

Breaking silos: Can the emerging field of Ayurvedic - Biology contribute to advancement of Indian health science

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Abstract

This paper narrates 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, is the first attempt to systematically explore convergence of biological phenomena of health and wellness, derived from different cultural viewpoints. Here, 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, drug design, food science, regenerative biology, Ayu-Genomics.

Introduction

This paper 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.

1. Historical context of inter-cultural exchanges of knowledge

Across centuries, there are hundreds of examples of transmission of knowledge across cultures. This transmission 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, material sciences, military, culinary practices, fine and performing arts and metaphysics³.

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 medicine⁴. Indians practised surgeries including those related to ophthalmology, orthopaedics, brain and caesarean section four millennia ago⁵. 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 innovations⁶. 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 colonised countries perhaps hold an erroneous belief that European sciences comprise the only universal way of understanding biological and physical change⁷. However, it may be argued that other cultural knowledge systems may also possess universal attributes and 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 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 they 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 point out 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.

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

In 2005, a pilot study was published by Prof. Bhushan Patwardhan's team, demonstrating the possibility of correlation between an individuals' phenotype as described in Ayurveda (*Prakriti vichar*) and their genotype (HLA- DRB1 gene polymorphisms)¹⁰. This study created a framework for the evolution of a new cross cultural field of research named by Patwardhan as ‘Ayu-genomics’¹¹. It illustrated that biological concepts relating to human classifications derived from completely different cultural views of nature such as *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 program aptly named as ‘Ayurvedic Biology’ by Dr. MS Valiathan, a distinguished and celebrated cardiac surgeon^{12,13}. The program was endorsed by the Indian Academy of Sciences and supported for ten years by the Department of Science and Technology, Govt. of India. The narration below

summarises research within the decadal program as well as few illustrative examples of related research work during and after that time. This article is not a review of Ayurvedic-biology research in India, which has been progressing on a small scale for over two decades in centres located in Pune, Mumbai, Bangalore, Delhi, Varanasi, 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 framework 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.

2.1. Ayu-Genomics

The first dimension that Dr. Valiathan's decadal program focussed on was the interpretation of Ayurveda's human classification system in the language of contemporary biology. Ayurveda posits 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. In their study, Govindrajan P et.al., investigated the relationship between *doshaprakriti* with whole genome SNPs (single nucleotide polymorphisms)¹⁴. Utilizing an Indian genome reference, and employing various bioinformatic tools, they reported that 52 SNPs were sufficiently robust to capture characteristics of *prakriti* classifications. Further analysis of differential SNPs revealed that 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 4 SNP

markers of PGM1 that strongly associated with *pitta* and the rate of allelic mutations were comparatively less in *pitta* group, thus indicating the reserved genetic pattern and robust metabolic nature of *pitta* individuals described in Ayurveda¹⁴. It appears that genotype–phenotype correlations are contributing to new practical applications. Two other studies from Dr Mitali Mukherjee's group 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's significant potential for further research in demonstrating how Ayurveda based human classification and disease classification (See 2.7) which require mere physical and clinical observations, can be utilised as a complementary diagnostic as well as prognostic for personalising clinical treatments.

2.2. Ayurveda pharmacology and medicinal plants

A second dimension of research undertaken by Dr. 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 very different and systemic framework for assessing pharmacological activity. Ayurveda pharmacology in fact has had a very productive track record; the biological activities of over 1500 species, and over 3,00,000 herbal formulations have been computerised by the CSIR-TKDL program¹⁷. Shukla et.al., assessed if transcriptomic signatures of certain herbs could reveal why they were recommended for a specific *doshaprakriti*, despite belonging to diverse taxonomic groups¹⁸. 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 e.g., 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 quite different but having similar pharmacological function. The chemical basis of one such substitution, *Cyperus rotundus* for *Aconitum heterophyllum* has been studied¹⁹. Together, these studies highlight the potential of understanding natural product chemistry and pharmacology by using drug principles established in Ayurveda.

2.3. Unique therapies and Ayurveda regenerative biology

A third dimension explored by Dr. Valiathan's team of researchers 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 via the colonic route (enema). In one study, a personalised *basti* regimen along with diet and lifestyle advice was administered to obese individuals²⁰. 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 6-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 individuals²¹. Pathway enrichment analysis showed around 61 metabolic pathways such as phospholipid biosynthesis, choline metabolism, and

lipoprotein metabolisms were overexpressed, post-study. A daunting task in the further research studies is to devise study protocols that can interrogate and capture the strengths of multi-variate personalised 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% as compared to control and the standard drug resveratrol, as well as resulted in about two-fold enhancement in fecundity²³. A preliminary *in-vitro* study of two *rasayana* herbs *Tinospora cordifolia* and *Withania somnifera* on mesenchymal stem cells (MSCs) has also been reported²⁴. Cellular proliferation and senescence were measured after the application of leaf (*Tinospora cordifolia*) and root (*Withania 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 investigations of Ayurveda precepts in *rasayana* have the potential to contribute to improving not only quality of life but also clinical outcomes. These studies give a mere glimpse of the potential awaiting 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.

2.4. Herbo-mineral drugs

A fourth distinct dimension explored in the Dr. Valiathan's initiative was in the field of pharmaceuticals. It assessed the safety of highly specialised 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) investigation of *rasasindura*²⁶, 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 utilise nano-drug delivery mechanisms. Interestingly, two *rasayana bhasma* preparations, *rasasindura* and *amalaki*, have been tested in *Drosophila 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 deal with oxidative stress²⁷. In another study, 18 different classical *bhasma* formulations containing copper, iron, zinc, mercury, and gemstone-based preparations were investigated²⁸. 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 as per classical methods²⁸. Future areas of investigations can be considered at the clinical-level, such as testing efficacy of *bhasmas*. Perhaps, understanding the fundamental science of *bhasma* preparation can help with designing innovative drug delivery mechanisms and adjuvants.

2.5. Food science and dietetics in healthy and diseased conditions

We propose the addition of food science as a fifth dimension to take Dr 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

personalised nutrition²⁹ which require 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 acid³⁰, despite it containing high levels of polyphenols, a class of compounds that are known to inhibit iron uptake³¹. An iron *shodhana* (detoxification) hypothesis, that is, chelation of iron by *amla*'s chemical constituents to prevent the toxic effects of iron overload in the gut, is used to explain *amla*'s role in these formulations³¹. Chemistry apart, *Amla*'s utility can also be explored to design snacks (as groundnut chikki or flour-based crisp) 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 as 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 breakdown³². *Amla* is also known to inhibit DPP4 (dipeptidyl peptidase-4)³³, a critical modulator of systemic glucose metabolism. 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 lifespans, 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 investigations to build the evidence-base for ghee chemistry and biology holds enormous promise. In preliminary studies, we observe ghee supplementation to improve locomotion in neurodegenerative disease models in worms (*C. elegans*) and flies (*D. melanogaster*) (unpublished work). At the chemistry end, 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 personalised nutrition using the *prakriti-dosha* framework, needs critical evaluation. Around 140 phenotypic characteristics comprising of anatomical, physiological and behavioural attributes have been used to arrive at three *dosha* constitutions – *vata*, *pitta* and *kapha*. The *dosha* clusters suggest susceptibility to more than two hundred diseases; more if various pheno-subtypes are considered. In addition, nearly 600 botanicals have been typed to the *dosha*'s and recommendations are made based on *prakriti-dosha siddhanta* to personalise nutrition according to an individual's unique *prakriti*. Both proof-of-concept for the theoretical underpinning as well as practical application in order to design a personalised nutrition tool for the masses are active research areas at TDU. But to fully realise the potential of this approach, pan-Indian longitudinal cohort studies are necessary.

2.6. New framework for drug design

A sixth dimension we propose is based on the pioneering work by Prof Ashok Vaidya is the utilisation of reverse pharmacology both to validate Ayurvedic treatments, as

well as develop innovative clinical therapy protocols³⁴. 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 set 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 investigation³⁵. Currently, four classical Ayurveda formulations: *Nisha-Amalaki*, *Vasanta Kusumakara Rasa*, *Nishakathakadi* and *Lodhrasavam* prescribed for the management of diabetes syndrome (*Prameha*), are being investigated in this framework using cell-based, model animal and clinical techniques. 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 ($\approx 65\%$) and α -glucosidase ($\approx 95\%$)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 patients³⁶. *Vasanta Kusumakara Rasa* and *Nishakathakadi* were observed to modulate key GIGD events like DPP4 inhibition ($\approx 60\%$) and increasing GLP-1 ($\approx 40\%$) secretion, in addition to increasing pancreatic beta-cell proliferation (unpublished work). 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 investigated, pharmacology of Ayurvedic formulations could contribute to novel solutions for chronic metabolic diseases such as Non-alcoholic Fatty Liver Disease (NAFLD), diabetes and obesity.

Ayurveda describes several strategies for improving and maintaining brain health: *Medhya* and *Medhyarasayanas* which are being investigated at the theoretical, experimental and clinical levels^{37,38}. In neurodegenerative disease models of *C. elegans* the 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 reduce Alzheimer's disease phenotypes in human A β expressing transgenic *C. elegans* strains in addition to extending their lifespan (unpublished). While model animal work provides pre-clinical 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 years 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 formulation and drugs, for application not only in clinical science but also fundamental biology is waiting to be explored.

2.7. 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, as 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., ischemic stroke, parkinsonism), are further sub-classified by Ayurveda, based on disease onset, severity, location of disease symptoms and individual *doshaprakriti* amongst others. Observations at the Institute of Ayurveda and Integrative Medicine healthcare hospital (Bangalore), indicate that this stratification allows for personalized treatment protocols and hence, better clinical outcomes in diseases such as stroke³⁹. 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, Ayurveda disease classification system would also be cost-effective as they merely require 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 arthritis⁴⁰, osteoporosis, stroke, infertility, urinary tract infections, non-healing diabetic wounds⁴¹, immuno-compromised conditions, 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 endeavor that requires physician scientists.

Discussion:

In this article, we traced the history of Ayurvedic biology research that stemmed from the efforts of Dr. Valiathan and outline seven dimensions where “Ayurvedic – biology” can serve as a seed for innovation (Fig. 1). The transfusion of knowledge from both modern biology and Ayurveda can sow the seeds for the 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 bio regulation, pathogenesis, multi targeted drug-design, immuno- modulation and, personalised 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 recognising complexity alongside limitations of available knowledge frameworks, the pursuit of knowledge from multiple perspectives is an imperative. The fact that functional relationships and novel insights due to confluence between Ayurveda and biology have not only taken place, but also yielded innovative outputs is a wakeup call to decolonialize minds and systematically pursue cross-cultural and trans-disciplinary knowledge. Indian scientists can take a lead in such innovation because of their cultural legacy and proficiency in western sciences.

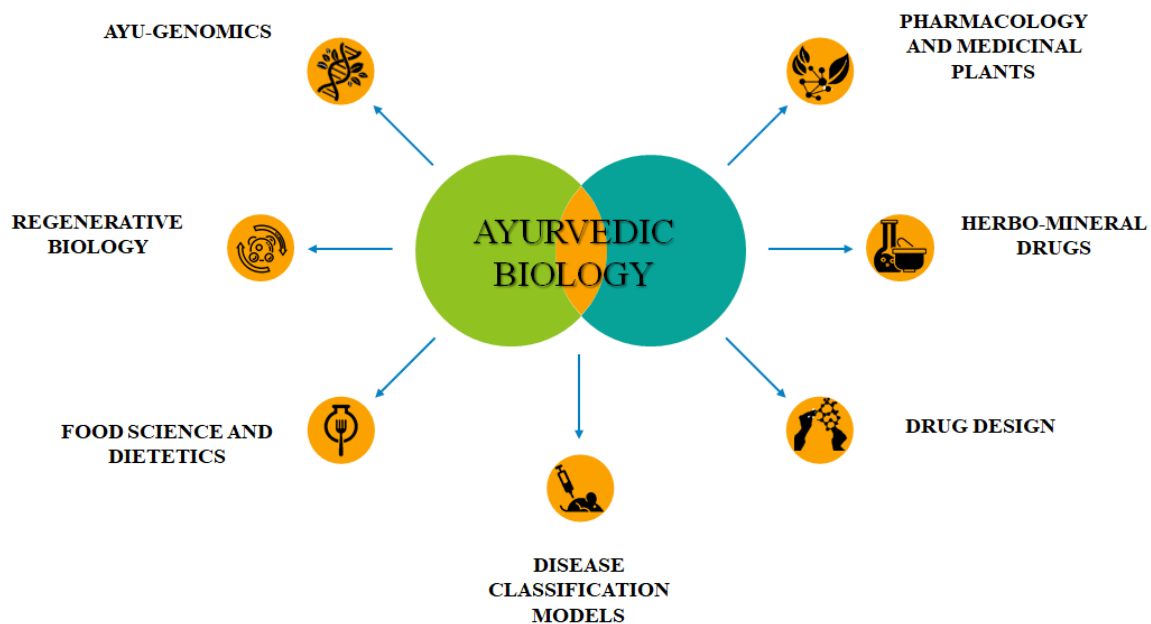


Figure 1: The seven dimensions available for exploration that can arise from the fusion of Ayurveda frameworks and biomedical science.

Conflict of Interest:

The authors of this article declare that there is no conflict of interest regarding the publication of this paper.

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