

*Medal Lecture***Ayurvedic Biology: The First Decade****

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In the long history of India, few events were more transformational than its encounter with the West, which spared no aspect of human endeavor in the country. European – especially British – influence became so pervasive, and at once so profound, in India's polity, jurisprudence, communication, literature, science and medicine that it has become a part of the Indian reality today. The story of the European encounter with India in the field of medicine is unique in so far as European medicine came to occupy the space of main stream while Ayurveda continues to exist side by side and enjoys popularity. Since independence, Government policy has encouraged "integration" of the two systems with debatable results.

Europe Meets Ayurveda

A notable event in the 16th century CE was the arrival of a Portuguese physician – Garcia da Orta – in Goa, who settled down to practice medicine for 36 years. He was a witness to the heavy mortality among Portuguese citizens in Goa where their population had shrunk and several Governors had died thanks to epidemics and the scourge of tropical diseases. Portuguese physicians were too few to take care of European patients and they were further handicapped by total unfamiliarity with diseases such as dysentery, cholera and malaria, not to speak of snake bites. Their attention quickly turned to native physicians whose practice was largely based on Ayurveda but also included local traditions. Garcia was a keen observer and became the first European to write a book on India's medicinal plants, the first to mention *Rauwolfia serpentina*, and the first to give a graphic description of cholera. He also wrote a classic "Colloquies on the Simples and Drugs of India" in 1563 which dealt with materia medica and medicinal botany of the East and medicine in general. He described the appearance and habitat of plants, parts used in the treatment of diseases and his own recommendations for treatment. The Colloquies written in Latin became a best-seller in Europe and was translated into several European

languages within a few years because colonial powers were greatly interested in the medicinal plants of India which were reportedly successful in treating tropical diseases. They also seemed to recognize opportunities for a profitable trade in medicinal plants. In the 17th century, Van Rheed, the Dutch Governor in Kochi, took keen interest in the study of spices and medicinal plants on the Kerala Coast. His interest was triggered by the observation that the common people of Kerala were healthy and did hard labour despite what he regarded as the poor quality of their diet. He attributed this to their habitual diet featuring a variety of spices such as turmeric, cloves, cardamom and pepper. He assembled a team of almost a hundred people including herbalists, teachers of botany, an Ayurvedic physician, clergymen, artists, engravers and lots of field workers to survey the wealth of tropical plants. The survey extended all the way from Goa to Kanyakumari and took over 30 years. The result was the publication of a major classic "Hortus Malbaricus" in 12 volumes from Amsterdam which won universal praise. Linneus admired the book and wished he had access to it before the publication of his "Systema Naturae". Hortus Malbaricus listed over 700 plants with their names in Malayalam, Latin, Sanskrit and Arabic and provided exquisite illustrations

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and information on the medical applications of plants. The interest in the medicinal plants of India continued to mount in India and Europe and taxonomy became a highly popular subject. The advent of the Botanical Survey of India added further impetus to medicinal plant studies which became even a part of the first year curriculum for medical students in Kolkata in the 19th century. Taxonomy attracted pioneers such as Roxburgh in Kolkata – much admired by JC Bose, Ainslie in Chennai and many others. From the 16th century to the end of the 19th, taxonomy reigned and provided the tool for biologists to study the role of plants in medical therapy.

A significant development in the twentieth century was the beginning of pharmacologic studies by Sir RN Chopra in the Kolkata School of Tropical Medicine. His highly acclaimed work involved botanical identification of plants, chemical analysis, pharmacologic studies of compounds on living tissues *in vitro* and *in vivo* as well as biochemical and biophysical changes brought about in mammalian organisms on administering active compounds. His stated aims were “to make Indian pharmacology self-supporting by enabling her to utilize locally produced drugs economically, under standard laboratory conditions and to discover remedies from the claims of Ayurvedic, Tibbi and other indigenous sources, suitable to be employed by the exponents of Western medicine”. Chopra was hailed as the “Father of Indian pharmacology” which became the new tool for the scientific community to investigate Ayurveda. From this stage, it was but a short step to natural products chemistry which attracted a small army of talented Indian scientists led by stalwarts such as Asima Chatterjee and Govindachari. The plants chosen for study were so extensive and the scientific data collected on their constituents so impressive that India became a world leader in natural products chemistry. The work continues in the National Laboratories and Universities in India and hope springs eternal that “magic” molecules to counter serious ailments such as cancer and dementia may emerge from the long search for plant-derived drugs.

Modern Biology and Ayurveda

Throughout the twentieth century, research in Ayurveda was more or less confined to the study of

medicinal plants, medicinal chemistry and search for new chemical entities. There was hardly any clinical research as clinical trials were alien to Ayurveda. Though PC Ray characterized 600 BC to 800 AD as the “Ayurvedic Period” in India’s history of science, thanks to the Ayurvedic provenance of chemistry, basic research involving biology and immunology received little attention despite the discovery of the double helix and the dramatic developments in molecular biology and immuno-genetics. It was inevitable that Ayurveda would soon be viewed through the window of molecular biology in the twenty-first century. The Decadal Vision Document “Towards Ayurvedic Biology” published by the Indian Academy of Sciences in 2006 clearly foresaw a new frontier of biology where the tools and methods of molecular biology would be employed to study the concepts, procedures and the mechanistic basis of therapeutic effects in Ayurveda. The main difficulties in organizing these investigations are the following:

- Identifying concepts, procedures, and mechanistic ideas, which would lend themselves to experimental tests.
- Designing experiments and protocols on the basis of descriptions and directions in ancient texts.
- Creating partnerships between scientists and Ayurvedic experts.
- Overcoming skepticism among scientists and Ayurvedic experts.
- Obtaining financial support for the initiative.

These difficulties were overcome thanks to the visionary support of Dr R Chidambaram, PSA to the Government of India who saw the merit of launching “A Science Initiative in Ayurveda (ASIIA)” as a part of his programme of “Directed Basic Research”. The ideas for the initial round of projects in ASIIA had been suggested in the Decadal Vision Document. The projects approved under “A SCIENCE INITIATIVE IN AYURVEDA” (ASIIA) were as follows:

- Genomic Variation Analysis of Human Dosha Prakriti based on Principles of Ayurveda.
- **Amalaki Rasayana:**
 - a. Biological effects on *Drosophila* model.

- b. Effects on the genomic stability of neurons and astrocytes in rat brain.
- Immunological and metabolic effects of Panchakarma.
- Microstructure of Bhasmas: a case study on Rasasindura.
- Genomic study of medicinal plants which counter the deranged doshas.

The projects done and published on Prakriti, Rasayana, Panchakarma and Rasasindura are briefly discussed below as they illustrate the approach in ASIIA to study a concept (Prakriti), mechanistic basis of procedures (Rasāyana and Panchakarma) and the effect of traditional processing on the composition and structure of a product (Bhasma).

Genomic Basis of Prakriti

A basic concept in Ayurveda is prakriti or the constitutional type of all individuals. It postulates that prakriti is fixed at conception and has three primary types – vata, pitta and kapha. Etymologically, they indicate respectively motion, digestion/transformation, accumulation and their correlates. In traditional practice, the three constitutional types or prakriti are determined by the physician on the basis of physical, mental and behavioural traits which are listed in the classical texts such as Charaka Samhita. This determination is indispensable for the practice of Ayurveda because prakriti determines an individual's predisposition to diseases and response to treatment. Though the possible relationship of prakriti with genomics was hypothesized over a decade ago (Patwardhan *et al.*, 2005), no study had convincingly correlated prakriti with genomic variations. In a multi-centric study involving scientific and Ayurvedic institutions in Hyderabad, Manipal, Pune and Bangalore, 3416 normal healthy males between 20-30 years were screened and their prakriti determined by Ayurvedic physicians on the basis of characteristic traits. This was followed by an independent determination by using Ayusoft, a software, which had been developed by quantifying the traits listed in Ayurvedic texts (Mahalle *et al.*, 2013). Subjects for the study were selected only when the results of the two assessments were concordant (Rotti *et al.*, 2014). Single dosha prakriti with high percentage of one

dosha is rare and most individuals have dual dosha prakriti with one as dominant. In the present study individuals with 60% or more dominance of one prakriti as determined by Ayusoft were chosen from the screened subjects and 262 individuals selected for analysis using approximately one million genetic markers (SNPs) (Govindaraj *et al.*, 2015). After extensive genetic and statistical analysis, 52 genetic markers out of one million were identified, which were sufficient to differentiate the three dosha prakriti – vata, pitta and kapha – despite their recruitment from different ethnic, linguistic and geographical backgrounds. Principal Component Analysis of the SNPs classified the 262 individuals into the respective vata, pitta and kapha groups irrespective of their ancestry, which represents its power in categorization. It was also found that a gene *PGMI* correlates with the phenotype of pitta which has specific characteristics such as digestion and metabolism. It is of great interest that *PGMI* gene is in the center of many metabolic pathways, which would suggest that the function of the gene directly correlates with the role of pitta in metabolism as described in Ayurveda. It would therefore appear that the phenotypic classification of vata, pitta and kapha in Ayurveda has a genetic basis and the traditional prakriti-based classification of patients does resonate with personalized medicine.

The genomic basis of prakriti is corroborated by another study which employed DNA methylation as the marker for differentiating the three prakriti phenotypes. Rotti *et al.* (2015) subjected whole blood DNA of 147 healthy male individuals belonging to vata, pitta and kapha phenotypes to methylated DNA immunoprecipitation and microarray analysis followed by the validation of prakriti specific signatures through bisulfite DNA sequencing. Pathway analysis of prakriti specific genes indicated cluster enrichment of genes associated with transport events in kapha, cell membrane and morphogenesis in pitta, and regulation of transcription in vata prakriti. Authors went on to show methylation of *CDH22* gene in kapha prakriti associated with higher BMI. They concluded that “differential DNA methylation signatures in three distinct prakriti phenotypes demonstrate the epigenetic basis of Indian traditional human classification which may have relevance to personalized medicine”.

Micro level studies in biology are known to delve so deep as to miss the wood for trees! In our context, the genomic studies receive support from a collateral observation at the population level. Among the 3416 subjects screened for the prakriti study in three centers, a significant correlation was noted between prakriti and BMI (Rotti *et al.*, 2014). Whereas BMI less than 20 constituted 10% kapha prakriti subjects, over 25 formed 89% of kapha subjects suggesting a strong linkage between high BMI and kapha prakriti. Data in Table 1 speak for themselves.

Table 1: Prakriti – BMI Association

BMI	Vata	Pitta	Kapha
< 20	71%	19%	10%
21 - 25	32%	21%	47%
> 25	11%	44%	79%

Rasayana

Rasayana is one of the eight branches of Ayurveda, which bears testimony to the zest for living in ancient India. According to Ayurveda, body depletes constantly and the depleting tissues need to be replenished regularly by the intake of food and drinks to prevent decay. The assimilable part of digested food is transported as nutrient sap (rasa) to the tissues through countless channels. As age advances, the flow of nutrient sap to the tissues tends to decline due to various causes such as poor intake of food, weak digestion in the stomach and the narrowing of body channels. If uncorrected, this could lead to several infirmities of old age which may be crippling. Rasayana literally meant facilitation of the transport of nutrient sap to the target tissues. The rasayana procedure could be done indoors or outdoors but both required the intake of formulations which were popularly called rasayanas. While the ancient texts promised extraordinary results for rasayana for improving intellectual and physical capacity, there was no demonstrable evidence in biological terms to support the claims. In a study conducted by Swain *et al.* (2012) Amalaki Rasayana prepared by Arya Vaidya Sala, Kottakkal was given to adult Wistar rats which were sacrificed at 3, 9 and 15 months and isolated cell suspensions of neurons and astrocytes from their brain examined. The results showed convincingly that, compared to controls, the neurons

and astrocytes in the rasayana fed group showed significantly less DNA damage in brain cells. This clearly affirmed the beneficial effect of Amalaki Rasayana therapy on the maintenance of genomic stability.

In a series of studies on administering Amalaki Rasayana to *Drosophila melanogaster*, Dwivedi *et al.* (2012) reported formulation-specific effects on several parameters of the fly's life including the size of the salivary glands, hnRNP levels in larval tissues, thermo-tolerance of larvae/adult flies, median life span, starvation tolerance and fecundity in larvae and adults. In another study (Dwivedi *et al.*, 2013) the same authors showed that dietary supplement of Amalaki Rasayana suppressed neuro-degeneration in fly models of Huntington's and Alzheimer's disorders without side effects. Other observations included the prevention of the accumulation of inclusion bodies and heat shock proteins, suppression of apoptosis, elevation of the levels of heterogeneous nuclear ribonucleo proteins and improved ubiquitin – proteasomal system for better protein clearance in affected cells. Dwivedi *et al.* (2015) have also shown that the suppression of apoptosis by Amalaki Rasayana in fly models of neuro-degeneration applies only to induced apoptosis and not to developmental apoptosis. This would suggest that the rasayana empowers the rasayana-fed flies to tolerate greater insults without triggering a cell death response.

Panchakarma

No procedure in Ayurveda received greater public notice than panchakarma which is used widely in India and abroad and has even cast its mantle on tourism. Literally, panchakarma means “five procedures” which are the oral administration of oily preparations (snehana), body fomentation (svedana), emesis (vamana), purging (virechana), and enema (basti). When panchakarma is carried out for head disorders, it is designated nasal purging (nasya). The first two are compulsory in every application but the remaining three are used as per clinical indications by the physician. Vāgbhaṭa states that diseases are synonymous with the serious disequilibrium of three doshas – vata, pitta and kapha – which increase singly or in combination and obstruct the constant flow of substances through countless channels which permeate the body. To remove the obstruction in

channels caused by accumulated doshas, panchakarma is prescribed as an effective therapeutic measure. The administration of oily substances lubricates and dislodges the obstructing doshas in the channels, fomentation dilates the channels and drives the doshas into the alimentary canal, and the three evacuative procedures expel them through the mouth, anus and nose. As the widely acclaimed benefit of panchakarma therapy is likely to involve metabolic and immunological events, Thatte *et al.* (2015) studied the use of therapeutic basti (enema) which is a popular Ayurvedic intervention for treating obesity. Thirty two obese individuals with a body mass index (BMI) ≥ 30 kg/m² received a course of therapeutic enemas followed by specific diet and life style regimen for 32 days. Clinical examination and measurement of metabolic and immune parameters were done before starting Panchakarma (S1), immediately after completion (S2) and 90 days after the completion of therapy (S3). The subjects showed significant reduction in weight ($P < 0.001$) with a marked decrease in serum interferon (IFN)- γ ($P < 0.02$), interleukin (IL-6) ($P < 0.002$), and significant increase in the production of (IFN)- γ in culture supernatants of PBLs stimulated with anti-CD-3 monoclonal antibodies at S2 which further increased at S3 ($P < 0.002$). This contrasted with a gradual reduction in IL8 production. A significant correlation was noted between IL-6 and IL-8 levels at S1, S2 and S3. A positive correlation was observed between IgG and IL6 levels at S2 and S3. They concluded that the basti procedure (panchakarma applied to the treatment of obesity) modulates immune responses by regulating insulin resistance - causing pro-inflammatory cytokines, immunoglobulins and functional properties of T-Cells.

Bhasma

In the extensive Ayurvedic formulary, medicinal plants claim dominance and drugs derived from metals and minerals take only third place after animal products. Among metallic products, mercury which was hardly mentioned by Charaka, Suśruta and Vāgbhaṭa acquired great importance in subsequent centuries. Indeed rasaśāstra based on mercury became an important subspeciality of Ayurveda and Srisailam became a noted centre for rasaśāstra studies and practice. Though mercury was also widely used in Europe in the 19th century and less widely in the first

half of the twentieth as diuretics, dental amalgam etc., it is no longer used in modern medicine because of high toxicity. Its use even in dental amalgam is forbidden. However in traditional Ayurveda, and even more in Siddha system, bhasmas as powdery preparations derived from mercury have been used for centuries and the traditional practitioners have claimed that toxic events on administering the bhasmas are rare. This riddle has defied a scientific explanation for many years as the presence of mercury shown by chemical analysis in the bhasmas would bar their therapeutic application. A possible approach for solving the riddle could be a microstructural characterisation of the bhasma which is the product of a complex series of processes spread over several days in Ayurveda. In a study reported from the Bhabha Atomic Research Centre, X-ray Absorption Fine Structure (XAFS) investigation of Rasasindura – a well-known and frequently used mercury derived bhasma – was carried out by Ramanan *et al.* (2015). The Rasasindura was prepared according to standard protocol by Arya Vaidya Sala, Kottakkal, following three distinct steps (i) Pre-treatment of Hg and S with herbal and milk products (ii) Mixing of Hg and S along with herbal ingredients and grinding for five days to produce Kajjali – an intermediate product (iii) Thermal treatment at 600°C of dried Kajjali in porcelain pots, with porcelain lid totally covered with seven layers of clay-smear cloth. The whole pot is covered with clay for total sealing and heated in an open hearth furnace for 24 hours. The cooled pots are opened to collect the bhasma, which appears as a fine dust of brick red colour sticking to the inside surface of the porcelain lid.

The study by Ramanan *et al.* (2015) (showed that Rasasindura has the same structure as non-toxic α -HgS and toxic chemical forms, viz. elemental Hg⁰, organo-Hg are completely absent. Their results demonstrated that nano-crystal ($D_{\text{Rasa}} \approx 24\text{nm}$) units of Rasasindura are robust, defect-free and free of organic molecules. The absence of toxic chemical forms in the virgin medicine (before consumption) could explain its claimed non-toxicity and its robust character would imply nanoparticle integrity during drug release. The report also noted that “Ayurvedic synthesis yielded a better controlled end product than laboratory-based red (α)-HgS: lower size dispersion and better ordered coordination configuration”. Better

size control and coordination ordering could be related to the surfactant-like effect of herbs and prolonged annealing respectively. These controlled parameters could warrant the efficacy of targeted delivery for the Ayurvedic drug.

Task Force in Ayurvedic Biology

The selected reports on the research done in the first round of completed projects give an indication of the aims, policies and performance of ASIIA in less than a decade. Metaphorically, the projects are new sprouts appearing here and there on the ancient but living tree of Ayurveda. As the Task Force in Ayurvedic Biology succeeds ASIIA under the Science and Engineering Research Board, collaboration between scientific and Ayurvedic institutions across India would expand and the number, range and significance of projects would grow in the years ahead. Already young scientists have begun to pursue questions arising from the findings in the first round of projects. For example, could MR spectroscopy monitor the biochemical changes in the brain when Amalaki Rasayana promotes genomic stability in rats? This trend suggests that research in Ayurvedic Biology could become self-regenerating in the second decade and the sprouts here and there would engulf the entire tree!

The Task Force as constituted today consists of biologists, physicians, Ayurvedic experts, and science administrators. Notified on the DST website, it receives project proposals throughout the year, but meets twice a year. All proposals are refereed by scientists and Ayurvedic experts who share an interest in the topic and only those projects which seek to apply the methods of modern science to study the concepts, procedures or the mechanistic basis of therapeutic events in Ayurveda are considered for support. To avoid wasteful duplication of support offered by other agencies, research related to the development of drugs from herbal extracts and clinical trials for safety and efficacy are excluded from the agenda of the Task Force. Once approved, projects are monitored yearly by a Monitoring Committee which may, and not infrequently does, suggest course corrections. All projects are required to involve scientific and Ayurvedic institutions as partners since the Task Force expects to develop a joint culture of

science and Ayurveda in research in the next decade. The early indications are that the initiative to promote Ayurvedic Biology will not fail due to the inherent weakness of scientific ideas but it could languish due to the poverty of response from the scientific and Ayurvedic fraternities.

Conclusion

Literally, Ayurveda means knowledge of life – life in all its forms and varied conditions. The central theme of Ayurveda is the relief of suffering but the center is enlivened by a vibrant background of ideas, topics and images which enhance the power to heal. The range of questions and ideas in the Ayurvedic canvas is as old as the hills and offers enough of interest to the philosopher, physician, environmentalist and biologist. How did the universe with its stupendous diversity evolve from a beginningless, undifferentiated, amorphous existence (*pariṇāma*)? What is the nature of the relationship between the universe and the human body which is composed of identical elements and is a cosmic resonator (*panchabhuta*)? If life span is predetermined by destiny, is Ayurveda of any avail (*daiva*)? If humans “exploit nature” and exhaust resources by “overuse and misuse of senses”, how could one remedy the devastation of the habitat (*janapadodhwamsana*)? Is there a code of conduct which prevents a whole class of diseases brought on by faulty living (*prajñāparādha*)? How does one treat the illness of elephants and horses who are our friends in peace and war (*Gajayurveda, Aswayurveda*)? What about the diseases of plants (*vrikshayurveda*)? What makes mongoose, pigs and dogs sniff and pick plants to nibble when they are sick and not otherwise? Why do fish in the river, lakes and ocean differ in shape and swimming style? One could go on. While the rich quarries of Ayurveda provide plentiful cues for inquiry by the tools of modern science, an investigator of traditional medicine would acknowledge, lest hubris should mar his effort, that Ayurveda is more than a sum total of scientific studies. He would note that the philosophical tradition of Ayurveda would insist that we conceive of the reality of Ayurveda as a whole, which expresses itself not only in scientific insights, but also in Nature which comprehends “innate disposition, beneficence, time, chance, destiny and the evolution of all that exists” (Sharma, 2002).

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