



Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward?

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Drug discovery strategies based on natural products and traditional medicines are re-emerging as attractive options. We suggest that drug discovery and development need not always be confined to new molecular entities. Rationally designed, carefully standardized, synergistic traditional herbal formulations and botanical drug products with robust scientific evidence can also be alternatives. A reverse pharmacology approach, inspired by traditional medicine and Ayurveda, can offer a smart strategy for new drug candidates to facilitate discovery process and also for the development of rational synergistic botanical formulations.

Drug discovery scenario

Drug discovery is no longer a game of chance or just limited to the availability of new technology. Better understanding of various approaches and key learning from the past with the appropriate strategy for the future is essential to make a significant difference [1].

During the past few years a large number of approved new drug applications have originated from the biotechnology industry and analysts expect a continuation of pharmaceutical-biotechnology alliances to help expand pipelines [2]. Similarly, natural products have contributed nearly half of all small molecules approved in this decade. It has been suggested that the current drug discovery approach of finding 'new entity drugs', if shifted to 'combining existing agents' may be helpful. Therefore natural product drug discovery based on ethnopharmacology and traditional medicines may also be considered as attractive strategic options [3].

Seeking innovative paradigms

The age of the blockbuster drugs seem to have become a distant dream [4]. For instance, in 2008 only 21 new molecular entities were approved by US FDA and so few are anticipated to become blockbusters. The usual distinctions drawn between breakthrough and me-too drugs may not be very relevant today [5]. Despite very stringent and demanding regulatory processes, postapproval or postmarket-

ing withdrawal of new drugs continues. It is argued that the safety of new agents cannot be known with certainty until a drug has been in the market for many years [6]. This has led to a re-examination of the process of drug regulation and increased concern that the current process is inadequate for the protection of public health [7]. The United States Food and Drug Administration (US FDA)'s Drug Watch and Drug Advisory Committee briefings on the new anticoagulant Ximelagatran from AstraZeneca, the Cox II inhibitor, Vioxx from Merck and the case of the cancer vaccine Provenge approval of Dendreon are typically indicative [8,9].

Societal expectations about drug safety and efficacy are rising while R&D productivity in the pharmaceutical industry is falling. The Critical Path Initiative of FDA was intended to modernize drug development by incorporating recent scientific advances, shows a proactive policy approach to enhance innovation opportunities in a public/private partnership model [10]. We suggest that traditional medicine may offer better routes to the discovery, development and delivery of new drugs with enhanced performance in terms of cost, safety and efficacy. To this end, we believe that the basic principles, experiential wisdom, holistic approach and systematic database of Ayurveda (Box 1 and Fig. 1) may offer useful bioprospecting tools and an efficient discovery engine [11].

Rediscovering history

The history of medicine reveals that most of the early discoveries resulted from either serendipity or folklore approaches, often involving poisonous sources and not really from traditional

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BOX 1

Ayurveda – the knowledge of life

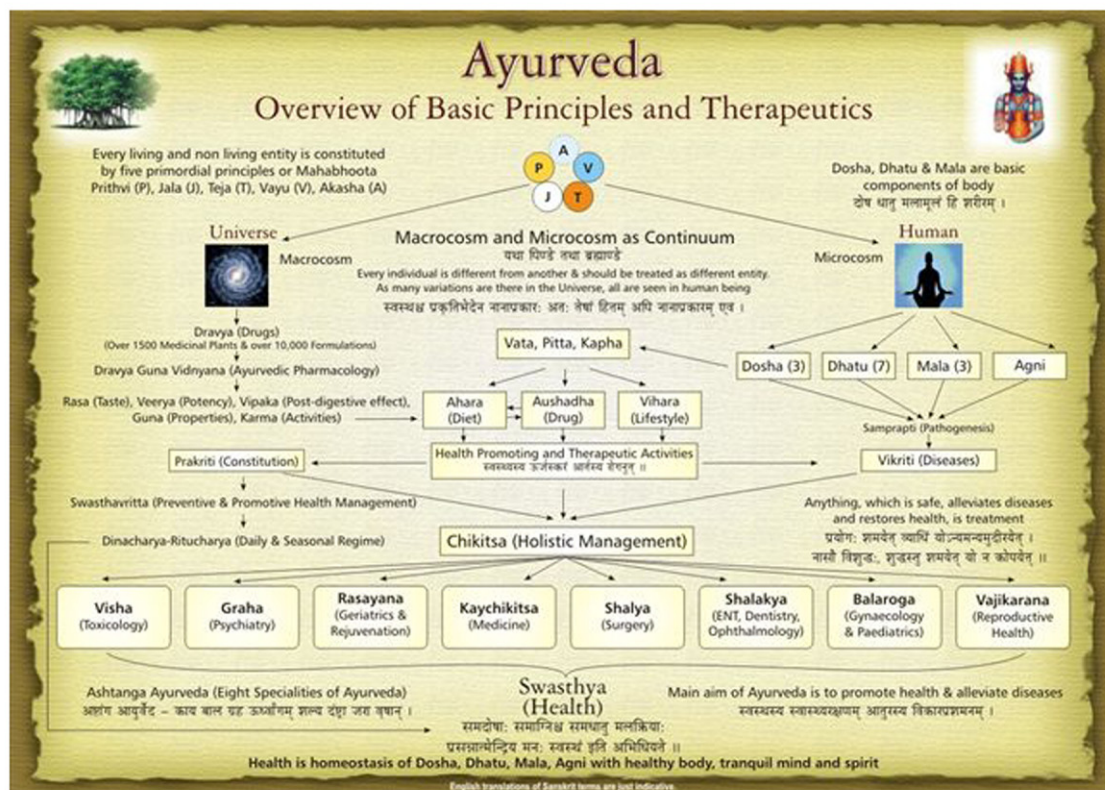
- Ayurveda is one of the oldest still extant, health traditions in the world. Originating in India Ayurveda is based on *Sankhya* philosophy, which means 'rational enquiry into the nature of the truth'. Sanskrit meaning of *Ayu* is life and *Veda* is knowledge or science.
- *Charak Samhita* (1000 BC) and *Sushrut Samhita* (100 AD) are the main classics. Ayurveda materia medica give detailed descriptions of over 1500 herbs and 10,000 formulations. *Madhav Nidan* (800 AD) a diagnostic classic provides over 5000 signs and symptoms.
- Life in Ayurveda is conceived as the union of body, senses, mind and soul. The concept of *Prakriti* or human constitution plays a central role in understanding health and disease in Ayurveda, which is similar to modern pharmacogenomics.
- With over 400,000 registered Ayurveda practitioners, Government of India Department of AYUSH (Ayurveda, Yoga, Unani, Siddha and Homeopathy) has responsibility to regulate quality, education and practice.

medicines. The mass screening of plants in the search for new leads or drugs is vastly expensive and inefficient. Yet, traditional knowledge based bioprospecting offered better leads for the treatment of AIDS and cancer. It is estimated that over 100 new natural product-based leads are in clinical development [12]. About 60%

of anticancer and 75% of anti-infective drugs approved from 1981 to 2002 could be traced to natural origins [13]. A multidisciplinary approach combining natural product diversity with total, combinatorial synthetic and biosynthesis may provide an apt solution to the current innovation quandary [14].

Combinatorial chemistry approaches based on natural products from traditional medicine are being used to create screening libraries that closely resemble drug-like compounds [15]. Since most of these compounds are part of routinely used traditional medicines, their tolerance and safety are relatively better known than other synthetic chemical entities entering first-in-human studies [16]. For instance, Piramal Life Sciences Ltd., Mumbai has a unique and diverse library of over 5600 natural product extracts from Indian medicinal plants inherited from the Hoechst Research Center. Their first lead, NPB-001-05, has demonstrated efficacy in various cellular and animal models, and is currently undergoing human clinical trials for chronic myeloid leukemia. The second lead, NPS31807, is being developed for the treatment of chronic inflammatory disorders including rheumatoid arthritis. The third lead, NPH30907, has been developed as a topical formulation with good antidermatophyte activity against a panel of microorganisms [17]. Thus, similar to microbiological sources, traditional medicine-based bioprospecting may offer promising new leads with compounds generally recognized as safe [18].

A large number of promising lead molecules that have come out of Ayurveda include *Rauwolfia* alkaloids for hypertension, Psoralens



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FIGURE 1

Ayurveda: overview of basic principles and therapeutics.

for vitiligo, *Holarrhena* alkaloids for amoebiasis, guggulsterons as hypolipidemic agents, *Mucuna pruriens* for Parkinson's disease, piperidines as bioavailability enhancers, baccosides for mental retention, picosides for hepatic protection, phyllanthins as antivirals, curcumines for inflammation, withanolides and many other steroidal lactones and glycosides as immunomodulators [19].

There is growing evidence to show that old molecules are finding new applications through a better understanding of traditional knowledge and clinical observations. For instance, forskolin has been revisited as adenylate cyclase activator, to treat conditions including obesity and atherosclerosis [20]. Similarly, antimicrobial berberine alkaloids are being investigated in dyslipidemia with a mechanism different from statins [21].

Reverse pharmacology

The traditional knowledge-inspired reverse pharmacology described here relates to reversing the routine 'laboratory-to-clinic' progress to 'clinics-to-laboratories' [22]. Earlier, the term reverse pharmacology has been used in relation to ligand-independent orphan functions that can modulate well-defined drug targets, but this review does not cover such aspects [23]. Reverse pharmacology is defined here as a rigorous scientific approach of integrating documented clinical experiences and experiential observations into leads by transdisciplinary exploratory studies and further developing these into drug candidates or formulations through robust preclinical and clinical research [24]. In this process 'safety' remains the most important starting point and the efficacy becomes a matter of validation. The novelty of this approach is the combination of living traditional knowledge such as Ayurveda and the application of modern technology and processes to provide better and safer leads.

Sir Ram Nath Chopra and Gananath Sen laid the foundation of reverse pharmacology of medicinal plants by pursuing the clinically documented effects of Ayurvedic drugs [25]. *Rauwolfia serpentina* Benth, was a major discovery via this approach. Sen and Bose were able to convincingly demonstrate the antihypertensive and tranquillizing effects of the plant and also observed unique side effects such as depression, extra pyramidal syndromes, gynecomastia among others [26]. This effort led to a watershed for new antidepressants, anti-Parkinson's drugs and prolactin-reducing drugs [27]. Reserpine is an example of an antihypertensive alkaloid from *Rauwolfia* that became available from such an approach.

Some promising work was undertaken almost two to three decades ago through a joint drug research program between the Indian Council of Medical Research (ICMR) and the Council for Scientific and Industrial Research (CSIR) of the Government of India. The cholesterol-lowering drug, Guggulipid, was developed from *Commiphora mukul*, taking the lead from Ayurveda [28]. The Drug Controller General of India (DCGI) approved this drug for marketing in 1986. Guggulipid is being manufactured and marketed by Cipla Pharmaceuticals Limited, but the limited availability of authentic raw material has remained a limiting factor for its widespread use. A memory enhancer developed from *Bacopa monnieri* by the Central Drug Research Institute, Lucknow is also licensed and marketed. Regrettably, the great potential of such approaches has not been fully explored to create globally competitive products.

In an attempt to pull industry and academia together to explore the potential of herbal drug development, CSIR, under the national network project known as New Millennium Indian Technology Leadership Initiative (NMITLI), has instigated drug development projects on psoriasis, osteoarthritis, hepatitis and diabetes [29]. To this end, the ICMR has recently established an Advanced Center of Reverse Pharmacology with initial focus on malaria, sarcopenia and cognitive decline. We present here a few case studies where a reverse pharmacology approach has been used to expedite the drug development process.

Psoriasis

Psoriasis is one of the most common dermatological diseases, affecting approximately 2% of the world population with no preventive or curative therapy. Under the NMITLI project, Lupin Limited in India undertook the development of a single plant-based oral formulation adopting a reverse pharmacology approach [30]. The botanical drug product (*Desoris*) is an extract of a single plant that effectively modulates cellular function, leading to an improvement in psoriatic lesions [31]. Extensive studies led to the filing of an Investigational New Drug (IND) application in India. This product has been developed to conform to FDA guidelines for botanical drug products and DCGI norms on new drug development. Currently, this product is undergoing Phase 3 clinical trials across different centers in India.

Vaccine adjuvant

Despite centuries of vaccine use, still alum salts remain universal vaccine adjuvants licensed for human use. They have limitations, however, in engaging cellular immunity. Various immunostimulants from natural and synthetic origin are being studied either to replace or complement alum salts in vaccine formulations [32]. A project to develop herbal vaccine adjuvants using a reverse pharmacology approach based on Ayurveda and other studies [33,34] has been supported by the Department of Science and Technology (DST) of India and was undertaken by the Interdisciplinary School of Health Sciences, University of Pune with the Serum Institute of India as an industrial partner. The project used flow cytometry to monitor the effects of fractions on antigen-specific protective immunity and test materials were screened using *in vivo* potency assays for pertussis or diphtheria. These models are routinely used in potency testing of vaccines [35,36]. Within three years, this project identified several semi-pure leads with considerable efficacy with respect to polysaccharide, toxoid and recombinant groups of vaccines. Further, these leads were found to modulate T-helper cell immunity, which is crucial for efficient cellular and humoral immunity. A detailed safety profile of one of the leads has been established, which is found to be over 20 times more potent than its effective preclinical immunomodulatory dose.

Traditional herbal formulations

We suggest that drug discovery need not be always confined to the discovery of a single molecule. Many analysts believe that the current 'one drug fits all' approach may be unsustainable in the future. The growing interest in polypill concept is indicative of the need to collectively address multiple targets, risk factors or symptoms [37]. In the management of polygenic syndromes and conditions there is renewed interest in multi-ingredient

synergistic formulations [38]. We suggest that rationally designed polyherbal formulations also could be explored as an option for multitarget therapeutic and prophylactic applications. Both TCM and Ayurveda, over thousands of years have developed various practical theories to create polyherbal formulations in which multiple agents contained in one formula act synergistically [39].

Development of standardized, synergistic, safe and effective traditional herbal formulations with robust scientific evidence can also offer faster and more economical alternatives. For instance, Ayurvedic texts include thousands of single or polyherbal formulations [40]. These have been rationally designed and have been in therapeutic use for many years. Sufficient pharmacoepidemiological evidence, based on actual clinical use, can be generated to support their safety and efficacy [41]. Systematic data mining of the existing formulations' huge database can certainly help the drug discovery processes to identify safe candidates and synergistic formulations.

The FDA and a few other agencies have come up with practical guidelines for botanical 'drug' development [42]. A botanical drug product often has unique features and may include complex mixtures with as yet unknown active ingredients. Some botanical drugs, including cascara, psyllium and senna, are included in the over-the-counter drug review. No botanical products are, however, currently approved or marketed as prescription drugs. The FDA recognizes that prior human experience with botanical products may be documented in many different forms and sources, some of which may not meet the quality standards of modern scientific testing. The FDA, maintains, however, the same standards for safety and efficacy for marketing approval whether it is a botanical-sourced product or a purified chemical. The Botanical Guidance simply recommends the use of different types of data for preliminary safety consideration. It also considers large quantities of mostly anecdotal human data in place of well-controlled animal studies and human trials in an IND [43]. In such a situation, traditional medicine data remains very important.

Traditional herbal formulations could follow such regulatory guidance to create scientific evidence base with robust chemistry, manufacturing and controls. Department of Ayurveda, Yoga, Unani, Siddha, Homeopathy (AYUSH) in India has recently established a Research Center at the University of Mississippi, Oxford, MS, USA to facilitate scientific investigations on Indian herbal drugs. Such efforts should help improve quality assurance, enhancing the chance of regulatory approvals and improving the acceptance of botanical drug products and formulations.

Thus, if safe and effective herbal formulations are developed in accordance with stringent regulatory guidelines on a par with any modern drug, we hope that the conventional skepticism against herbals may slowly wane. Issues related to the appropriateness of conventional biomedical and clinical models for evaluating efficacy of traditional medicine remain, however, very crucial. A holistic approach based on systems biology seems much more suited to study therapeutic efficacy and pharmacodynamics of traditional medicine-based drug development [44]. It can also be argued that instead of randomized controlled trials, strategies of pragmatic clinical trials may be better suited for traditional medicine-inspired reverse pharmacology approaches [45]. We pre-

sent here two case studies where herbal formulations were successfully developed using such strategies.

NMITLI scheme

The osteoarthritis herbal drug development project under the NMITLI scheme involved a network of 16 national research institutions, modern medicine hospitals and pharmaceutical industries from India (Fig. 2). Following literature search [46] and several rounds of national level consultations with Ayurvedic physicians and scholars, judiciously short-listed botanical drugs entered a parallel track of animal pharmacology and open label observational studies by clinicians. The project used a traditional knowledge-guided platform where the base formulation was optimized with additional ingredients to obtain desired therapeutic activities. All the formulations were manufactured under Good Manufacturing Practices in accordance using FDA guidance to Industry for botanical drugs. The preclinical evaluation was designed on the basis of a systems approach, wherein the assay battery involved targets relevant to inflammation, pain, immunomodulation and chondroprotection in human explant models of OA cartilage damage [47]. This led to the design a few variants of synergistic polyherbal formulations that were found to be safe and devoid of any genotoxicity or mutagenic activity. The short-listed formulations entered a series of randomized clinical trials together with known drugs, glucosamine and celecoxib, for comparison. Finally the best formulation was selected that led to one Indian and one Patent Cooperation Treaty (PCT) applications. A dossier of necessary data required for possible regulatory submissions was also prepared [48,49]. Thus, this project was completed in five years with an expenditure of about 2 million US dollars. Currently, CSIR is in the process of identifying a suitable industrial partner for further development, optimization, manufacturing, registration and marketing.

Tanga project

In Tanzania, The Tanga AIDS Working Group (TAWG) has used indigenous knowledge (IK) in an attempt to alleviate suffering from HIV/AIDS. The group has treated over 4000 AIDS patients with herbs prescribed by local healers. The impact has been most significant in reducing opportunistic diseases accompanying HIV infection. The Tanga regional hospital, a modern medicine facility, has been involved in testing patients for HIV, treating them and providing counseling. With support from the World Bank's Indigenous Knowledge for Development Program, TAWG has organized community-to-community exchanges, involving their healers, people living with AIDS and staff working with patients to provide medical care and alternative income generating opportunities, in exchange of IK with other communities in Tanzania [50]. Such experiences are also important in scientific or rational drug discovery process. A crucial challenge is to lever local and global knowledge systems effectively to resolve development challenges. To facilitate this process, the Global Research Alliance (GRA) and the World Bank have initiated a partnership between the TAWG and the US National Institutes of Health to cooperate on the scientific validation of the efficacy of these herbal treatments. During the recent launch of the Global Indigenous Knowledge and Innovation Partnership (GIKIP) in New York, the Tanga project

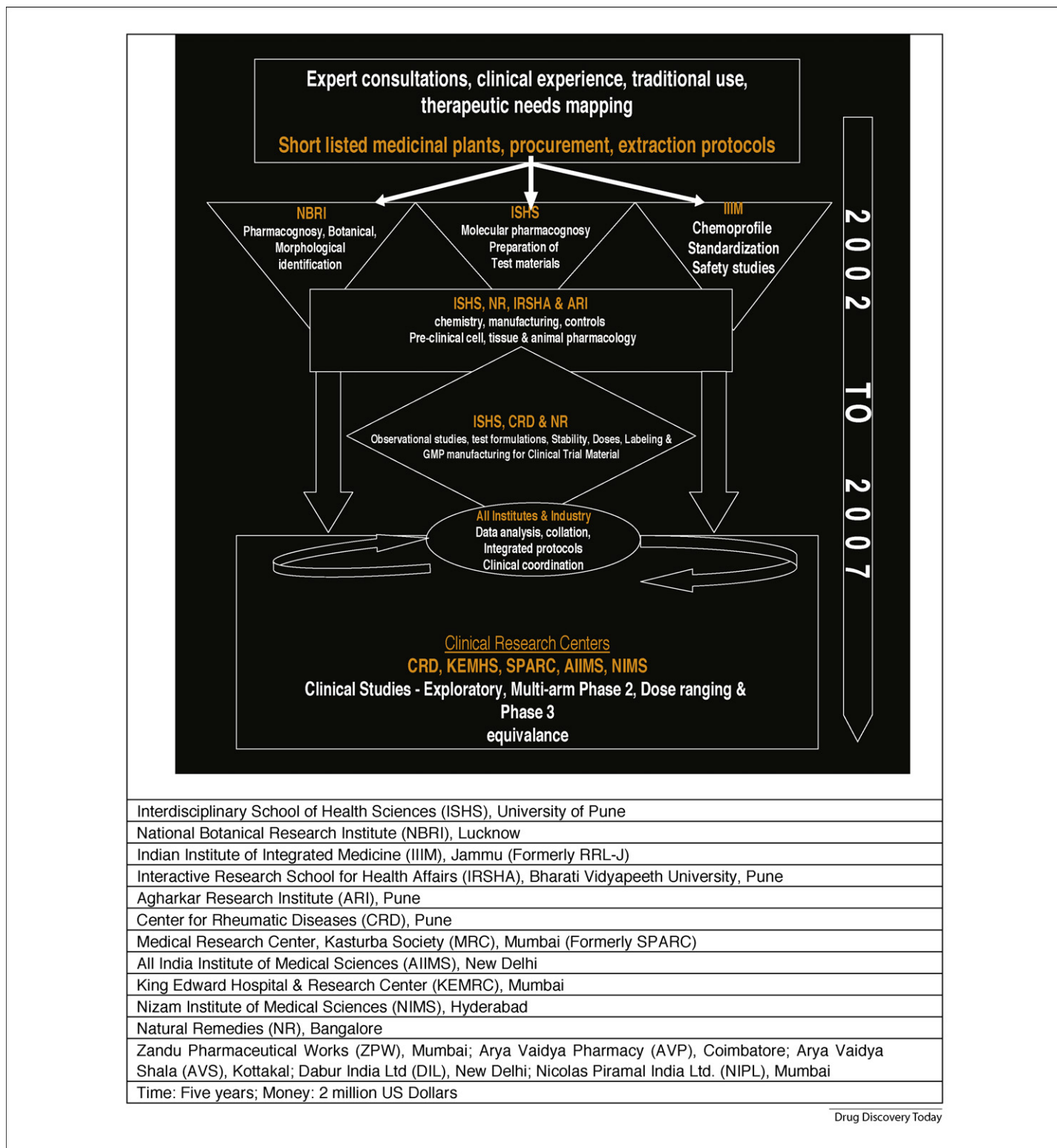


FIGURE 2

NMITLI osteoarthritis project: national institutional network, steps and responsibilities.

was showcased prominently (http://www.research-alliance.net/GIKIP_Launched.html).

Future perspectives

Drug discovery and development is an extremely complex, technology and capital-intensive process that is facing major chal-

lenges with the current target rich-lead poor situation. A major cause of attrition in drug discovery is due to toxicity in human trials and it is known that drugs with novel mechanisms have higher attrition rates. Better validated preclinical targets with proof-of-concept of better efficacy and safety of drugs can, however, mitigate such attrition risks. We propose that the reverse

pharmacology approach can be useful in this process and help in reducing failure rates [51].

Seeking new synergistic combinations and improvements in bioavailability are innovative strategies, that can play a significant role in drug development. For instance, in animal studies, a combination of artemisinin derivative and curcumin has been reported to show a synergistic interaction in killing *Plasmodium falciparum* leading effectively to total survival [52]. There have been several studies on piperine showing its combination improved bioavailability of synthetic drugs such as propranolol, theophylline and rifampicin. The clue for piperine as a bioenhancer came from Ayurveda [53]. Such bioavailability enhancing activity may have numerous advantages in drug development including reduction in dose, toxicity and treatment costs.

Herbalome is an ambitious project from China that is expected to undertake high-throughput screening, toxicity testing and clinical trials to identify active compounds and toxic contaminants in popular recipes to identify scores of drug candidates [54]. It is believed that drugs based on traditional medicine may provide a cost-effective alternative to protein-based or other biotech-based expensive therapeutics [55]. Multisite mechanisms of action of herbal preparations from the crude extracts may offer greater chances for success where conventional single-site agents have been disappointing.

Single drugs, however, may not be an optimal way to treat a patient, with so many characteristics that are so individual, associated, of course with the challenges of genetic diversity. Genome-wide functional screening against disease targets may be the practical approach. Combining Ayurveda and functional genomics in a systems biology scenario may reveal the pathway analysis of crude and active components [56]. Pharmacogenomics is now significantly influencing drug discovery and genotyping is recommended for drugs that are metabolized by enzymes whose genes have inactivating polymorphisms [57]. Efforts to correlate genotype and phenotype-based traditional methodology of classifying humans into three major Prakriti types or constitutions described in Ayurveda have opened an exciting scientific chapter and will help the progress of individualized medicine approaches [58,59].

The issue of protecting intellectual property rights poses special challenges in such approaches based on natural resources. The Traditional Knowledge Digital Library (TKDL) developed by CSIR and AYUSH offer unique technologies (<http://www.tkdil.res.in/>). The TKDL has been able to provide a scientific classification structure to traditional knowledge, resulting in an altogether new resource classification system. The issues relating to patenting of new products that rely on old knowledge are also important. The European Patent Office has been recently given access to the TKDL database so that patent applications relying on Indian traditional remedies can be blocked at an early stage. Similar arrangements with the US Patent Office and others are also underway.

Another ambitious project named AyuSoft involves systems standardization for an integrated, intelligent and communicative decision support system (<http://ayusoft.cdac.in/>). AyuSoft has converted classical Ayurvedic textual knowledge into comprehensive, authentic, intelligent and interactive repositories with complex analytical tools that can be used as a powerful discovery

resource [60]. A systematic medicinal plants database also remains very crucial and important tool for bioprospecting. NAPRALERT – a relational database of natural products developed by the University of Illinois at Chicago (<http://www.napralert.org/>) and the online Encyclopedia of Indian Medicinal Plants developed by the Foundation for Revitalisation of Local Health Traditions (FRLHT) now known as Indian Institute of Ayurveda and Integrative Medicine (IIAIM), Bangalore, India (<http://www.frlht.org.in/>) are two most available valuable resources.

The World Health Organization's Commission on Intellectual Property and Innovation in Public Health has also recognized the promise and role of traditional medicine in drug development for affordable health solutions [61]. Many countries for example India, China, Korea, Malaysia, Brazil, South Africa, Australia and the like are becoming increasingly aware of the value of their traditional knowledge. On the other hand, the global pharmaceutical industry is looking for innovative solutions to expedite the discovery process. Therefore, innovative approaches inspired by traditional knowledge like Ayurveda may aptly occupy this niche strategy to expedite drug discovery and development process especially in the existing global economic environment.

Admittedly, despite the vast potential and possibilities, as of now, very few success stories have emerged from Ayurveda. This may be because most of the work in this field has remained within the clinics of traditional practitioners or confined to academic research laboratories and not taken seriously by industries that are strong in research and development. Therefore, path-breaking initiatives like NMITLI in India are crucially important. The Government of India's golden triangle project integrating biomedicine, modern sciences and traditional medicine is indicative of a trend where traditional sciences like Ayurveda are increasingly embracing the scientific evidence-base and the spirit of robust research [62].

Finally, after this discussion of traditional medicine-inspired approaches to drug discovery, we return to the question posed in the title: Can Ayurveda show the way forward? We can offer an assertive answer, albeit with caveats. Great traditions like Ayurveda and TCM certainly offer sound rationale, valuable experiential wisdom and a large database of botanical resources. For several reasons, researchers involved in the modern drug discovery have started revisiting ancient traditional knowledge and ethnopharmacology, especially to develop new, effective synergistic drug combinations for management of difficult to treat conditions like cancer and dementia. Many promising leads like curcumins, withanoloides and the like offer a great hope, and need to be taken to their logical conclusions. A paradigm shift in innovation strategy is needed, involving, among other things, revisiting the vast possibilities that the Ayurveda and other global traditional knowledge bases offer. A strong conduit between Ayurveda, academia and industry coupled with robust evidence-based research and mutually respected public private partnership is possibly the right way forward.

Conflict of interests statement

RAM was the former director general of CSIR, which, during his tenure, made major investments in drug discovery programs, that used the reverse pharmacology-based approach, involving several

public-private partnerships. Further, CSIR, during RAM's tenure, financially supported and managed the national program NMITLI, that in turn supported osteoarthritis and psoriasis research referred to in this article. RAM is the president of GRA and one of the founding members of GIKIP that has championed the Tanga project. RAM is also a member of the Board of Directors as well as a member of the Scientific Advisory Board of Piramal Life Science, which has been referred to in this manuscript. RAM is also a member of the Board of Directors of Reliance GeneMedix, a pharmaceutical company with business in multiceutics. BP has been the principal investigator of NMITLI supported osteoarthritis and vaccine adjuvant and AyuSoft projects referred to in this manuscript. BP is also honorary scientific advisor to FRLHT/IIAIM that has been referred here. Both the authors state that they do not have any competing financial interests related to this article.

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