and developments; therefore, new ideas must be respected for the betterment of global community.

As a consequence of expanding urbanization, rapid reduction in natural resources is leading to global warming and disrupted natural habitat caused a threat to the sustainability of traditional medicine. Traditional medicine being entirely dependent on natural resources like herbs, minerals, and animal products, would get extinct if heritage of an alternative way is not considered well in time, Ayurveda presents some unique sustainable models where animals and plants are used without posing any threat to their existence. In the current context, these ideas may give us a new insight to refine our outlook at natural resources used in traditional medicine to save natural resources which are facing a threat to their existence.

1.2.2 Sustainable Healthcare in Ayurveda

Sustainability in healthcare can be presented in Ayurveda at multiple levels such as preventive care, primary healthcare, resource utilization, and novel applications which is an ecologically sustainable medicinal system. For past several decades, *Ayurveda* and other traditional medical systems have faced the problem of nonavailability of genuine raw material. Manufacturers of Ayurveda-based medicines, have unsuccessfully tried to meet the demands by seeking alternatives for the conventional herbs or other ingredients, which are either not available or have lost their identity. Overexploitation, changes in global environment, and loss of delicate ecosystems due to urbanization collectively resulted in convergence of gene pool, growth of species with poor endurance and consequent loss of such species has been increasingly seen. As the resources are not easily available in future, TM will become more expensive. Producers of TM are going for mass production without considering intricacy of plant cultivation and their utilization, as described

traditionally due to demand-oriented market pressures and poor quality checks in the TM. Ayurveda with regard to their utilization of natural products for human welfare in an eco- and bio-friendly way that takes care of the human health with an equal concern for the surrounding environment (Mukherjee et al., 2012).

1.3 Ayurveda-Traditional System of Medicine in India

Ayurveda is the 'Science of life' which promotes wellness at physical, psychological, spiritual, and social realms of human existence (Mukherjee et al. 2012). This ancient healthcare system originated around 5000 years back in Vedic text Atharvaveda which contains various references to Ayurvedic medicine and allied aspects of healthcare. The growth and development of Ayurveda and other traditional systems of Indian Medicine was promoted by the Department of Indian Systems of Medicine and Homoeopathy (ISM&H) under the Ministry of Health and Family Welfare in March 1995. In November 2003, it was renamed as Department of AYUSH where each letter of the acronym 'AYUSH' represents officially recognized systems of medicine Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy. In 2014, Ministry of AYUSH was constituted for systematic development in all spheres of Indian Medicine and to bridge the prevailing gaps in healthcare delivery and outreach of health services by policy formulation, execution of programs for augmenting the domain, quality and outcomes in inclusive terms. *Sowa-Rigpa* has also been given recognition and added in AYUSH. The AYUSH systems are being promoted in India as the preferred systems of living and practice for a healthy India. The mission of AYUSH is to undertake and support activities of education and communication, human resource development, drug administration, medicinal plants research and development, international collaboration and enhancement of public information regarding AYUSH-based health services. For the mainstreaming of AYUSH services through a program called National Health Mission (Srivastava et al. 2016), the public perception regarding AYUSH is being developed through the utilization of the potentiality, strength, and revival of Ayurveda (Patwardhan 2014). For the development of AYUSH, COE organizations have been upgraded to National Accreditation Board for Hospitals (NABH), National Accreditation Board for Testing and Calibration Laboratories (NABL), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP) levels to achieve higher standards (Katoch et al. 2017).

Standardization of Ayurvedic drugs for the purpose of effective quality control 645 monographs of quality standards of single drugs and 252 monographs of quality standards of multi-ingredient formulations are published in two parts of Ayurvedic Pharmacopoeia in 13 volumes. For 265 standardized formulations from classical texts are published in four volumes of the National Ayurvedic Formulary. Pharmacopoeial standards of identity, purity, and strength of ASU drugs have been envisaged like identification, chemical constituents and limits of heavy metals, pesticide residue, aflatoxins, and microbial load. Various scientific laboratories and Pharmacopoeial Laboratory for Indian Medicine (PLIM) an appellate laboratory

under the provisions of Drugs and Cosmetics rules work on standardization and creating Standard Operating Procedures for Ayurvedic drugs using analytical tools (Mukherjee et al. 2010). Standard Operating Procedures (SOP) of manufacturing processes of formulations, assays, atlas of chromatography, Pharmacognosy atlas are being added to the quality standards of drugs to facilitate the testing procedures, estimation of marker compounds and phytochemical standard materials. The National Medicinal Plants Board (NMPB) under Ministry of AYUSH support policies and programs for the growth of trade, export, conservation, and cultivation of medicinal plants. They provide support for survey, conservation strategies of medicinal plants, herbal gardens, linkage for joint forest management programs, research, and development. Restrictions are enforced for rampant deforestation for the collection of raw materials of medicinal value from the wild sources (Katoch et al. 2017).

For promotion of industry-institutional collaboration Drugs & Pharmaceuticals Research Programme (DPRP) in 1994–1995 and to help the industry in promoting exports Pharmaceutical Export Promotion Council (Pharmexcil) constituted a National committee for Ayurveda medicines. The Ministry of AYUSH has focused its attention on standardization and quality control of Ayurvedic drugs for globalizing the Ayurveda system and its products. Testing for heavy metals, viz. mercury, arsenic, lead, and cadmium in all herbal Ayurvedic drugs is mandatory for export (Katoch et al. 2017). These measures aim for greater impetus to consumer awareness, consumer and doctor benefit, global acceptance and safety. In order to promote evidence-based healthcare documentation of clinical safety and efficacy of Ayurvedic medicines (Patwardhan 2011); clinical trials following 'Good Clinical Practice' (GCP) for AYUSH has been developed to generate quality data. The Central Council for Research in Ayurvedic Sciences (CCRAS) is working on coordination, formulation, development, and promotional research on Ayurveda which includes research on clinical, drug, and literature on Ayurvedic Sciences.

Apart from regulation and research increased awareness and improved access to traditional medicines is needed (Srinivasan and Sugumar 2017). The Ministry of AYUSH, through National AYUSH Mission (NAM) is enabling access to services, strengthening educational institutions, enforcement of quality control of drugs, and continuous availability of raw materials in the States/UTs (Srinivasan and Sugumar 2017).

1.4 Role of TMS in Health Care

India has a wide array of tradition knowledge systems related to health. While modern medical science and technology have gained dominance, practices using both old and new systems, co-exist. Unwritten knowledge passed on through the oral tradition and practiced is 'folk practice'. Systematized and duly codified texts receive greater legitimacy as 'traditional' or 'alternative' systems. Modern medical research has started verifying traditional medicines and this has led to their increasing adoptions.

The acronym AYUSH represents Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy, and Sowa-Rigpa for which a network of government services have been set up by the center and the states. Amchi or Tibetan Medicine in the western Himalayan region and acupuncture also receive state support in some regions. The folk medicine has survived with little or no official support. While anthropologists have documented folk knowledge, and botanists have documented medicinal plants and their folk uses, the official approach has been to view them as knowledge base on medicinal plants and herbs that can be exploited as economic resources for commerce.

Organization, training and practices of each form of health knowledge change with regional contexts. Such interaction between diverse forms of knowledge on health has been at an informal level but need to be viewed holistically as a 'health service system'. Health care starts from the home and goes through the primary and secondary level services to the tertiary level i.e., hospital. That it includes use of various knowledge systems and use of one or all of these are desirable as a part of continuum of care for realistic, cost-effective context-specific plans for health services, based on rational criteria of effectiveness, safety, accessibility, and affordability.

Three possible directions for strengthening AYUSH are, (a) contribution within the to strengthen AYUSH services through improved quality of infrastructure, human resources, supplies, R&D, and management verticals, (b) enhance interactions between the systems and encourage cross-referrals between them, by placing all services under one roof, and (c) develop integrated medicine for primary and secondary care protocols.

1.4.1 Role of National Rural Health Mission

The National Rural Health Mission (NRHM) has created the opportunity for co-locating services of the AYUSH at the CHCs and PHCs (leaving out yoga and naturopathy). This has been termed as the 'mainstreaming of AYUSH'. 'Revitalization of the local health traditions' is integral to NRHM strategies, but its modalities are yet to be finalized. During the appraisal of State Programme Implementation Plans for NRHM, only some states allocated substantial funds for co-location of AYUSH at rural health facilities as well as other activities, while others were not planning for such a strategy at all. Surprisingly, several states went beyond the activities envisaged in the NRHM framework to strengthen co-location. The NRHM has created an environment in which the states could undertake 'innovations'.

Commercialization of these systems as a part of the 'medical and health industry' that includes the providers is a loss making proposition in many ways. While these add to health care costs, they take away natural resources from the reach of local communities and destroy a non-commercialized model of health care as a community activity available to all. In an age when 'user fees' and service 'packages', 'medical tourism' and 'health spas' are becoming a corporatized model of health

care, the folk herbalists and home remedies provide a diametrically opposite version for a holistic and equitable health service system.

1.4.2 Changing Scenario of TMS in Health Care

Under the NRHM, 4981 AYUSH doctors and 934 Paramedics have been recruited on contract for co-location. As reported by states, about 44% of DHs, 24% of CHCs, and 17.6% of PHCs have co-location of AYUSH providers. Sixteen have allocated 1–3% of their NRHM budgets for this component, four have budgeted 3–10% and 12 states have budgeted over 10%. Drugs, equipment and buildings are funded by the department of AYUSH, while the NRHM flexi pool funds the health service providers hired on contract for co-location. The IPHS provide the guide lines for the level of services at each facility, from subcenters to PHC to CHC to DH.

These guidelines give the HR requirement, space and building, medicines and equipment and of a herbal garden in the SC and PHC premises. Co-locations seem to be the only activity followed promptly across all states, but at varied levels. States such as, Gujarat, Rajasthan, Himachal Pradesh, and J&K, with strong AYUSH base in the public health have rolled out the recruitment of AYUSH doctors for PHCs and CHCs under the NRHM to a greater degree than others. However, while continuing to strengthen its AYUSH services, Kerala is reluctant to co-locate them. There are reports of the State Directorates/Cell of AYUSH not being involved in the activities of mainstreaming under NRHM, leading to loss of synergy and lack of technical supervision for the co-located personnel.

The role of AYUSH doctors and paramedics in the co-located facilities needs much more attention for quality service delivery. While the role of AYUSH and LHT can be significant in RCH, this has not been adequately worked out. *Punarnavadi Mandoor*, the anti-anemia Ayurveda medicine, is the only one to have been widely included in the program. AYUSH doctors are being given training in SBA in only six states and IMNCI in three states. Since both require procedures specific to Allopathy such as injections and episiotomy and prescription of allopathic medicines, the legal issues need to be dealt with.

Training of AYUSH doctors in managerial and public health functions is not adequately planned. Membership of AYUSH doctors in the SHS, DHS, and RKS (planning, management and monitoring bodies created under NRHM) at various levels has been reported by most States, but their level of involvement is not known. Many additional and innovative activities are planned across states but their micro planning and implementation needs much more technical and managerial assistance.

District level planning has been done on mainstreaming of AYUSH under NRHM in a few states (as per the CRM). Planning for ensuring adequacy of appropriate AYUSH drugs is lacking. There are various additional inputs planned by some states under the following heads:

1. **IEC/BCC:** Sensitization activities for the general public about AYUSH and LHT.

2. **Specialty clinics/wards:** Half the states mention special AYUSH clinics or wards, especially a Ksharasutra therapy wing for anorectal diseases and Panchkarma clinics for intensive and specialized treatment at the CHC or DH.
3. **AYUSH health programs:** States like Orissa, Punjab, and Andhra Pradesh write in the PIPs about school Yoga programs and Yoga camps. The Tripura PIP also mentions sensitization of Primary school teachers regarding importance of yoga,'Suposhanam'. The special nutrition program for the tribal women is stated in the Rajasthan PIP. Ayurveda Mobile Units is also an activity mentioned in the Rajasthan state PIP.
4. **Outreach activities:** Utilization of AYUSH doctors for the Mobile Medical Units in some States, such as Jharkhand, Himachal Pradesh, J&K, and Orissa. Call centers for AYUSH in Madhya Pradesh and Tripura is a major innovation mentioned in their PIPs.
5. **Establishment of AYUSH epidemic cells:** Tamil Nadu and Kerala are using AYUSH in public health for preventive activities and epidemic control, e.g., Homeopathy for responding to the Chikungunya outbreaks. RAECH (Rapid action epidemic cell of homeopathy) in Kerala is a major AYUSH activity highlighted in the state PIP.
6. **Local health traditions:** The IPHS prescribes the setting up of an herbal garden within the space available in the subcenter and PHC premises. Most state PIPs have not mentioned this activity in particular, however, some states have for example—Chhattisgarh PIP has mentioned an innovative activity—the 'Ayurveda Gram' concept; 'Dadi ma ka batua' is an innovative scheme stated in the J&K PIPs, which plans to include traditional home remedies in the AYUSH drug kit; Madhya Pradesh has an innovation called Gyaan ki Potli which too plans to include prevalent and useful local health traditions/remedies which are accessible and affordable for various ailments as a step forward for LHT revitalization and Haryana has planned for courses on Local health traditions for the unemployed youth.
7. **Development of Medicinal Plants Resources:** The National Medicinal Plant Board (NMPB), the State Medicinal Plant Boards (SMPB) and NRHM are working in collaboration to preserve the large medicinal flora and their utilization in the primary health care. The 'Ayurveda gram yojna' must be explored and innovatively followed in the States.

1.4.3 Management and Technical Strengthening

Almost half the states have planned some strengthening of management and technical support to the AYUSH services. States like Rajasthan mention in the PIPs of year 2008–2009 about the formation of the State AYUSH Monitoring Cell (SAMC) for AYUSH services. Chhattisgarh too has a separate technical wing in the SHSRC for AYUSH. On a similar pattern, under the NRHM, Kerala, Jharkhand, Mizoram, Tripura, Delhi and Goa have planned for establishing a resource center or a separate cell for AYUSH.

India, with its 'Traditional Medical System' can be a world leader in the field. India's rich and mature indigenous medical heritages include Ayurveda, Yoga, Unani, Siddha, Homeopathy, Naturopathy, and Tibetan/Amchi Medicine. The size of the AYUSH sector in India is impressive. There is tremendous growth in the AYUSH education sector. Table 1.1 provides the status of infrastructure facilities in AYUSH.

1.4.4 Major Gaps and Technical Assistance Needs

The AYUSH services in the public sector are getting strengthened. However, the requirements for making full use of the opportunity are not yet adequately conceptualized or planned for. Some concerns that emerge are: inadequate inputs for optimizing the collocation strategy; relocating doctors from the well-established AYUSH facilities means weakening of AYUSH since they lose independent space, and there is loss of services to patients; no plans to orient the allopathic doctors to the strengths and role of AYUSH and LHT. Their non-appreciation is based on ignorance of research findings at the frontiers of modern medicine and the experiential knowledge of common people. Assessment of the role of AYUSH personnel under NRHM and in the public health system as a whole for mainstreaming of AYUSH and revitalization of local health traditions in an integrated and comprehensive manner was done (Samal, 2015).

Inputs by AYUSH doctors in co-located facilities toward fulfilling the service, training and capacity building for National Health Programs and Public Health need to be well defined. Orientation of the health personnel other than that of the AYUSH systems for sensitizing them toward AYUSH and the local health traditions is required. This should enhance the cross-referral systems, thereby optimizing the provision of benefits for all systems to patients. Drugs and equipment need to be reflected in the PIPs, based on a needs—assessment and monitoring of supplies.

The challenge to the public health system is how it visualizes the place of AYUSH and LHT within the health service system of the country. International experience shows how viewing them as the base to build upon for a continuum of care, from home to community, to health centers and dispensaries, to hospitals; letting each system grow according to its own epistemological orientation; and cross-referral based on mutual appreciation and respect serves people the best. It is to be hoped that the NRHM will be able to foster this spirit.

1.5 Conservation of Traditional Knowledge

The conservation of traditional knowledge is done by TKDL program deals with the documentation of existing knowledge on Ayurvedic systems of medicine in the form of an original proprietary database, which is fully protected by national and international laws of intellectual property rights. The Traditional Knowledge Resource Classification (TKRC) has converted 140,000 pages of information, containing

Table 1.1 Summary of infrastructure facilities under AYUSH

Facility	Ayurveda	Unani	Siddha	Yoga	Naturopathy	Homeopathy	Sowa-Rigpa	Total
Hospitals	3186	259	291	8	17	225	0	3986
Beds	43,358	3352	2051	185	682	6958	0	56,586
Dispensaries	17,102	1621	848	235	101	7259	33	27,199
Registered practitioners (IQ and NIQ)	443,704	51,110	9125	N/A	2485	293,455	0	799,879
Registered practitioners	294,162	38,672	5685	N/A	2349	246,792	0	587,660
UG colleges	393	52	10	N/A	26	221	0	702
Admission capacity (UG)	25,407	2945	580	0	1730	16,173	0	46,835
PG colleges	137	11	2	0	3	50	0	203
Admission capacity (PG)	4188	127	94	0	47	1080	0	5536
Exclusively PG colleges	3	3	1	0	0	2	0	9
Admission capacity (exclusive PG)	156	75	46	0	0	72	0	349
Total AYUSH colleges	396	55	11	0	26	223	0	711
Total admission capacity	29,751	3147	720	0	1777	17,325	0	52,720
Manufacturing units	7718	625	214	0	0	397	0	8954

36,000 formulations from 14 texts of Ayurveda. These documents have patent-compatible format in various languages, viz. translation of Sanskrit shlokas not only in Hindi but also in English, French, German, Spanish, Japanese, etc. The information includes names of plants, Ayurvedic description of diseases under their modern names, therapeutic formulations, etc.

1.6 Validation of Traditional Medicine

Ensuring therapeutic efficacy, safety, and rationalization of QC of TMs are critical and essential aspects for scientific validation (Mukherjee et al. 2017). The demands of traditional medicines are rising day by day and about three-quarters of the world's population currently use herbs and other forms of traditional medicines to treat disease. Even though marvelous advancement occurred in Allopathic system of medicines, there are many areas in which allopathic medicines have failed to prove its efficiency. Nowadays, people have more faith toward traditional medicines then modern medicines due to occurrence of many side effects of modern medicines. The prime reasons for acceptance of traditional medicines are accessibility, associability, and affordability in developing countries. Major thrust areas of research for validation of TM includes: (1) phytochemical and pharmacological screening, (2) phyto-informatics, (3) DNA-bar coding, (4) metabolomic study (5) reverse pharmacology, (6) safety evaluation, (7) quality control and standardization, (8) clinical evaluation, etc. (Mukherjee et al. 2017). Systematic investigations and standardization of medicinal plants needs to be done for quality, safety, and efficacy. Apart from analytical chemical fingerprinting techniques e.g., high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC); macroscopic and microscopic studies, genetic finger-printing methods should be done. LC-MS/MS may be also used for standardization (Mukherjee et al. 2017). Since traditional medicines often have numerous active ingredients, it could be used to measure the whole body's response to the mixture of compounds (Patwardhan and Mashelkar 2009).

1.6.1 Chemo-Profiling and Standardization of Traditional Medicine

In order to assess the quality of herbal traditional medicine chemical profiling is required for standardization of herbs, marker compound quantification, spurious drug determination, comparative fingerprint analysis for consistency of stability and quality of TMs. Botanicals from wild sources have the greatest challenge for ensuring consistent product quality (Harwansh et al. 2014). Environmental factors including geographical location, availability of light and water, temperature variations, soil conditions, nutrients, and that affect the phyto-constituents present in plants. Factors like cultivation and harvesting techniques and storage practices determines the quality parameters for plant extracts and final product. Substantial variation in composition, quality and therapeutic effects are observed in botanical

extracts obtained from crude plant material show (Harwansh et al. 2015). Therefore, standardization of herbal drugs includes certification of quality raw material, assessment of intermediates, and finished product. DNA-based markers can also be used in identification of inter/intra-species variations because the genetic composition is unique for each species and is not affected by age, physiological conditions and environmental factors.

According to the monographs of the American Herbal Pharmacopoeia (AHP), the use of single or multiple chemical markers is crucial for QC along with proper cultivation, collection and quality, optimum extraction and standardization of raw materials. The evaluation of herbal medicine should be done in a better way to get fruitful results (Mukherjee et al. 2009).

Chemical fingerprints relate the chemical composition to biological activity for product standardization and validation which can be used to authenticate plant material, identification, and quantification of active compounds (Mukherjee et al. 2007b). Marker components may be classified as active principles, active markers and analytical makers, while biomarkers may be defined as pharmacological active. Chemical makers are frequently used for assuring quality consistency of natural products derived from botanical sources. Ideally, the chemical markers chosen should be bioactive (Mukherjee and Wahile 2006). However, marker compounds may not be pharmacologically active all the time but their presence is well established in products with characteristic chemical features (Mukherjee et al. 2017). Biologically active reference standard (BRS) or pharmacologically active reference standard (PRS) are also marker compounds. Determination of single or several marker compounds by a developed method are becoming popular for the identification/authentication of herbal drug components (Katoch et al. 2017).

1.6.2 Plant Metabolomics

Metabolomics is the quantitative and qualitative assessments of 'whole-set of metabolites' that occur in plants. It may be defined as the systemic study of the individual chemical fingerprints of all the metabolites in a biological system, which are the final products of its gene expression, is known as metabolome (Lee et al. 2017). The plant secondary metabolites are health care products or lead compounds for new drug development which have renewed interest in pharmaceutical and nutraceutical research (Newman and Cragg 2007). A targeted metabolomics study involves characterization of a set of defined metabolites and usually combines NMR-MS techniques. An array of metabolites can be intercepted by leading the way to major revelation in our understanding of cell biology, physiology and medicine (Cox et al. 2014). Metabolomics study has diverse fields of application and can be divided into four areas: (1) the metabolomics profiling—the quantitative and qualitative estimation of a set of compounds (2) target compound analysis—the quantification of specific metabolites, (3) metabolomic fingerprinting—sample classification by rapid global analysis, and (4) metabolite chemo-analysis—the qualitative and quantitative analysis of all metabolites (Ulrich-Merzenich et al. 2007).

These may assist evidence-based phyto-therapeutics research which may lead to a change of paradigm in the development and application of multicomponent botanical therapeutics (Wang et al. 2017a).

Metabolites profiling can identify the plant secondary metabolites by comparing the nature of compounds as the output of sensors (analytical detectors) are known as 'profiling' which are then classified and statistically analyzed by chemometrics (Noteborn et al. 2000). Metabolite identification is based on their spectral peaks and calibration curves which comprehensively examines entire range of metabolites in a sample by the mutual application of various analytical techniques (Glassbrook and Ryals 2001). Metabolomics reveals the phenotypic changes in the function of metabolic systems. However, among the 'omic' sciences metabolomics presents the terminal view of the biological system (Gahlaut et al. 2013) Metabolomics and phytomics provide mechanisms for assuring consistent quality and efficacy of herbal medicine. Traditional medicines contain multiple phyto-constituents and pharmacological properties are complex systems as single medicinal plant extracts which are influenced by the time of collection, area of plant origin, and environmental conditions. Therefore, above mentioned strategies regarding various issues are needed for validation of TM (Mukherjee et al. 2007a).

1.7 Quality Assurance of Herbal Medicine

Herbal drugs have turned out to be an important part of new generation health system in many countries. It has been observed in recent times that herbal products are substituting the conventional medicines in many countries. Increased demand of herbal product leads to growing demand in global market (Gouveia et al. 2015). Quality of TMs is determined by identity, purity, content, physical, and biological properties which is importance for efficacy and safety of herbal products. Ensuring quality of herbal products begins from the field to the bedside of the patients, followed by post-marketing surveillances. WHO has developed technical guidelines on the safety and Quality Assurance (QA) of medicinal plants and herbal materials are essential to follow, which includes Good Agriculture Practices (GAP), Good Harvesting Practices (GHP), Good Storage Practices (GSP), Good Clinical Practices (GCP), Good Manufacturing Practices (GMP), and Good Laboratory Practices (GLP).

With the increase in the use of herbal medicine there is also an increase in the reports of toxicity and adverse reactions. Such undesirable reactions can be due to:

1. Side effects (usually these are predictable in nature)
2. Reactions which are resultant of overdose, over-duration, tolerance, dependence-addiction
3. Hypersensitivity, allergic, and idiosyncratic reactions
4. Mid-term and long-term toxic effects including liver, renal, cardiac, and neurotoxicity also genotoxicity and teratogenicity.

Herbal products, which are being marketed, are generally not thoroughly tested for their pharmacological and toxicological effects. In addition there has been a problem related to the quality of herbal products due to unexpected toxicity, which occurs due to use of poor quality of raw materials, misidentified herbs, adulterations, and contaminations. With the help of GMP, these quality issues can be addressed properly and manufacturing of herbal medicine can be improved. However, there are some issues, which cannot be neglected like some herbs which come from different countries that have different standards and regulations. Such matters have remained a problem so far. Due to reports of serious effects like hepatotoxicity, renal failure and allergic reactions, the regulatory authorities are facing questions regarding the safety of marketed herbal medicines. The World Health Organization has developed guideline for the monitoring of herbal safety within the existing pharmacovigilance framework (Shaw et al. 2012). The primary steps in quality assurance are as follows:

1.7.1 Classical Systematics in Species Authentication and the Utility of Good Agricultural and Collection Practice (GACP)

In many developed countries like Australia, Canada, Europe, and the USA, the quality assurance and control of the herbal ingredient (raw materials) is the main job of the product license holder who should ensure the efficacy and compliance of the herbs with the respective national regulatory framework. The sponsor of the herbal medicine, in turn, has to place specific systems and requirements for approval of ingredients (raw materials) through the supply (value) chain back to the ingredient source and manufacture to assure quality. Many but not all international firms tend to adopt vendor audit programs to qualify herb source and ingredient manufacture by stringent GMP protocols. With the outsourcing of authentic herbs the quality assurance of the herbal ingredients throughout the supply chain begins. To establish the purity of the ingredient, authenticating the starting material is the major requirement. Authentication is often difficult when the herbs are purchased from local market with no traceability of their origin, although now days due to proper understanding and knowledge, medicinal herbs are sourced either from organized cultivation or by wild-crafting (Govindaraghavan 2008).

1.7.2 Genomic Profiling and DNA Barcoding in Species Authentication

Plant authentication can be done by genomic profiling and DNA barcoding, which are considered to be complementary techniques to classical systematic approaches helping in unequivocal identification of plant species. DNA barcoding in plants was promoted by The Plant Working Group of CBOL (Consortium for the Barcode of Life) in 2004. It was observed that single locus barcode was not sufficient for authentication of plant species, so two-locus combination was recommended for

authentication. These two-locus combinations are chloroplast genes maturase K (matK) and ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit (rbcL). The need for inclusion of third locus to increase the rate of identification is currently under debate. Sufficient variability for species identification can be exhibited by Deoxyribonucleic acid barcodes and this system can be amenable to ease in referencing (Govindaraghavan 2008).

1.7.3 Macroscopic and Microscopic Characterization of Sorted Plant Materials

Medicinal plant authentication can be done based on macroscopic and microscopic character sets of sorted plant parts along with their phytochemical (metabolite) profiles. The pharmacopoeial monographs, mentions the identification of the species based on the morphological and microscopic characters of dried and sorted plant parts based on their roots, leaves, berries/fruits, bark, flowers, seeds and husks, or derived products such as gum/resins (Govindaraghavan 2008).

1.7.4 Phytochemical Profiling of Plant Parts as a Tool for Identification and Characterization

The phytochemical profiling tools constitute high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography (HPLC) in addition to gas chromatography (GC) with detectors like ultraviolet (UV) and visible (Vis) light-based photodiode array (PDA) with mass spectrometry (MS) (Govindaraghavan 2008). Chemical profiling is essential in order to assess the quality of traditional herbal preparations (Sen and Chakraborty 2017).

1.7.5 Guidelines for Good Plant Authentication and Identification Practice (GPAIP)

An outstanding good practices guideline regarding plant identification for herbal industry has been provided by Agriculture and Agri-Food Canada. With the help of this example, it has been recommended to the industries manufacturing herbal medicines that GPAIP should be followed as the herbal ingredients undergo change in every step of the process across the supply chain.

1.7.6 Assurance of the 'Purity' of Botanical Raw Materials: Impurity Profiling

To obtain good quality of herbal ingredient, the main focus should be on its purity, i.e., it should be free from impurities, which can ensure quality end product. There

are many components, which fall under the category of impurities like heavy metals, pesticide residues, aflatoxins/mycotoxins, etc. The contaminated soil is the major source of heavy metal contaminations in medicinal plant species. It has been reported that over 500 plant species are known to accumulate heavy metals and in some species, heavy metal concentrations in aerial parts exceed critical toxicity levels (Govindaraghavan 2008).

1.8 Pharmaceuticals, Nutraceuticals, Phyto-Pharmaceuticals Inspired from Ayurveda

Healthcare research has shifted toward quality is an urgent need for direct traditional medicine-inspired natural product research (Cordell and Colvard 2012). Approximately, 70% of cancer and 42% of rheumatic patients use complementary and alternative medicine (Ernst and Cassileth 1998). Scientifically validated botanicals Ispaghula, Garlic, Ginseng, Ginger, Gingko, St. John's Wort, and Saw palmetto are regular in practice by modern physicians (Wetzel et al. 2003). Therefore correct identification and authentication of traditional medicinal herbs is essential as quality of the source determine the final product (Franz et al. 2011). Integrated strategies should be considered for the validation of Ayurvedic medicines at each and every step (Mukherjee et al. 2012). Globalization and reinforcement of Ayurvedic medicine is necessary for the establishment of the evidence-based healthcare claims. There has been a development in the education and communication to disseminate the sources of Ayurvedic knowledge interpretable in Western terminology, and a variety of texts are now available online. The National Institute of Indian Medical Heritage (http://niimh.nic.in/) under the CCRAS, Ministry of AYUSH has published e-Samhitas of all the main classical works on Ayurveda, such as the Samhitas (*Charaka Samhita, Sushruta Samhita*) and other books like *Astanga Hridaya, Ashtanga Sangraha,* and *Bhavaprakash Nighantu* which are available online (Mukherjee et al. 2017).

These traditional resources provide the products including herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants, other plant materials, or combinations thereof as active ingredients (WHO 2013). Finished herbal products consist of herbal preparations made from one or more herbs (Bhatt 2016). In India, the AYUSH drugs are regulated by 'Ministry of AYUSH'. However, the regulatory requirements for phyto-pharmaceuticals are governed by the Central Drugs Standards Control Organization (CDSCO). By legal definition regulatory provisions for phyto-pharmaceuticals and regulatory submission requirements for scientific data on quality, safety, and efficacy to evaluate and permit marketing of a herbal drug on similar lines to synthetic, chemical moieties (MHFW 2016). Phyto-pharmaceutical drug is defined as purified and standardized fraction with defined minimum four bioactive or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include

administration by parenteral route (MHFW 2016). According to Schedule Y, Appendix I B it is mandatory to submit evidence-based data along with the application in order to conduct clinical trials or import or manufacture of a phyto-pharmaceutical drug in the country (MHFW 2016). These phyto-pharmaceutical drugs are considered as NDA which includes standard requirements for a new drug safety and pharmacological information, human studies, and confirmatory clinical trials.

The new regulation for phyto-pharmaceutical is in line with regulations in developed countries involving data generation on scientific evaluation (Narayana and Katiyar 2013). Now the Indian scientists would discover and develop phyto-pharmaceutical drugs for as yet unmet medical needs from herbal drugs (Bhatt 2016). CSIR-Central Drug Research Institute has developed phyto-pharmaceutical drugs including standardized extracts of *Bacopa monnieri* (CDRI 08), *Picrorhiza kurroa* (Picroliv), *Commiphora mukul* (gugulipid,) and *Dalbergia sissoo* for memory enhancement, liver health, lipid disorders, and bone health, respectively. These phyto-extracts were defined by chemical markers and pharmacologically active ingredients, pharmacognosy, preclinical efficacy assessments in appropriate disease models, preclinical pharmacokinetics, and safety studies.

1.9 Global Harmonization and Regulatory Status of Traditional Medical Systems (TMS)

The popularity of Traditional and Complementary Medicine (TCM) worldwide is increasing and specifically in some developing countries where the native healers play a significant role as main health providers in rural areas. For instance in Africa, Lao, People's Democratic Republic most of the populations have traditional health practitioners. About one-fourth Europeans use TCM while China, North Korea, South Korea India, and Vietnam have introduced traditional healthcare as a mainstream health system. The safety, quality, and efficacy of TM services cannot be assured if there is no appropriate regulation of practices and practitioners. However the equality is missing in the regulation of TCM products, practices, and practitioners in the pace of progress. Whereas regulation of herbal medicines is progressing faster compared to TCM practices, the practitioners are lagging behind. This situation presents a serious challenge as there is a lack of knowledge and experience regarding the formulation of meaningful national policies. This is causing absence of regulation and a lack of proper integration of TM services into the health service delivery system. The WHO Traditional Medicine Strategy 2014–2023 has been formulated responding to these needs and challenges identified which devotes more attention than its predecessor to health services and systems, products, practices, and practitioners (Burton et al. 2015).

1.10 Clinical Trial and Pharmacovigilance of TM

Clinical trial and pharmacovigilance of TM will be discussed under the broad areas including geriatric, metabolic, infectious and inflammatory diseases and cancer because their combined disease burden contributes to lion's share of diseases afflicting the Indian population. Geriatric diseases will consider Alzheimer's disease and Parkinson's disease, metabolic diseases will cover diabetes, hypertension, and osteoporosis, infectious diseases will include tuberculosis, malaria, leishmaniasis and AIDS, inflammatory diseases will consider chronic obstructive pulmonary disease and rheumatoid arthritis, and cancer will cover breast, prostate, and lung cancers. These broad disease areas and their specific disease types are reviewed with respect to clinical assessment of various TM products. Given the overall paucity of clinical trials in the area of TM, we considered all trials done anywhere in the world regardless of their quality.

1.10.1 Geriatric Diseases

1.10.1.1 Alzheimer's Disease and Cognition Deficit

Alzheimer's disease (AD) is a neurodegenerative irreversible disease characterized clinically by progressive memory deficits, impaired cognitive function, and altered, inappropriate behavior. Evidence obtained from ethnobotanical studies suggests that various traditional medicinal plants used in China, India, Iran, the USA, Southwest Nigeria, and Europe have a salutary effect in AD-type neurodegeneration (Eckert 2010; Tewari et al. 2018). Ethnobotanical survey of 37 species of medicinal plants used for memory enhancement and anti-aging effects were found to belong to 28 families with potential anticholinesterase and neuroprotective actions (Dos Santos-Neto et al. 2006). Out of these plants, clinical trials have been carried out with *Ginkgo biloba*, *Salvia officinalis*, *Melissa officinalis*, *Papaver somniferum*, *Crocus sativus*, and *Bacopa monnieri* having therapeutic effects for the treatment of cognitive impairment of AD (Akhondzadeh et al. 2003, 2010; Tian et al. 2010; Farooqui et al. 2018). In addition, several polyherbal formulations including 'Di-tan decoction', Yi-Gan San, Ba Wei Di Huang Wan, and YishenHuazhuo decoction were found to have significant memory improvement in patients with AD (Dos Santos-Neto et al. 2006; Zhang et al. 2015). However, methodological limitations such as poor study design, relatively small sample size, and invalid statistical analysis have been noted (Tian et al. 2010). Given that multiple clinical trials have been carried out with *Ginkgo biloba* extract EGb 761 and Huperzine A (Chinese herb) for AD, meta-analysis of the trials that included randomized placebo-controlled modes showed high risk of bias (Yang et al. 2013; Gauthier and Schlaefke 2014).

In a double-blind, placebo-controlled cross-over study showed that acute supplementation of CDRI 08 (enriched in bacosides A and B) produced adaptogenic and nootropic effects (Benson et al. 2014). In addition, a couple of clinical trials confirmed that CDRI 08 has salutary effects on memory, mood, and mental alertness

as the healthy volunteers treated with CDRI 08 displayed improved speed of visual information processing, learning rate and memory consolidation, decreased anxiety and improved performance on 'working memory' (the ability to hold information and actually do something with that information) and 'visual information processing' (a measure of the ability to sustain attention) as compared to placebo-treated group (Stough et al. 2001, 2008).

1.10.1.2 Parkinson's Disease

Parkinson's disease (PD) is one of the most common age-related neurodegenerative disorders of the central nervous system (CNS), affecting about 3% of the population over the age of 65 worldwide. Reports from ethnobotanical surveys done in Asian countries including China, India, Japan, and Korea provide an inventory of herbal medicine for the treatment of PD (Wang et al. 2008; Song et al. 2012). These surveys suggest that in recent years herbal medicines such as *Acanthopanax*, *Alpinia*, and *Astragalus* (Li et al. 2013b) have attracted considerable attention to treat PD, particularly in China. Based on traditional Chinese medicines, the medicinal herbs belong to 24 genera and 18 families. These herbal medicines could be an alternative and valuable source for anti-PD drug discovery. In addition, couple of polyherbal formulations—Dangguijakyak-san (Hwang et al. 2011) and a modified Yeoldahanso-tang (Bae et al. 2011) showed anti-PD effects. Clinical trials have also been carried out with *Ginseng*, *Ginkgo biloba*, *Mucuna pruriens,* and *Banisteria caapi* which suggested neuroprotective properties in PD patients (Bega and Zadikoff 2014; Guanti et al. 1976). The meta-analysis included 19 randomized controlled trials involving 1371 participants to assess the efficacy and safety of Chinese herbal medicine (CHM) paratherapy in patients with PD. In this meta-analysis, patients receiving CHM adjunct therapy plus WCM (western conventional medication) exhibit significant improvement in their PD symptoms as evidenced by improvements in their UPDRS (Unified Parkinson Disease Rating Scale) scores compared to WCM controls in spite of some methodological limitations. According to the safety assessment of this meta-analysis, the CHM add-on therapy for PD is generally safe and well tolerated (Wang et al. 2012).

1.10.2 Metabolic Diseases

1.10.2.1 Diabetes

Reports from ethnobotanical surveys done in Africa, South Asia, and China provide an inventory of herbal remedies for diabetes mellitus (DM), which suggest hundreds of herbs and botanicals in use globally. From these surveys, it appears that in India alone 37 medicinal plants belonging to 25 families are being used for the treatment of DM (Mohammed et al. 2015). In addition, at least nine polyherbal products are in the market having a significant sale in India. Clinical trials have been carried out with *Coccinia indica*, *Momordica charantia*, *fenugreek seeds*, *Azadirachta indica,* and *Ficus racemosa* in type 2 DM patients. However, all these studies suffer from limitations such as small sample size and trial duration, inappropriate randomization,

lack of blinding and hence non-application of intention-to-treat analysis. Outcome measures were often not quantitative (Ocvirk et al. 2013). Meta-analyses were attempted with 108 trials examining 36 herbs/botanicals (single or in combination) involving >4000 patients with type 2 DM or impaired glucose tolerance (Choudhury et al. 2018). However, heterogeneity in terms of outcome measures and a small number of trials for each agent precluded formal meta-analyses.

1.10.2.2 Hypertension and Associated Cardiovascular Diseases

Hypertension is a chronic visceral medical complication in which blood pressure (BP) in the arteries is elevated (Tabassum and Ahmad 2011). The use of herbal medicines to treat hypertension is growing all over the world, particularly across the developing countries because of their wide biological and medicinal activities, higher safety margins and lesser cost. For example, several polyherbal Chinese medicines including Tongxinluo, Xuefu Zhuyu decoction (XZD), and Zhen Wu decoction (ZWD) have been reported to be effective in treating mild-to-moderate hypertension (Wang et al. 2014, 2015b; Xiong et al. 2015b). Reports for ethnobotanical investigations/surveys done in many developing countries such as African nations and South Asia (India and Pakistan) utilize sustainable herbal plants for drug discovery (Davids et al. 2016; Malik et al. 2018). From an inventory, 27 medicinal plants from 22 families are used for the treatment of hypertension. Most commonly used antihypertensive species were *Apiaceae*, *Rosaceae* and *Papaveraceae* (Baharvand-Ahmadi et al. 2016). Clinical trials have been carried out with *Rauwolfia serpentina*, *Allium sativum*, *Ginkgo biloba*, *Hibiscus sabdariffa*, *Salicin* (the source of aspirin) from *Salix alba* (willow bark), *Crataegus laevigata*, *Terminalia arjuna*, *Achillea wilhelmsii*, *Centella asiatica,* and *Combretum micranthum* which indicate blood pressure (BP) lowering effect as well as safety of these plants in hypertensive patients (Mashour et al. 1998; Haji Faraji and Haji Tarkhani 1999; Walker et al. 2006; Tabassum and Ahmad 2011; Chrysant and Chrysant 2017; Seck et al. 2017).

A recent surge in the popularity of CHM has led to several clinical trials which reported efficacy of this kind of treatment in hypertensive patients. These trials ranged from case reports and case series to controlled observational studies and randomized clinical trials (Wang and Xiong 2012). A meta-analysis evaluating the effectiveness of ZWD and XZD included seven trials involving 472 hypertensive patients and 15 studies involving 1364 hypertensive patients, respectively. These herbal medicines are more effective in lowering BP, improving lipid profile, lowering homocysteine, and improving hemorheology when compared with clinically approved antihypertensive drugs (nifedipine, captopril, hydrochlorothiazide, valsartan, and amlodipine) used as monotherapy (Wang et al. 2015b; Xiong et al. 2015b). However, some limitations associated with studies included poor methodological quality, selective bias, small sample size, and inadequate reporting on clinical data (Xiong et al. 2015a, b).

Guggulsterone containing gugulipid showed significant lipid-lowering effect in 80% hyperlipidemic patients who participated in the trial; and the drug showed no adverse effect which resulted in its marketing approval from the Drug Controller General of India in 1986. A clinical trial in Indian patients with hyperlipidemia, upon

treatment with 50 mg gugulipid b.d. and with a diet rich in fruits and vegetables reported significant lipid-lowering effect as compared to placebo-treated group. After 36 weeks of receiving a combination of diet and gugulipid, patients showed a lipid-lowering efficacy comparable to allopathic medicine and that too without any severe side effects (Singh et al. 1994). Gugulipid also showed lipid-lowering effect in a multicentric (held in seven Indian cities) open trials where 500 mg t.d.s. was administered for 8 weeks and the effect of gugulipid was better than clofibrate (the standard drug) particularly in enhancing HDL-cholesterol (Nityanand et al. 1989). However, hyperlipidemic patients eating the western diet failed to respond to gugulipid given for 8 weeks at 1000- or 2000-mg (Szapary et al. 2003). Whether prolonging gugulipid treatment with non-western diet (western diet is typically rich in fat-derived calorie) could have shown hypolipidemic effect in western patients remains conjectural. Nonetheless, available pieces of evidence are promising and warrant additional multicentric randomized placebo-controlled trials to confirm the hypolipidemic impact of gugulipid.

The standardized water extract of stem bark of *Terminalia arjuna* (Roxb. ex DC.) Wight and Arn was given to patients with chronic heart failure (CHF) in combination with standard medical therapies (angiotensin converting enzyme inhibitor or an angiotensin II type 1 receptor blocker and a beta-blocker) for 12 weeks to assess add-on efficacy of the extract in comparison to patients receiving only standard medical therapies. The findings showed that the extract was well tolerated but produced no change in the primary outcome measure, i.e., left ventricular ejection fraction, when added to evidence-based pharmacotherapy in patients of CHF. Among the secondary outcome measures, the extract helped to (a) preserve RBC catalase activity and functional capacity (distance covered in 6 min walk); and (b) increase antioxidant reserve and quality of life in some patients as compared to placebo patients (Maulik et al. 2016).

1.10.2.3 Osteoporosis

Osteoporosis is characterized by low bone mass and microarchitectural deterioration resulting in increased fracture risk that occurs primarily with aging. The skeletal efficacy of a variety of medicinal plants tested thus far can be divided by their mechanisms that are either calcium regulatory, hormonal regulatory or bone remodeling regulatory types. Survey of medicinal plants in human use in China, India, and Korea has enlisted *Herba epimedii*, *Fructus ligustri lucidi*, and *Fructus psoraleae* for their skeletal efficacy demonstrated in preclinical setting. Polyherbal preparation made from CHM, OST-6, and BHH-10 reported safety and bone conserving effect in postmenopausal osteoporosis (PMO) (Irshad Ahmed et al. 2002; Cho et al. 2018). However, this trial suffers from limitations including small population size, short study duration, and nonavailability of compliance data.

FuFang with phytoestrogen-rich (icariin) epimedium is safe and effective in the prevention of postmenopausal bone loss based on a 5-year multicentre placebo-controlled study on 194 postmenopausal women, which underscores its potential in reducing fragility fracture (Deng et al. 2012). Anti-osteoporosis effect of FuFang was mediated by attenuating bone resorption via the increased production of

anti-osteoclastogenic cytokines, osteoprotegerin. A meta-analysis of 12 random control trials involving 1816 patients observed significant bone mass density (BMD) increase at femur and spine over the placebo group (Wang et al. 2013). Future studies must be conducted with large sample size and longer duration for substantiating the current primary findings.

A standardized extract of leaves of *Dalbergia sissoo* rich in caviunin 7-*O*-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside] showed safe bone conserving effect in patients with postmenopausal osteoporosis. The underlying mechanism appears to be significant suppression of the elevated pro-inflammatory cytokine, tumor necrosis factor-α in the osteoporotic patients (Meeta et al. 2019).

1.10.3 Infectious Diseases

1.10.3.1 Tuberculosis

Ethnobotanical study reports suggest a rich source of herbal anti-tuberculosis drugs in Nigeria, China, India, Russia, and the UK. A total of 36 plants belonging to 20 families have been proposed for the management of tuberculosis in Nigeria. The most frequently used herbs were *Cola acuminate*, *Garcinia kola*, *Vitellaria paradoxa*, *Costus afer*, *Pycnanthus angolensis,* and *Aframomum melegueta* for TB treatment (Liu et al. 2008; Ogbole and Ajaiyeoba 2009; Wang et al. 2015a). Studies were done with *Allium sativum*, *Erythrina abyssinica*, *Abelmoschus esculentus*, *Adhatoda vasica,* and *Ocimum basilium* in pulmonary tuberculosis patients for their anti-mycobacterial activity, and were found to be useful as adjuvant therapies to improve the efficacy of conventional antimycobacterial therapies; to decrease their adverse effects; and to reverse multidrug resistance due to the genetic plasticity and environmental adaptability of mycobacterium (Sharifi-Rad et al. 2017).

A meta-analysis of 30 RCTs involving 3374 participants of MDR-TB given CHM combined with clinically approved chemotherapy, which showed that CHM plus chemotherapy arm had improved sputum bacteria conversion, lung lesions resorption, cavity closure, abnormal liver and kidney functions, and gastrointestinal symptoms compared with chemotherapy arm alone (Wang et al. 2015a).

1.10.3.2 Malaria

Artemisinin, isolated from *Artemisia annua* is the most potent antimalarial drug for the discovery of which Tu Youyou received Nobel Prize for Physiology or Medicine in 2015. Artemisinin acts against all malaria-causing organisms in the genus *Plasmodium*. An ethnobotanical survey of Indian antimalarial plants identified a total of 22 species of plants belonging to 17 botanical families mostly from Assam. Out of these Verbenaceae, Menispermaceae, and Acanthaceae are the most commonly used to treat malaria and its associated symptoms (Namsa et al. 2011). Clinical studies were done with Quinine, *Cryptolepis sanguinolenta*, *Artemisia annua*, *Cochlospermum planchonii*, *Argemone mexicana*, *Vernonia amygdalina*, *Azadirachta indica*, and Ayush-64 for safety and efficacy of herbal preparations for their antimalarial preparation activity (Willcox and Bodeker 2004; Challand and

Willcox 2009; Tabuti 2008; Mueller et al. 2004; Willcox 2011). Data suggested the efficacy of these phyto-preparations in patients infected with *Plasmodium falciparum* and *Plasmodium vivax*. A plant decoction, AM-1 formulation composed of *Jatropha curcas*, *Gossypium hirsutum*, *Physalis angulata,* and *Delonix regia* was found to eliminate malarial parasites (*Plasmodium falciparum* and *Plasmodium malariae*) from the peripheral blood of infected subjects (Ankrah et al. 2003).

1.10.3.3 Leishmaniasis

Based on ethnobotanical reports, 98 types of plants have been identified and recorded for their use in the treatment of three genera of Leishmania spp. The most commonly plants used as anti-leishmanial activity were *Artemisia species*, *Allium sativum*, *Achillea millefolium*, *Peganum harmala,* and *Thymus vulgaris* (Soosaraei et al. 2017). A number of plants have been assessed for anti-leishmanial effects including *Nyctanthes arbor-tristis*, *Withania somnifera* Dunal (ashwagandha) and *Allium sativum*, *Bidens pilosa* (*Asteraceae*) and *Punica granatum* (*Punicaceae*). The extracts of ashwagandha *bidens*, *Allium sativum pilosa* and *Punica granatum* have been reported to have a potent leishmanicidal effect (Panda and Luyten 2018; Garcia et al. 2010; Sharma et al. 2009). Furthermore, a randomized clinical trial suggested that *Juniperus excelsa* can be used as an adjuvant treatment in addition to cryotherapy for cutaneous leishmaniasis (CL) as it can decrease the duration and success rate of CL treatment without any significant adverse effects (Parvizi et al. 2017).

1.10.3.4 Acquired Immunodeficiency Syndrome

Ethnobotanical evidences indicate that traditional medicines are commonly used by HIV-positive patients in Zimbabwe, South Africa, and Uganda (Gail et al. 2015; Monera and Maponga 2012; Lamorde et al. 2010). In ethnobotanical surveys, 75 plant species belonging to 66 genera and 41 families were found to be in use in treating one or more HIV/AIDS-related infections in the aforementioned African countries (Kisangau et al. 2007). Survey data has shown that *Moringa oleifera* Lam is commonly used for medicinal and nutritional purposes among HIV-positive patients in Zimbabwe (Monera and Maponga 2012). Studies carried out in HIV-infected patients using various medicinal plants such as *Allium sativum*, *Dicoma anomala*, *Aloe* spp., *Hypoxis hemerocallidea*, *Sutherlandia*, St. John's wort (*Hypericum perforatum*) and andrographolide from *Andrographis paniculata*, revealed serious adverse effects on the pharmacotherapies that are clinically approved for AIDS and thus raised important safety concerns for their use (Mugomeri et al. 2016; Mills et al. 2005; Langlois-Klassen et al. 2007; Calabrese et al. 2000).

In India, clinical studies of Boxwood (*Buxus sempervirens*), Andrographolide (*Andrographis paniculata*), and neem (*Azadirachta indica*), as well as Siddha combination therapy RAN (*Rasagandhi mezhuga, Amukkara chooranum*, and *Nellikkai lehyam*) were done (Fritts et al. 2008).

In India, a nonrandomized, placebo-controlled, investigator-blinded trial with a polyherbal formulation (PHF) was compared with highly active antiretroviral

therapy (HAART) for safety and efficacy in treating HIV/AIDS. PHF consisted of ingredients from 58 different plant species appears to provide protection against AIDS development by delaying the kinetics of CD4 cell reduction leading to significant improvements in the T-cell profile of the infected subjects culminating in decreased viral load (Asokan et al. 2013). Eight herbal products were tested in nine randomized placebo-controlled trials involving 499 patients with HIV infection and full-blown AIDS patients. The results showed that preparations called SPV30, IGM-1 (CHM), and SH delayed the progression of HIV-related symptoms (Liu et al. 2005).

1.10.4 Inflammatory Diseases

1.10.4.1 Chronic Obstructive Pulmonary Disease

Two polyherbal formulations including bushen naqi huoxue and Yufeining (YFN) (in China) and hochu-ekki-to (in Japan) were studied and found to be effective with no adverse effects in COPD patients and act as an anti-inflammatory agent (Hong et al. 2018; Ram et al. 2011). Clinical trials have also been carried out with *Panax ginseng*, *Salvia miltiorrhiza*, *Swasakasathirku churnam,* and *Hedera helix*. However, limitations including small sample size and poor methodological quality preclude these from being included in a meta-analysis (Guo et al. 2006).

Meta-analyses of 11 trials comprising total of 925 patients for CHMs add-on to SFP (Salmeterol and Fluticasone Propionate), showed efficacy and safety of these herbal medicines in COPD when compared with SFP alone. Use of 11 different CHM (seven herbal decoctions, one pill, and remaining three were capsules) showed increase in forced expiratory volume in 1 s, St. George's Respiratory Questionnaire (SGRQ) scoring and frequency of exacerbations. Out of 11 CHMs, Runfeijianpibushen decoction and Renshenbufei pills with SFP showed better effect in improving St. George's Respiratory Questionnaire (SGRQ) scoring when compared with SFP alone and other CHMs (herbal decoctions and capsules) (Chung et al. 2016).

1.10.4.2 Rheumatoid Arthritis and Osteoarthritis

Ethnobotanical surveys on traditional medicinal plants for inflammation carried out in India, China, Korea, and Nigeria covered 485 plant species belonging to 100 families, traditionally used in arthritis. Among 100 plant families the ones with anti-inflammatory effects are Malvaceae, Leguminasae, Fabaceae, Euphorbiaceae, Compositae, Araceae, Solanaceae, Liliaceae, Apocynaceae, Lauraceae, and Rubiaceae (Choudhary et al. 2015). Clinical trials with Borage seed oil (*Borago officinalis*), Tripterygium wilfordii Hook F, curcumin (*Curcuma longa*), feverfew (*Tanacetum parthenium*), *Zingiber officinale*, and *Angelica sinensis* resulted in reduction in swelling and tender joint counts, shortened the duration of morning stiffness, and decreased erythrocyte sedimentation rate; and C-reactive protein and rheumatoid factor (Soeken et al. 2003; Chang et al. 1997; Wang et al. 2017b; Daily et al. 2016; Lee et al. 2014).

A meta-analysis of a CHM, Zhengqing Fengtongning (ZQFTN) from 11 studies on RA patients (508 patients received a combination of CHM and methotrexate and 448 patients received methotrexate only) showed that pain relief and morning stiffness in the combination group were significantly better than the methotrexate group alone. However, joint swelling and tender joint count were not different between the combination and methotrexate groups. Taken together, using ZQFTN combined with MTX appears to have better overall effects and lower side effects as compared with methotrexate alone in RA patients (Chen et al. 2015) (Wang et al. 2017b).

A standardized extract of *Boswellia serrata* containing 3-acetyl-11-keto-β-boswellic acid with β-boswellic acid was assessed in 48 patients of osteoarthritis having a minimum pain visual analog scale of >4. This was a randomized double-blind trial followed up for 120 days. Patients were given extract of *Boswellia serrata* b.d. in tablet form (dose 170 mg × 2). The extract significantly reduced joint pain and improved mobility along with decrease in the serum levels of C-reactive protein, a potent inflammatory marker. In addition, radiographic improvements were apparent from reduced osteophytes. Furthermore, the extract was well tolerated and devoid of any severe adverse effects (Majeed et al. 2019).

1.10.5 Cancer

1.10.5.1 Breast Cancer

Ethnobotanical studies/surveys were done for numerous herbal drugs of China, and other Asian countries, having purported anticancer properties. Collectively, 72 plants that belong to 44 families are utilized for cancer treatment out of which most commonly used plants belong to *Compositae* and *Lamiaceae* (Chung et al. 2015; Abu-Darwish and Efferth 2018). Clinical trials were done on breast cancer patients with *Herba Scutellaria barbata* (HSB), Flavopiridol derived from *Dysoxylum binectariferum Hook.f.* (Meliaceae), *Panax ginseng*, *Camellia sinensis*, *Curcuma longa*, Soy-derived phytoestrogens, *Radix astragalus*, *Rhizoma atractylodis macrocephalae*, and *Angelica sinensis*. Findings of these trials showed boosting of the immune system, pain relief, anti-inflammatory effect, alleviation of fatigue, protection against chemotherapy-induced cyto- and gastrointestinal toxicity, and protection against other side effects from chemo- and radiotherapies (Liao et al. 2013; Safarzadeh et al. 2014; Yin et al. 2013). Meta-analysis studies with 33 RCTs included 2098 patients, in which 1066 patients received CHM as an adjunct therapy and 1032 received standard chemotherapy. Among CHMs, *Radix astragalus*, *Rhizoma atractylodis macrocephalae*, and *Angelica sinensis* were most frequently used herbs. Combined therapy (CHM combined with chemotherapy) significantly decreased adverse effects caused by chemotherapy alone, including nausea and vomiting at toxicity grade of III–IV, WBC reduction at toxicity grade of III–IV, and platelet reduction at toxicity grade of I–IV or III–IV (Zhu et al. 2016).

1.10.5.2 Lung Cancer

Lung cancer is the most common malignancy worldwide and a leading cause of cancer-related deaths. Non-Small cell lung cancer (NSCLC) is the most common form of lung cancer, which accounts for approximately 85% of all lung cancer cases (Li et al. 2013a). An ethnopharmacological survey on herbal drugs used for the treatment of lung cancer was conducted in the Middle East, Africa, India, Turkey the Far East, and Europe. In these studies, 72 medicinal plants belonging to 44 families were used for the treatment of lung cancer, however, the most frequently used were decoctions of *Ephedra alata*, *A. dioscoridis*, and *A. palaestinum* (Abu-Darwish and Efferth 2018; Jaradat et al. 2016). Traditionally, phytochemicals such as Vinorelbine, Abraxane and herbal plants like, *Platycodon grandiflorum* (*Campanulaceae*), *Morus alba* (*Moraceae*), *Prunus armeniaca* (*Rosaceae*), *Rhus verniciflua* (*Anacardiaceae*), *Perilla frutescens* (*Labiatae*), *Stemona japonica* (*Stemonaceae*), *Tussilago farfara* (*Compositae*), and *Draba nemorosa* (*Brassicaceae*) have been used to treat lung cancer. These herbs are mainly used in lung cancer to reduce therapy-associated toxicity and cancer-related symptoms and sometimes to directly increase anticancer effects. Numerous types of polyherbal formulations used for lung cancer treatment such as Sheng-mai injection, Gu-jin Granule, Feiji Recipe, Dixiong Decoction, Liangxue Jiedu Houxue Decoction, QingjinRunfei Decoction, and Shenqi-Fuzheng injection increased the survival rate among patients (Yin et al. 2013; Raj Parikh et al. 2014; Safarzadeh et al. 2014).

A meta-analysis of 22 studies was conducted on 1819 participants. The participants included patients with non-small cell carcinoma and radiotherapy pneumonitis (RP) who were (a) administered herbal medicines (*Ophiopogonis radix*, *Adenophorae radix*, *Astragali radix*, and *Angelicae sinensis radix*) during radiotherapy and (b) patients who underwent radiotherapy without herbal medicines. The study observed that the number of patients who developed RP decreased significantly in the herbal medicine plus radiotherapy group as compared with the radiotherapy alone group. In addition, quality of life also significantly increased in the HM (herbal medicine) plus radiotherapy group compared with the radiotherapy alone group. A few studies assessed safety of herbal medicines and latter were found to be safe (Kim et al. 2018).

1.10.5.3 Prostate Cancer

Ethnopharmacological/ethnobotanical information revealed 57 plant species belonging to 30 families are used for the treatment of prostate cancer. For the treatment of benign prostate hyperplasia *Juglans regia*, *Quercus infectoria*, *Sambucus ebulus,* and *Zea mays* were used for the treatment of symptoms (Jaradat et al. 2017). Clinical studies have been done in India, China, Africa, Australia, the USA, and other Western countries with medicinal herbs such as saw palmetto, pomegranate, soy isoflavones, *H. hemerocallidea*, *Camellia sinensis*, *Wedelia chinensis*, *Panax ginseng*, *Allium sativum*, *Ginkgo biloba*, and *Prunus africana* (pygeum). These herbs showed an antiproliferative effect against prostate cancer cells, suppressed androgenic activity and showed potential for reducing the risk of prostate cancer

(Safarzadeh et al. 2014; Abrams 2018; Yin et al. 2013; Gratus et al. 2009; Steenkamp 2003).

Other polyherbal CHM formulations such as Chai-Hu-Jia-Long, Gu-Mu-Li-Tang, Suan-Zao-Ren-Tang, Ban-Xia-Xie-Xin-Tang, and Ba-Wei-Di-Huang-Wan are used for improving the survival rate of metastatic prostate cancer patients. In addition, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang relieved the symptoms of hypogonadism, including insomnia, hot flushes, and erectile dysfunction, but did not change serum testosterone levels. In patients with benign prostatic hyperplasia, Ba-Wei-Di-Huang-Wan improved nocturia or incomplete bladder emptying and also prevented osteoporosis (Liu et al. 2016). A meta-analysis comprising 14 randomized clinical trials and three open-label trials, involving 4280 patients, were analysed for *Serenoa repens* extract (Permixon) for the treatment of symptomatic benign prostatic hyperplasia (BPH). These trials were of different size (22–1100 patients) and duration (21–720 days). In this, Permixontrials for treating men with BPH showed a significant improvement in peak flow rate and reduction in nocturia above placebo (Boyle et al. 2004).

Review of clinical trials with TM indicates a clear deficiency in high quality trials in every disease area dealt here. All trials assessed safety and tolerability of TMs and these were largely established. However, efficacy of TMs alone or as an adjunct to allopathic medicine in majority cases appear to fall short of drawing a satisfactory conclusion due to the lack of large randomized controlled trials.

Regulation of TMs is in its infancy. Adverse events arising from consumption of TMs are attributable to factors including use of wrong species of plants due to incorrect pharmacognosy, adulterated plant materials and contamination with heavy metals, pesticides, and other hazardous substance beyond allowable limits. Worldwide, regulators have applied stringent quality control of TMs to minimize the chance of adverse events caused by the aforementioned factors. However, adverse events related to the use of TMs are far more complex than in the case of mainstream pharmaceuticals. For example drug–drug interaction between TMs and conventional pharmaceuticals is an important safety factor for which the availability of data is scarce. Also, because unlike pharmaceutical drugs TMs do not carry disease cure claims, pharmacovigilance similar to that of the former is unlikely to work for TMs. Indeed, not much literature, if any is available on the pharmacovigilance of TMs.

References

Abrams DI (2018) An integrative approach to prostate cancer. J Altern Complement Med 24 (9-10):872–880

Abu-Darwish MS, Efferth T (2018) Medicinal plants from near east for cancer therapy. Front Pharmacol 9:56

Akhondzadeh S, Noroozian M et al (2003) Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 74(7):863–866

Akhondzadeh S, Shafiee Sabet M et al (2010) A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology 207(4):637–643
Ankrah NA, Nyarko AK et al (2003) Evaluation of efficacy and safety of a herbal medicine used for the treatment of malaria. Phytother Res 17(6):697–701
Anon (2004) New alternative medicine guide launched amidst increasing reports of adverse reactions. Bull World Health Organ 82(8):635–636
Asokan M, Lone IN et al (2013) Evident stabilization of the clinical profile in HIV/AIDS as evaluated in an open label clinical trial using a polyherbal formulation. Indian J Med Res 137 (6):1128–1144
Bae N, Ahn T et al (2011) The neuroprotective effect of modified Yeoldahanso-tang via autophagy enhancement in models of Parkinson's disease. J Ethnopharmacol 134(2):313–322
Baharvand-Ahmadi B, Bahmani M et al (2016) An ethnobotanical study of medicinal plants administered for the treatment of hypertension. J Renal Inj Prev 5(3):123–128
Bega D, Zadikoff C (2014) Complementary & alternative management of Parkinson's disease: an evidence-based review of eastern influenced practices. J Mov Disord 7(2):57–66
Benson S, Downey LA et al (2014) An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood. Phytother Res 28(4):551–559
Bhatt A (2016) Phytopharmaceuticals: a new drug class regulated in India. Perspect Clin Res 7 (2):59–61
Boyle P, Robertson C et al (2004) Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. BJU Int 93(6):751–756
Burton A et al (2015) Building WHO's global strategy for traditional medicine*. Eur J Integr Med 7:13
Calabrese C, Berman SH et al (2000) A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res 14(5):333–338
Challand S, Willcox M (2009) A clinical trial of the traditional medicine Vernonia amygdalina in the treatment of uncomplicated malaria. J Altern Complement Med 15(11):1231–1237
Chang DM, Chang WY et al (1997) The effects of traditional antirheumatic herbal medicines on immune response cells. J Rheumatol 24(3):436–441
Chen XM, Huang RY et al (2015) Systemic review and meta-analysis of the clinical efficacy and adverse effects of zhengqing fengtongning combined with methotrexate in rheumatoid arthritis. Evid Based Complement Alternat Med 2015:910376
Cho Y, Lee S et al (2018) The efficacy and safety of herbal medicine BHH10 in postmenopausal women with osteoporosis: study protocol for a phase II, multicenter, randomized, double-blinded, placebo-controlled clinical trial. Trials 19(1):482
Choudhary M, Kumar V et al (2015) Medicinal plants with potential anti-arthritic activity. J Intercult Ethnopharmacol 4(2):147–179
Choudhury H, Pandey M et al (2018) An update on natural compounds in the remedy of diabetes mellitus: a systematic review. J Tradit Complement Med 8(3):361–376
Chrysant SG, Chrysant GS (2017) Herbs used for the treatment of hypertension and their mechanism of action. Curr Hypertens Rep 19(9):77
Chung VC, Wu X et al (2015) Effectiveness of Chinese herbal medicine for cancer palliative care: overview of systematic reviews with meta-analyses. Sci Rep 5:18111
Chung VC, Wu X et al (2016) Chinese herbal medicine and salmeterol and fluticasone propionate for chronic obstructive pulmonary disease: systematic review and network meta-analysis. Medicine (Baltimore) 95(20):e3702
Cordell GA (2011) Sustainable medicines and global health care. Planta Med 77(11):1129–1138
Cordell GA, Colvard MD (2012) Natural products and traditional medicine: turning on a paradigm. J Nat Prod 75(3):514–525
Cox DG, Oh J et al (2014) The utility of metabolomics in natural product and biomarker characterization. Biochim Biophys Acta 1840(12):3460–3474

Daily JW, Yang M et al (2016) Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. J Med Food 19(8):717–729

Davids D, Gibson D et al (2016) Ethnobotanical survey of medicinal plants used to manage high blood pressure and type 2 diabetes mellitus in Bitterfontein, Western Cape Province, South Africa. J Ethnopharmacol 194:755–766

Deng WM, Zhang P et al (2012) Five-year follow-up study of a kidney-tonifying herbal Fufang for prevention of postmenopausal osteoporosis and fragility fractures. J Bone Miner Metab 30 (5):517–524

Dos Santos-Neto LL, de Vilhena Toledo MA et al (2006) The use of herbal medicine in Alzheimer's disease-a systematic review. Evid Based Complement Alternat Med 3(4):441–445

Eckert GP (2010) Traditional used plants against cognitive decline and Alzheimer disease. Front Pharmacol 1:138

Ernst E, Cassileth BR (1998) The prevalence of complementary/alternative medicine in cancer: a systematic review. Cancer 83(4):777–782

Farooqui AA, Farooqui T et al (2018) Ayurvedic medicine for the treatment of dementia: mechanistic aspects. Evid Based Complement Alternat Med 2018:2481076

Franz CM, Huch M et al (2011) Enterococci as probiotics and their implications in food safety. Int J Food Microbiol 151(2):125–140

Fritts M, Crawford CC et al (2008) Traditional Indian medicine and homeopathy for HIV/AIDS: a review of the literature. AIDS Res Ther 5:25

Gahlaut A, Shirolkar A et al (2013) beta-sitosterol in different parts of Saraca asoca and herbal drug ashokarista: quali-quantitative analysis by liquid chromatography-mass spectrometry. J Adv Pharm Technol Res 4(3):146–150

Gail H, Tarryn B et al (2015) An ethnobotanical survey of medicinal plants used by traditional health practitioners to manage HIV and its related opportunistic infections in Mpoza, Eastern Cape Province, South Africa. J Ethnopharmacol 171:109–115

Garcia M, Monzote L et al (2010) Screening of medicinal plants against Leishmania amazonensis. Pharm Biol 48(9):1053–1058

Gauthier S, Schlaefke S (2014) Efficacy and tolerability of Ginkgo biloba extract EGb 761(R) in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. Clin Interv Aging 9:2065–2077

Glassbrook N, Ryals J (2001) A systematic approach to biochemical profiling. Curr Opin Plant Biol 4(3):186–190

Gouveia BG, Rijo P et al (2015) Good manufacturing practices for medicinal products for human use. J Pharm Bioall Sci 7(2):87–96

Govindaraghavan S (2008) Quality assurance of herbal raw materials in supply chain: challenges and opportunities. J Diet Suppl 5(2):176–212

Gratus C, Damery S et al (2009) The use of herbal medicines by people with cancer in the UK: a systematic review of the literature. QJM 102(12):831–842

Guanti G, Mollica G et al (1976) rDNA and acrocentric chromosomes in man. I. rDNA levels in a subject carrier of a 8p/13p balanced translocation and in his unbalanced son. Hum Genet 33 (2):103–107

Guo R, Pittler MH et al (2006) Herbal medicines for the treatment of COPD: a systematic review. Eur Respir J 28(2):330–338

Haji Faraji M, Haji Tarkhani A (1999) The effect of sour tea (Hibiscus sabdariffa) on essential hypertension. J Ethnopharmacol 65(3):231–236

Harwansh RK, Mukherjee K et al (2014) Cytochrome P450 inhibitory potential and RP-HPLC standardization of trikatu--a Rasayana from Indian Ayurveda. J Ethnopharmacol 153 (3):674–681

Harwansh RK, Mukherjee PK et al (2015) Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress. Life Sci 141:202–211

Hong M, Hong C et al (2018) Effects of the Chinese herb formula Yufeining on stable chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled trial. Medicine (Baltimore) 97(39):e12461

Hwang DS, Kim HG et al (2011) Dangguijakyak-san, a medicinal herbal formula, protects dopaminergic neurons from 6-hydroxydopamine-induced neurotoxicity. J Ethnopharmacol 133(2):934–939

Jaradat NA, Al-Ramahi R et al (2016) Ethnopharmacological survey of herbal remedies used for treatment of various types of cancer and their methods of preparations in the West Bank-Palestine. BMC Complement Altern Med 16:93

Jaradat NA, Zaid AN et al (2017) Ethnopharmacological survey of medicinal plants practiced by traditional healers and herbalists for treatment of some urological diseases in the West Bank/Palestine. BMC Complement Altern Med 17(1):255

Katoch D, Sharma JS et al (2017) Government policies and initiatives for development of Ayurveda. J Ethnopharmacol 197:25–31

Kim KI, Jun JH et al (2018) Oral administration of herbal medicines for radiation pneumonitis in lung cancer patients: a systematic review and meta-analysis. PLoS One 13(5):e0198015

Kisangau DP, Lyaruu HV et al (2007) Use of traditional medicines in the management of HIV/AIDS opportunistic infections in Tanzania: a case in the Bukoba rural district. J Ethnobiol Ethnomed 3:29

Lamorde M, Tabuti JR et al (2010) Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda. J Ethnopharmacol 130(1):43–53

Langlois-Klassen D, Kipp W et al (2007) Use of traditional herbal medicine by AIDS patients in Kabarole District, western Uganda. Am J Trop Med Hyg 77(4):757–763

Lee WY, Chen HY et al (2014) Treatment of rheumatoid arthritis with traditional chinese medicine. Biomed Res Int 2014:528018

Lee KM, Jeon JY et al (2017) Application of metabolomics to quality control of natural product derived medicines. Biomol Ther (Seoul) 25(6):559–568

Li SG, Chen HY et al (2013a) The efficacy of Chinese herbal medicine as an adjunctive therapy for advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 8(2):e57604

Li XZ, Zhang SN et al (2013b) Recent advances in herbal medicines treating Parkinson's disease. Fitoterapia 84:273–285

Liao GS, Apaya MK et al (2013) Herbal medicine and acupuncture for breast cancer palliative care and adjuvant therapy. Evid Based Complement Alternat Med 2013:437948

Liu JP, Manheimer E et al (2005) Herbal medicines for treating HIV infection and AIDS. Cochrane Database Syst Rev 3:CD003937

Liu Q, Garner P et al (2008) Drugs and herbs given to prevent hepatotoxicity of tuberculosis therapy: systematic review of ingredients and evaluation studies. BMC Public Health 8:365

Liu JM, Lin PH et al (2016) Complementary traditional Chinese medicine therapy improves survival in patients with metastatic prostate cancer. Medicine (Baltimore) 95(31):e4475

Majeed M, Majeed S et al (2019) A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel Boswellia serrata extract in the management of osteoarthritis of the knee. Phytother Res 33(5):1457–1468

Malik K, Ahmad M et al (2018) Ethnobotany of anti-hypertensive plants used in Northern Pakistan. Front Pharmacol 9:789

Mashour NH, Lin GI et al (1998) Herbal medicine for the treatment of cardiovascular disease: clinical considerations. Arch Intern Med 158(20):2225–2234

Maulik SK, Wilson V et al (2016) Clinical efficacy of water extract of stem bark of Terminalia arjuna (Roxb. ex DC.) Wight & Arn. in patients of chronic heart failure: a double-blind, randomized controlled trial. Phytomedicine 23(11):1211–1219

Meeta A, Raut A et al (2019) A clinical study of a standardized extract of leaves of Dalbergia sissoo (Roxb ex DC) in Postmenopausal Osteoporosis. J Midlife Health 10(1):37–42

Mills E, Cooper C et al (2005) African herbal medicines in the treatment of HIV: hypoxis and sutherlandia. An overview of evidence and pharmacology. Nutr J 4:19
Mohammed A, Kumar D et al (2015) Antidiabetic potential of some less commonly used plants in traditional medicinal systems of India and Nigeria. J Intercult Ethnopharmacol 4(1):78–85
Monera TG, Maponga CC (2012) Prevalence and patterns of Moringa oleifera use among HIV positive patients in Zimbabwe: a cross-sectional survey. J Public Health Afr 3(1):e6
Mueller MS, Runyambo N et al (2004) Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria. Trans R Soc Trop Med Hyg 98(5):318–321
Mugomeri E, Chatanga P et al (2016) Medicinal herbs used by hiv-positive people in lesotho. Afr J Tradit Complement Altern Med 13(4):123–131
Mukherjee PK, Wahile A (2006) Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. J Ethnopharmacol 103(1):25–35
Mukherjee PK, Kumar V et al (2007a) Screening of Indian medicinal plants for acetylcholinesterase inhibitory activity. Phytother Res 21(12):1142–1145
Mukherjee PK, Rai S et al (2007b) Plants of Indian origin in drug discovery. Expert Opin Drug Discovery 2(5):633–657
Mukherjee PK, Sahoo AK et al (2009) Lead finding from medicinal plants with hepatoprotective potentials. Expert Opin Drug Discovery 4(5):545–576
Mukherjee PK, Venkatesh P et al (2010) Ethnopharmacology and integrative medicine - let the history tell the future. J Ayurveda Integr Med 1(2):100–109
Mukherjee PK, Nema NK et al (2012) Changing scenario for promotion and development of Ayurveda--way forward. J Ethnopharmacol 143(2):424–434
Mukherjee PK, Harwansh RK et al (2017) Development of ayurveda - tradition to trend. J Ethnopharmacol 197:10–24
Namsa ND, Mandal M et al (2011) Anti-malarial herbal remedies of northeast India, Assam: an ethnobotanical survey. J Ethnopharmacol 133(2):565–572
Narayana DA, Katiyar C (2013) Draft amendment to drugs and cosmetics rules to license science based botanicals, phytopharmaceuticals as drugs in India. J Ayurveda Integr Med 4(4):245–246
Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70(3):461–477
Nityanand S, Srivastava JS et al (1989) Clinical trials with gugulipid. A new hypolipidaemic agent. J Assoc Physicians India 37(5):323–328
Noteborn HP, Lommen A et al (2000) Chemical fingerprinting for the evaluation of unintended secondary metabolic changes in transgenic food crops. J Biotechnol 77(1):103–114
Ocvirk S, Kistler M et al (2013) Traditional medicinal plants used for the treatment of diabetes in rural and urban areas of Dhaka, Bangladesh--an ethnobotanical survey. J Ethnobiol Ethnomed 9:43
Ogbole OO, Ajaiyeoba EO (2009) Traditional management of tuberculosis in Ogun State of Nigeria: the practice and ethnobotanical survey. Afr J Tradit Complement Altern Med 7 (1):79–84
Panda SK, Luyten W (2018) Antiparasitic activity in Asteraceae with special attention to ethnobotanical use by the tribes of Odisha, India. Parasite 25:10
Parvizi MM, Handjani F et al (2017) Efficacy of cryotherapy plus topical Juniperus excelsa M. Bieb cream versus cryotherapy plus placebo in the treatment of Old World cutaneous leishmaniasis: a triple-blind randomized controlled clinical trial. PLoS Negl Trop Dis 11(10):e0005957
Patwardhan B (2011) Ayurveda GCP guidelines: need for freedom from RCT ascendancy in favor of whole system approach. J Ayurveda Integr Med 2(1):1–4
Patwardhan B (2014) Envisioning AYUSH: historic opportunity for innovation and revitalization. J Ayurveda Integr Med 5(2):67–70
Patwardhan B, Mashelkar RA (2009) Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? Drug Discov Today 14(15-16):804–811

Ram A, Balachandar S et al (2011) Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): current status and future perspectives. Fitoterapia 82(2):141–151
Safarzadeh E, Sandoghchian Shotorbani S et al (2014) Herbal medicine as inducers of apoptosis in cancer treatment. Adv Pharm Bull 4(Suppl 1):421–427
Samal J (2015) Role of AYUSH workforce, therapeutics, and principles in health care delivery with special reference to National Rural Health Mission. Ayu 36(1):5–8
Seck SM, Doupa D et al (2017) Clinical efficacy of African traditional medicines in hypertension: a randomized controlled trial with Combretum micranthum and Hibiscus sabdariffa. J Hum Hypertens 32(1):75–81
Sen S, Chakraborty R (2017) Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: importance, challenges and future. J Tradit Complement Med 7 (2):234–244
Sharifi-Rad J, Salehi B et al (2017) Medicinal plants used in the treatment of tuberculosis - ethnobotanical and ethnopharmacological approaches. Biotechnol Adv
Sharma U, Velpandian T et al (2009) Evaluation of anti-leishmanial activity of selected Indian plants known to have antimicrobial properties. Parasitol Res 105(5):1287–1293
Shaw D, Graeme L et al (2012) Pharmacovigilance of herbal medicine. J Ethnopharmacol 140 (3):513–518
Singh RB, Niaz MA et al (1994) Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia. Cardiovasc Drugs Ther 8 (4):659–664
Soeken KL, Miller SA et al (2003) Herbal medicines for the treatment of rheumatoid arthritis: a systematic review. Rheumatology (Oxford) 42(5):652–659
Song JX, Sze SC et al (2012) Anti-Parkinsonian drug discovery from herbal medicines: what have we got from neurotoxic models? J Ethnopharmacol 139(3):698–711
Soosaraei M, Fakhar M et al (2017) Medicinal plants with promising antileishmanial activity in Iran: a systematic review and meta-analysis. Ann Med Surg (Lond) 21:63–80
Srinivasan R, Sugumar VR (2017) Spread of Traditional Medicines in India: results of national sample survey organization's perception survey on use of AYUSH. J Evid Based Complement Alternat Med 22(2):194–204
Srivastava A, Gope R et al (2016) Are village health sanitation and nutrition committees fulfilling their roles for decentralised health planning and action? A mixed methods study from rural eastern India. BMC Public Health 16:59
Steenkamp V (2003) Phytomedicines for the prostate. Fitoterapia 74(6):545–552
Stough C, Lloyd J et al (2001) The chronic effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy human subjects. Psychopharmacology 156(4):481–484
Stough C, Downey LA et al (2008) Examining the nootropic effects of a special extract of Bacopa monniera on human cognitive functioning: 90 day double-blind placebo-controlled randomized trial. Phytother Res 22(12):1629–1634
Szapary PO, Wolfe ML et al (2003) Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. JAMA 290(6):765–772
Tabassum N, Ahmad F (2011) Role of natural herbs in the treatment of hypertension. Pharmacogn Rev 5(9):30–40
Tabuti JR (2008) Herbal medicines used in the treatment of malaria in Budiope county, Uganda. J Ethnopharmacol 116(1):33–42
Tewari D, Stankiewicz AM et al (2018) Ethnopharmacological approaches for dementia therapy and significance of natural products and herbal drugs. Front Aging Neurosci 10:3
Tian J, Shi J et al (2010) Herbal therapy: a new pathway for the treatment of Alzheimer's disease. Alzheimers Res Ther 2(5):30
Ubale S (2011) Twelfth international congress of ethnopharmacology, kolkata (India). J Ayurveda Integr Med 2(3):160
Ulrich-Merzenich G, Zeitler H et al (2007) Application of the "-Omic-" technologies in phytomedicine. Phytomedicine 14(1):70–82

Walker AF, Marakis G et al (2006) Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial. Br J Gen Pract 56(527):437–443
Wang J, Xiong X (2012) Outcome measures of chinese herbal medicine for hypertension: an overview of systematic reviews. Evid Based Complement Alternat Med 2012:697237
Wang X, Liang XB et al (2008) Therapeutic strategies for Parkinson's disease: the ancient meets the future--traditional Chinese herbal medicine, electroacupuncture, gene therapy and stem cells. Neurochem Res 33(10):1956–1963
Wang Y, Xie CL et al (2012) Chinese herbal medicine paratherapy for Parkinson's disease: a meta-analysis of 19 randomized controlled trials. Evid Based Complement Alternat Med 2012:534861
Wang ZQ, Li JL et al (2013) Chinese herbal medicine for osteoporosis: a systematic review of randomized controlled trails. Evid Based Complement Alternat Med 2013:356260
Wang J, Xiong X et al (2014) Chinese patent medicine tongxinluo capsule for hypertension: a systematic review of randomised controlled trials. Evid Based Complement Alternat Med 2014:187979
Wang M, Guan X et al (2015a) Chinese herbal medicine as adjuvant treatment to chemotherapy for multidrug-resistant tuberculosis (MDR-TB): a systematic review of randomised clinical trials. Tuberculosis (Edinb) 95(4):364–372
Wang P, Xiong X et al (2015b) Efficacy and safety of a traditional Chinese herbal formula Xuefu Zhuyu decoction for hypertension: a systematic review and meta-analysis. Medicine (Baltimore) 94(42):e1850
Wang M, Chen L et al (2017a) Metabolomics highlights pharmacological bioactivity and biochemical mechanism of traditional Chinese medicine. Chem Biol Interact 273:133–141
Wang X, Zu Y et al (2017b) Treatment of rheumatoid arthritis with combination of methotrexate and Tripterygium wilfordii: a meta-analysis. Life Sci 171:45–50
Wetzel MS, Kaptchuk TJ et al (2003) Complementary and alternative medical therapies: implications for medical education. Ann Intern Med 138(3):191–196
Willcox M (2011) Improved traditional phytomedicines in current use for the clinical treatment of malaria. Planta Med 77(6):662–671
Willcox ML, Bodeker G (2004) Traditional herbal medicines for malaria. BMJ 329 (7475):1156–1159
Xiong X, Li X et al (2015a) Chinese herbal medicine for resistant hypertension: a systematic review. BMJ Open 5(1):e005355
Xiong X, Wang P et al (2015b) Meta-analysis of the effectiveness of traditional Chinese herbal formula Zhen Wu Decoction for the treatment of hypertension. BMJ Open 5(12):e007291
Yang G, Wang Y et al (2013) Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS One 8(9):e74916
Yin SY, Wei WC et al (2013) Therapeutic applications of herbal medicines for cancer patients. Evid Based Complement Alternat Med 2013:302426
Zhang Y, Lin C et al (2015) Cognitive improvement during treatment for mild Alzheimer's disease with a Chinese herbal formula: a randomized controlled trial. PLoS One 10(6):e0130353
Zhu L, Li L et al (2016) Chinese herbal medicine as an adjunctive therapy for breast cancer: a systematic review and meta-analysis. Evid Based Complement Alternat Med 2016:9469276

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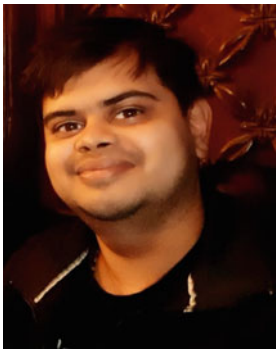

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