Breaking silos: can the emerging field of Ayurvedic biology contribute to the advancement of Indian health science

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This article describes the evolution of an emerging cross-cultural field of research called Ayurvedic biology. Ayurveda and biology both carry equivalent etymological meaning; the study of 'changes' in life processes. The difference lies in the systemic perspective of Ayurveda versus the molecular and mechanistic perspectives in biology. The field of Ayurvedic-Biology seeks to systematically explore the convergence of biological phenomena of health and wellness, derived from different cultural viewpoints. With illustrations of research from genomics, regenerative biology, drug discovery, food sciences and disease classification methods, this article indicates the potential of Ayurvedic biology for the advancement of health sciences.

Keywords: Ayurvedic biology, Ayu-genomics, drug design, food science, health and wellness, regenerative biology.

THIS article makes a case for recognition of Ayurvedic biology as a promising conceptual framework for interpreting biological phenomena. The argument is supported by illustrative examples of ongoing research in this field undertaken during the last two decades.

Historical context of inter-cultural exchanges of knowledge

Across centuries, there are hundreds of examples of transmission of knowledge across cultures. This resulted in 'cross-cultural fusion' of knowledge, techniques and resources, often times transforming the original knowledge to create new cultural ownerships and societal impacts[1,2].

The history of evolution of knowledge informs us that transmissions and fusions across cultures resulted in significant advances in fields as varied as mathematics, philosophy, logic, medicine, architecture, agriculture, materials science, military, culinary practices, fine and performing arts and metaphysics[3].

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While the cultural origins of knowledge are indicators of the historical competence of communities, there are instances where cross-cultural transfusion may erase the advantage of the original cultural innovators. A striking example of this is in the field of surgery, where it is well established that Ayurveda (*Sushrut Samhita*) transmitted surgery to the world of medicine[4]. Indians practised surgeries, including those related to ophthalmology, orthopaedics, brain and caesarean section four millennia ago[5]. Even as recently as the 18th century, the British learnt plastic surgery from India; but during the last three centuries, India has made no major surgical innovations[6]. The leaders of global surgery today are located in Europe, the US and other nations, and Indian health workers need to learn from them. Such cultural shifts in knowledge leaderships have occurred in several domains. They could even take place in the 21st century.

Scientists in the colonized countries perhaps hold an erroneous belief that European sciences comprise the only universal way of understanding biological and physical change[7]. However, it may be argued that other cultural knowledge systems may also possess universal attributes and the capacity to study and apply their knowledge of biological change in a different (non-atomic–molecular) framework. The test of a non-mainstream knowledge system should not be in its conformity to a singular method, principles or a set of concepts, however profound, but by evaluating if its theory and practice (in its own framework) can consistently be applied to transform and solve real-life problems[8,9]. In fact, Ayurveda and biology constitute a natural and appropriate combination because

both carry equivalent etymological meaning, that is, the study of 'changes' in life processes. Their difference lies in the systemic (Ayurveda) and molecular (biology) perspectives: methods of observation, schemes for classification and strategies for modulation of biological change.

This article will indicate in the limited context of health sciences, the potential of cultural partnership between Ayurveda and biology for expanding the frontiers of knowledge in health sciences.

A recent cross-cultural development underway in India in the domain of health sciences

In 2005, a pilot study by Bhushan *et al.*[10] demonstrated the possibility of correlation between an individual's phenotype as described in Ayurveda (Prakriti vichar) and his/her genotype (*HLA-DRB1* gene polymorphisms). This study created a framework for the evolution of a new cross-cultural field of research named as 'Ayu-genomics'[11]. It illustrated that biological concepts relating to human classifications derived from completely different cultural views of nature such as the panchmahabhutas (Ayurveda) and molecular biology can be systematically explored for convergence.

The seed of cross-cultural fusion in biology sowed by 'Ayu-genomics' was followed by a decadal research programme aptly named as 'Ayurvedic biology' by Valiathan[12,13], a distinguished and celebrated cardiac surgeon. The programme was endorsed by the Indian Academy of Sciences, Bengaluru and supported for ten years by the Department of Science and Technology, Government of India. The narration below summarizes research in the decadal programme as well as a few illustrative examples of related research work during and after the programme. This article is not a review of Ayurvedic biology research in India, which has been progressing at a small scale for over two decades in centres located at Pune, Mumbai, Bengaluru, Delhi, Varanasi and Manipal, and also more recently in reputed institutions in Kerala, Gujarat and Rajasthan. The initiatives outlined here are cited to illustrate the potential of the Ayurvedic biology conceptual frameworks using tools of microbiology, biochemistry, genetics and nanotechnology to not only interpret classical Ayurveda, but also synthesize it for adoption as an integrative medical practice.

Ayu-genomics

The first dimension that Valiathan's decadal programme focused on was the interpretation of Ayurveda's human classification system in the language of contemporary biology. Ayurveda posits that each human is composed of a combination of three innate phenotypic constitutions: vata, pitta and kapha. While each human has a unique level of the three constituents, the relative level amongst them leads to seven broad classifications, called the doshaprakriti of an individual. Govindraja *et al.*[14] studied the relationship between doshaprakriti and whole genome SNPs (single nucleotide polymorphisms). Utilizing an Indian genome reference and employing various bioinformatic tools, they reported that 52 SNPs were sufficiently robust to capture the characteristics of prakriti classifications. Further analysis of differential SNPs revealed that the *PGM1* (phosphoglucomutase) gene, which plays a central role in metabolism, contained potentially activity enhancing SNPs in the pitta group. This correlation is interesting because Ayurveda describes pitta-dominant individuals as having a robust metabolism. The study also identified four SNP markers of *PGM1* that were strongly associated with pitta and that the rate of allelic mutations was comparatively less in the pitta group, thus indicating the reserved genetic pattern and robust metabolic nature of pitta individuals described in Ayurveda[14]. It appears that genotype–phenotype correlations contribute to new practical applications. Two other studies also explored this topic and demonstrated the utility of combining Ayurveda-based phenotypic classifications with genomics, to explain human genetic variation across populations[15,16]. Given the explosion of omic-based technologies, there is significant potential for further research in demonstrating how Ayurveda-based human classification and disease classification, which require mere physical and clinical observations, can be utilized as a complementary diagnostic as well as prognostic for personalizing clinical treatments.

Ayurveda pharmacology and medicinal plants

A second dimension of research undertaken by Valiathan's team focused on understanding the indigenous pharmacology principles (dravya guna shastra) of medicinal plants. Knowledgeable readers would be aware that Ayurveda pharmacology has a different and systemic framework for assessing pharmacological activity. In fact, Ayurveda pharmacology has had a productive track record; the biological activities of over 1500 species and over 300,000 herbal formulations have been computerized by the CSIR-TKDL programme[17]. Shukla *et al.*[18] analysed whether transcriptomic signatures of certain herbs could reveal why they were recommended for a specific doshaprakriti, despite belonging to diverse taxonomic groups. Employing molecular biology and bioinformatic tools, their study found that although a majority of transcripts varied considerably between dosha-specific plant species, a small fraction was monomorphic across tissues. For example, in vata-pacifying herbs, cytochrome P450-like TATA box binding proteins were common, while in pitta-pacifiers, transcripts for a major facilitator superfamily transporter gene, heat stress protein genes and retrotransposons were commonly observed. Another avenue of

exploration is the pharmacological potential of plant substitutes that are detailed in the classical texts. Here too, Ayurveda classical texts suggest plant species that are taxonomically different but having similar pharmacological function. The chemical basis of one such substitution, *Cyperus rotundus* for *Aconitum heterophyllum* has been studied[19]. Together, these studies highlight the potential of understanding natural products chemistry and pharmacology using drug principles established in Ayurveda.

Unique therapies and Ayurveda regenerative biology

A third dimension explored by Valiathan's team in Ayurvedic biology was on the clinical outcome of specialized and unique therapeutic interventions of Ayurveda called panchakarma (detoxification). Basti is one such intervention in panchakarma, which involves insertion of medicated oils or decoctions through the colonic route (enema). In one study, a personalized basti regimen along with diet and lifestyle advice was administered to obese individuals[20]. Immunological as well as metabolic markers were reported to improve and remain so 90 days post-treatment. Broader plasma-level metabolomic changes were also reported in another study of six-day panchakarma treatment that included virechana (purgation) and nasya (administration of medicines through the nasal route), along with yoga, diet and oil-based massages in healthy individuals[21]. Pathway enrichment analysis revealed that 61 metabolic pathways such as phospholipid biosynthesis, choline metabolism and lipoprotein metabolism were overexpressed post-study. A daunting task in further research is to devise study protocols that can interrogate and capture the strengths of multivariate personalized treatments protocols for the same disorder, using contemporary biostatistical frameworks employed for clinical studies.

Readers may be unaware that Ayurveda has a clinically active theory and practice of 'regenerative biology' (Rasayana tantra)[22], which precedes the modern discipline of stem cells by 2000 years. Rasayana therapies and diets are posited to enhance longevity and quality of life. This principle was tested with pomegranate (*Punica granatum* L.) a classical rasayana. Supplementation of pomegranate juice in fly media enhanced the lifespan of *Drosophila melanogaster* (fruit fly) by 19% compared to control and the standard drug resveratrol, as well as resulted in about two-fold enhancement in fecundity[23]. A preliminary *in vitro* study of two rasayana herbs *Tinospora cordifolia* and *Withania somnifera* on mesenchymal stem cells (MSCs) has also been reported[24]. Cellular proliferation and senescence were measured after the application of leaf (*T. cordifolia*) and root (*W. somnifera*) extracts. The study reported increased cell viability as well as proliferation, and reduced senescence in MSCs derived from human umbilical cords. Given longer human lifespans and the potential of stem-cell therapies, rigorous studies of Ayurveda precepts in rasayana have the potential to contribute to improving not only the quality of life, but also clinical outcomes. These studies give a mere glimpse of the potential awaiting the discovery of Ayurveda's knowledge of regenerative biology, which has codified knowledge of pharmacology of herbs and clinical therapies that can regenerate cells, tissues, organs and even the entire human body.

Herbo-mineral drugs

A fourth distinct dimension explored by Valiathan's group was in the field of pharmaceutics. It assessed the safety of highly specialized herbo-metal–mineral preparations (bhasmas)[25], which have received flak because market samples often contain toxic levels of minerals and adulterants. An X-ray absorption fine structure (XAFS) study of rasasindura, a mercury-based bhasma, indicated that the classically prepared bhasma had nano-crystals of mercury in non-toxic structural form (α-HgS), and also suggested that they may utilize nano-drug delivery mechanisms[26]. Interestingly, two rasayana bhasma preparations, rasasindura and amalaki, have been tested in *D. melanogaster*. Of note, neither resulted in acute morbidity or major decrease in lifespan. Instead, both showed variable effects on life-history traits as well as ability to help the fly cope with oxidative stress[27]. In another study, 18 different classical bhasma formulations containing copper, iron, zinc, mercury and gemstone-based preparations were examined[28]. A neutron activation analysis performed on the bhasmas revealed that Ayurveda processing methods resulted in metals being modified to within the internationally certified safety margins, with no toxicity profiles. This study confirmed the quality assurance of Ayurveda *bhasmas* when prepared strictly according to classical methods[28]. Future areas of study can be considered at the clinical level, such as testing efficacy of the bhasmas. Perhaps, understanding the fundamental science of bhasma preparation can help with designing innovative drug-delivery mechanisms and adjuvants.

Food science and dietetics in healthy and diseased conditions

We propose the addition of food science as a fifth dimension to take Valiathan's efforts forward. This subject is of enormous contemporary relevance and unlike therapy, easier to adopt for public health. Ayurveda contains detailed guidance for personalized nutrition[29], which requires rigorous testing both at the level of dietetic practice and single nutrient studies. For example, Ayurveda prescribes the fruit of *Emblica officinalis* Gaertn., Indian

gooseberry (amla) to treat anaemia. In a cell-based assay, amla juice has been shown to increase iron absorption when compared to an equivalent dose of ascorbic acid[30], despite the fact that it contains high levels of polyphenols, a class of compounds that are known to inhibit iron uptake[31]. An iron shodhana (detoxification) hypothesis, that is, chelation of iron by the chemical constituents of amla to prevent the toxic effects of iron overload in the gut, is used to explain the role of Indian gooseberry in these formulations[31]. Chemistry apart, the utility of amla can also be explored to make snacks (as groundnut chikki or flour-based crisps) with other iron-dense ingredients, for addressing iron-deficiency anaemia, a major public health problem in India. Such approaches may be superior from a compliance perspective compared to iron fortification and iron–folic acid pills, because they are culturally acceptable food products.

Diabetes is another area of public health where Ayurveda-guided diet therapy and food science can play a positive role. For example, a combination of turmeric (*Curcuma longa* L.) and amla, known as nishamalaki, has been shown to inhibit α-amylase and α-glucosidase, two digestive enzymes that participate in carbohydrate breakdown[32]. Amla is also known to inhibit DPP4 (dipeptidyl peptidase-4), a critical modulator of systemic glucose metabolism[33]. Further studies are needed to understand how cell-based mechanisms observed with Ayurveda foods and drugs can modulate post-prandial glycaemic excursions, and the clinical efficacy of such treatments in real-world situations.

With increasing human lifespan, the area of healthy ageing and maintaining cognitive health would also benefit from the study of Ayurveda principles. For example, Ayurveda strongly advocates ghee (clarified butter) by itself or processed with herbs for maintaining cognitive health and as treatment in several disorders. Ghee holds a unique cultural and traditional presence in Indian households. Hence thorough and rigorous studies to build the evidence-base for ghee chemistry and biology hold enormous promise. In preliminary studies, we observed ghee supplementation to improve locomotion in neurodegenerative disease models in worms (*C. elegans*) and flies (*D. melanogaster*) (unpublished work). With regard to chemistry, functionalizing of ghee with herbs in a processing step called 'murchana', increased the stability of ghee by reducing its peroxide value (unpublished work).

In dietetics, the potential benefits of convergence between modern nutrition and Ayurveda, particularly in personalized nutrition using the prakriti–dosha framework, need critical evaluation. Around 140 phenotypic characteristics comprising anatomical, physiological and behavioural attributes have been used to arrive at the three dosha constitutions. The dosha clusters suggest susceptibility to more than 200 diseases; more if various phenosubtypes are considered. In addition, nearly 600 botanicals have been typed to the doshas and recommendations are made based on prakriti–dosha siddhanta to personalize nutrition according to an individual's unique prakriti. Both proof-of-concept for the theoretical underpinning as well as practical applications in order to design a personalized nutrition tool for the masses are active research areas at TDU. However, to fully realize the potential of this approach, pan-Indian longitudinal cohort studies are necessary.

New framework for drug design

A sixth dimension that we propose is based on the pioneering work by Ashok Vaidya, i.e. the utilization of reverse pharmacology both to validate Ayurvedic treatments as well as develop innovative clinical therapy protocols[34]. The 21st century is expected to witness the advent of a new genre of compound (multi-molecule) drugs that target multiple pathways and correct complex interconnected sets of causative factors (syndromes). Ayurveda already describes several poly-herbal formulations for chronic diseases such as diabetes, obesity and liver disorders. These are multifactorial diseases, wherein a targeted molecular drug approach is inadequate to address the complex biological changes underlining their etiopathology. Interestingly, Ayurveda principles and treatment converge with modern biology on adopting a gut-centred view of their management. Gastrointestinal-mediated glucose disposal (GIGD) is one framework under study[35]. Currently, four classical Ayurveda formulations, viz. nisha-amalaki, vasanta kusumakara rasa, nishakathakadi and lodhrasavam prescribed for the management of diabetes syndrome (prameha) are being studied in this framework using *in vitro*, animal model and clinical studies. The formulations are being studied in their classical dosage form instead of solvent extracts, to reflect the comprehensive bioactive nature of the classical formulations. A simulated *in vitro* digestion model revealed that nisha-amalakai and lodhrasavam inhibited digestive enzymes like α-amylase (≈65%) and α-glucosidase (≈95%)[32]. Lodhrasavam was also found to have anti-adipogenic effect in a cell-based model for adipogenesis, suggesting a basis for its use in obese diabetic patients[36]. Vasanta kusumakara rasa and nishakathakadi were observed to modulate key GIGD events like DPP4 inhibition (≈60%) and increasing GLP-1 (≈40%) secretion, in addition to increasing pancreatic beta-cell proliferation (unpublished). These preliminary studies together suggest that Ayurveda formulations may operate by affecting multiple non-overlapping pathways and this may perhaps explain their cumulative systemic effects. Despite a trove of such formulations existing, the evidence base for their efficacy in biomedical terms is weak. If systematically studied, pharmacology of Ayurvedic formulations could contribute to novel solutions for chronic metabolic diseases such as non-alcoholic fatty liver disease, diabetes and obesity.

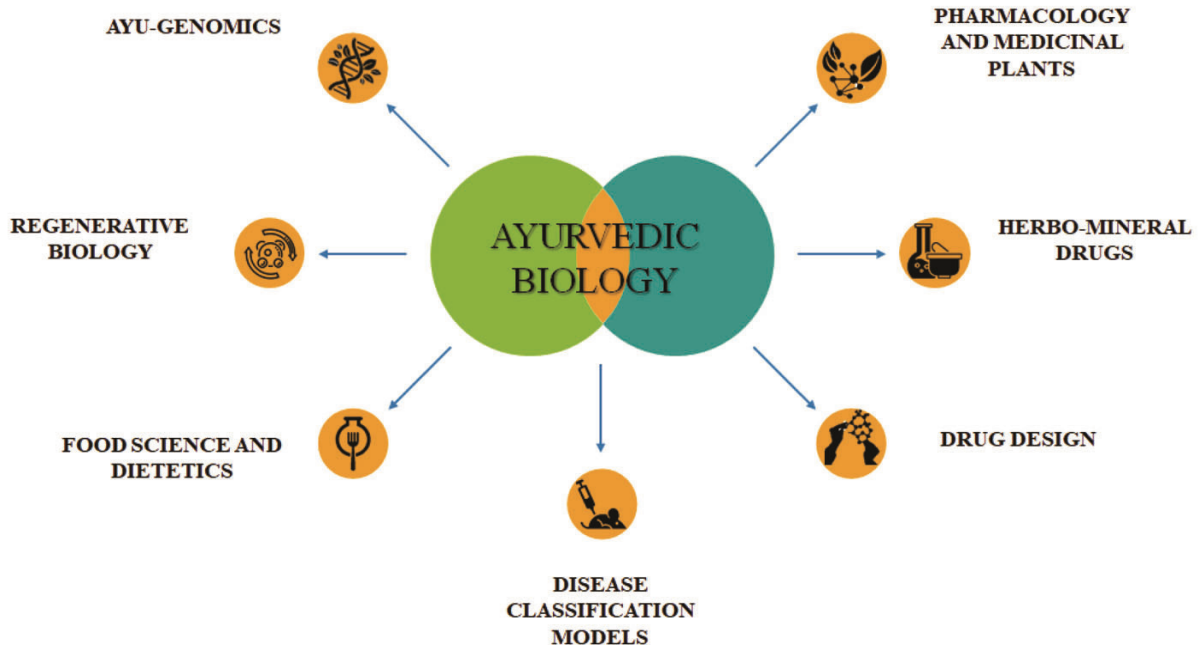

Figure 1. The seven dimensions available for exploration from the fusion of Ayurveda frameworks and biomedical science.

Ayurveda describes several strategies for improving and maintaining brain health: medhya and medhya-rasayanas which are being studied at the theoretical, experimental and clinical levels[37,38]. In neurodegenerative disease models of *C. elegans*, extracts of brahmi (*Bacopa monnieri*) and kapikatchhu (*Mucuna pruriens*) were found to have maximum protective effect against MPP+ iodide induced dopaminergic neuron degeneration (unpublished). Application of mandookaparni (*Centella asiatica*), brahmi and kapikatchhu also reduced Alzheimer's disease phenotypes in human Aβ expressing transgenic *C. elegans* strains, in addition to extending their lifespan (unpublished). While model organism work provides preclinical evidence as well as mechanistic details, the validation of this approach is complemented by clinical studies. Presently, the effect of brahmi ghrita (ghee-infused with brahmi) on different domains of cognition, stress, anxiety and sleep is being evaluated for 25–85-yr-old adults. Preliminary data from a community study indicate positive effect on cognition, and no adverse effects on the lipid and sugar profile of the participants. Overall, the immense potential in Ayurveda-based formulations and drugs for application not only in clinical science but also fundamental biology needs to be explored.

Disease classification models

The seventh dimension proposed is in the area of disease classifications in order to improve clinical prognosis. Biomedical clinical classification schemes capture limited variability in the presentation of symptoms, sometimes relying on a few biochemical markers, compared to Ayurveda which takes a holistic view. A difference in the granularity of disease classification systems between Ayurveda and contemporary biomedicine has been observed. Clinical trials design inclusion criteria to ensure that some level of homogeneity and therefore, controlled conditions can be obtained. However, even within the framework of these criteria, Ayurveda disease would treat them as a heterogenous population. For example, patients who appear with a uniform biomedical diagnosis (e.g. ischaemic stroke, parkinsonism) are further sub-classified by Ayurveda based on disease onset, severity, location of disease symptoms and individual doshaprakriti, amongst others. Studies at the Institute of Ayurveda and Integrative Medicine Healthcare Hospital, Bengaluru, indicate that this stratification allows for personalized treatment protocols and hence, better clinical outcomes in diseases such as stroke[39]. Studies are required to assess the utility of the Ayurveda disease classification system because, if effective, it can revolutionize disease classification systems and treatment strategies in the world of clinical medicine. Importantly, the Ayurveda disease classification system would also be cost-effective, as it merely requires a good set of questions and physical examination. The best Ayurveda physicians intuitively use an algorithm-based management protocol to diagnose variations and treat differentially in diseases such as rheumatoid arthritis[40], osteoporosis, stroke, infertility, urinary tract infections, non-healing diabetic wounds[41], immuno-compromised conditions, and metabolic, neurological and skin disorders. It will be important to standardize and validate these algorithm-based management protocols as

they can substantially change healthcare, an endeavour that requires physician scientists.

Discussion and conclusion

In this article, we trace the history of Ayurvedic biology research that stemmed from the efforts of Valiathan and outline seven dimensions where 'Ayurvedic biology' can serve as a seed for innovation (Figure 1). The transfusion of knowledge from both modern biology and Ayurveda can sow the seeds for growth of a new cross-cultural biology that may generate original contributions to the world of medicine and physiology. This development, enhanced with tools like artificial intelligence and machine learning can be expanded to pursue Ayurveda biology leads in fields like bioregulation, pathogenesis, multi-targeted drug design, immunomodulation, and personalized food and medicine, which are the challenges of this century. The exploration of a multi-cultural paradigm holds promise of a journey full of unexpected discoveries.

In an era that is recognizing complexity alongside limitations of available knowledge frameworks, the pursuit of knowledge from multiple perspectives is imperative. The fact that functional relationships and novel insights due to the confluence between Ayurveda and biology have not only taken place, but also yielded innovative outputs is a wake-up call to decolonize minds and systematically pursue cross-cultural and trans-disciplinary knowledge. Indian scientists can take a lead in such innovations because of their cultural legacy and proficiency in Western science.

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