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TRADITIONAL MEDICINE TO MODERN PHARMACOGENOMICS: A RELATION BETWEEN AYURVED AND MODERN MEDICINE ON THE MOLECULAR BASIS

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Abstract: *The recent decade has witnessed many landmark observations, which have added to the scientific credentials of Ayurveda. It is however believed that instead of a retrospective approach of looking into the Ayurveda through the scientific reappraisals, a prospective approach through primary understanding of Ayurveda followed by a search into scientific linkage would be more appealing. This article brings the simplified yet scientific decoding of the core concepts of Ayurveda that form the framework of this ancient science of health. These techniques will be applied for the mechanism-based screening and validation of Ayurvedic herbal drugs will be described in subsequent sections of this article.*
Keywords: *Ayurveda, szcience, tridosha, techniques*

Introduction: The entire world consists of teachers for the wise and enemies for the fools. Therefore, knowledge, conducive to health, longevity, fame and excellence coming even from an unfamiliar source should be received, assimilated and utilized with earnestness"[1] These words of wisdom should continue to guide the 600,000 practitioners of Ayurveda in India today, as well as 400,000 practitioners of modern medicine who may not have familiarity with our glorious ancient scientific heritage. Charak says that "The Science of life shall never attain finality. Therefore, humility and relentless industry should characterize your every endeavor and approach to knowledge. Epitomizing eastern philosophy for its concern to values related to health, Ayurveda is by and large considered to showcase traditional health care. Before the recent upsurge of traditional medicine in a global perspective, Ayurveda was persistently criticized for its ambiguity and philosophical tenets incomprehensible to occidental mind.

Molecular Biology and Molecular Medicine: There was an outstanding development of the 20th century science. Physical and chemical approaches to problems in biology became increasingly productive, giving rise to new concepts in molecular biology and molecular medicine. The confluence of several powerful methods of observation–chemical analysis, electromicroscopy, X- ray crystallography, electron spin resonance (ESR), and nuclear magnetic resonance (NMR) spectroscopy – eventually led to the determination of the precise double helix architecture of DNA, three dimensional configurations of protein molecules and amino acid sequences of their constituent polypeptide chains, and the precise characterization and 3-D strucuture of most biologically active molecules. The synthesis of complex lipids and carbohydrates, the function of cell membranes and partitioning of inorganic ions occur as a secondary consequence of the action of specific proteins. Many of these proteins are enzymes that catalyze the biochemical conversion of one molecule into another. Some are structural proteins such as collagen or elastin; others are regulatory proteins that direct how much of each enzyme or each structural protein is made, when and where.

All this new knowledge can be considered an elaboration of the Ayurvedic concept of *"Rasa Dhatu"* and should be eagerly assimilated by Ayurvedic physicians following

the exhortations of Charak, Sushruta and Vagbhata. We now appreciate the homeostasis is maintained among the 40 trillion cells in the human body through constant communication with each other through signalling molecules (proteins, peptides, amino acids, nucleotides, steroids, retinoids, eicosanoids and small molecules of diffusible and dissolved gases such as nitric oxide and carbon monoxide).

Table 1 : Molecular mechanism of action of Plant–derived drugs (lists herbal drugs whose mechanism of action at the molecular level has been established only in the last 30 years.)

Drug	Plant source	Clinical Observation	Molecular mechanism of action
Artemether	Qinshausu	resistant malaria	Heme–mediated decomposition of endoperoxide generating free radicals
Atropine	Atropa Belladona	Antispasmodic	MAch receptors
Caffeine	Coffee Arabica	Stimulant	Adenosine receptors
Cannabis indica	Indian Hemp	Sedation, antiemetic	Cannabinoid receptors CB1 CB2
Cocaine	Leaves of Coca	Addictive drug	Blocks DAT, NET, SERT
Colchicine	Colchicum autumnale	Relief of pain in gout	Inhibits release of leucocyte derived chemotactic factors
Digitalis	Foxglove	Relief of dropsy	N+K+ATPase
Emetine	Ipecacuana	Amoebtic dysentery	Inhibits protein synthesis in eukaryotic cells.
Ephedrine	Ephedra	Bronchodilator	α & adrenoreceptor agonist.
Eserine	Calabar beans	Pupil constriction	Reversible acetyl cholinesterase inhibitor
Morphine	Papavarum somniferum	Analgesic	Opioid receptors
Nicotine	Tobacco plant	Stimulant	Nicotinic Ach receptors
Quinine	Cinchona bark	Fever due to malaria	Inhibits haemozoin crystallization -aggregation of cytotoxic heme
Reserpine	Sarpagandha	Sedation Lower BP	Block VMAT 1, VMAT 2
Salicylic acid	Salixalba,Willow bark	Fever and pain Relief	Cox inhibitor NFκB inhibitor
Strychnine	Nux Vomica	Hyperexcitability Convulsions	Blocks glycine receptors
Vincristine	Vinca rosae	Anti-cancer	Binds to tubulin disrupts microtubule assembly.

Ayurvedic Immunomodulators: Ayurveda describes a number of drugs as Rasayana and Ojovardhak remedies, which are claimed to posses' immunomodulatory effect. Some of the Rasayans which have been subjected to scientific studies and found to possess immunomodulatory effect are Aswagandha (Withania somnifera), Shilajatu, Amalaki (Emblica officinalis), Tulasi (Ocimun sanctum), Guduci (Tinospora cordifolia), Pippali (Piper longum) and Punarnava (Boerhaavia diffusa), of which Guduci and Tulasi have been extensively studied.

The recent trend in evaluation of the herbal immunodulators is towards assessing the activity profile of the isolated principles in a battery of experiments with a view to identify the components responsible for the activity profile of the isolated principles in a battery of experiments with a view to identify the components responsible for the activity as also to understand the mechanism of their action. Amongst diverse class of compounds, it was observed the flavonol series possess the most potent anticomplementary activity. The potent antiphlogistic and antiallergic activity of the flavonoid wedelolactone from Rasayana drug Bhringraj (Eclipta alba and wedelia calandulacea) was found to be due to its 5-lipoxygenase inhibitory activity, suggesting that it act by free oxygen radical scavenger mechanism. The active principles of Guduci (Tinospora cordifolia), an important Rasayana drug, have been found to possess anticomplementary and immunostimulating activities. Previous studies on the extracts of Guduci reported antidiabetic, anti-inflammatory and hepatoprotective activities. Syringin (TC-4) inhibited the invitro immunohaemolysis of antibody coated erythrocytes. The reduced immunohaemolysis was found to be due to inhibition of the C3-convertase of the classical complement pathway. The commounds gave rise to significant increase in IgG antibodies in the serum. Humoral and cell mediated immunity

were also dose dependently enhanced. Macrophase activation was reported for cordioside (TC-2), cardiofolioside–A (TC-5) and Cordiol (TC- 7). These compounds induced significant increase in phagocytic activity by activation of the peritoneal macrophases. It is important recall here that macrophases play an important role in nonspecific and specific immune responses. In innate immunity, the phagocytosis of foreign bodies by macrophases and other phygocytes contributes to regulation of both humoral and cellular immune responses. Macrophases serve as effector cells to provide immune surveillance against tumour cells. Yastimadhu (Glycirrhiza glabra), another important Rasayana drug has been found to be immunostimulative, which accelerates lymphocytic transformation activation of macrophage and increases the leucocyte count. It also have antiallergic, antiinflammatory and antioxidant activity.

Ahar & Nutrition-Nutrigenomics: Ayurved lays great emphasis on *Ahar*, nutrition. It describes *Satwik Ahar* which enabled Rishis and Munis to live for hundred years. In today's parlence Satwik Ahar 400 g fruits and vegetables (*Kanda, moola and phala*) is a low caloric diet (1300 K. cal) which produces the least oxidative stress. It provides essential micronutrients and minerals, high fibre and potassium, low fat and sodium, and *osmotin* (vegetable analogue of mammalian adiponectin). Ayurveda lays great emphasis on breast milk which has ideal ω6-ω3 ratio and essential fatty acids EPA/DHA. Cow's ghee (12 gm) provides 1.2 g EPA/DHA, the essential daily requirement. It would be Interesting to study the various Ayurvedic *Ghruta* based medications for their EPA/DHA content comparing "fresh" ghee with "old" ghee recommended by Ayurveda.

Bioavailability of Ayurvedic Herbal Drugs: Bioavailability of Ayurvedic herbal drugs is a totally neglected subject. Devasagayam's group at BARC used the inverted loop of rat intestine to study the intestinal absorption of *Termenalia Arjuna* extracts as well as the active principle Baicalein. Almost 15% of the baicalein (4 mg/ ml) was recovered from the serosal surface as monitored by HPCL. Both acqueous and methanolic extracts of T. Arjuna were absorbed [2]. Haffkine Institute is establishing this facility where 40 single herbs described by Vagbhata will be studied for absorption: duodenum, jejunum, ileum, colon). This "blind spot" in herbal drug research is frustrating for clinicians who wish to translate the laboratory in vitro data to clinical application. The poor bioavailability of oral curcumin and resveratrol are important illustrative examples.

Medhya Rasayanas: Ayurveda has described 10 herbal drugs as Medhya Rasayanas- *Amalaki, Ashwagandha, Bramhi, Bhringhraj, Jatamansi, Jyotishmati, Mandukparni, Shankhapushpi, Vacha, Yashtimadhu.* A transgenic mouse model of Alzheimer's disease has now become commercially available. At birth these animals are absolutely normal. Within three months they develop all the changes: amyloid plaque deposition, amyloid angiopathy, Tau protein, loss of acetylcholine (*Cholinergic*) neurons, hypometabolism and hypoperfusion in parieto-occipital regions etc. and the animals die within the following 6 months. All these changes can be noninvasively shown by small animal PET/CT and optical imaging without sacrificing the animals. [3] This facility is now available at ACTREC, New Mumbai where a collaborative research project of Haffkine Institute is approved for studying the effect of the 10 medhya rasayans, single and in combinations, in 40 mice: first 3 months to assess the preventive potential and next 6 months to assess curative potential. At present there is no effective treatment for Alzheimer's disease yet $ 15 billion are spent annually on its treatment. If this study provides validation of Medhya Rasayans for prevention of Alzheimer's disease, a world market of $ 15 billion will be available to India..

Rasayana Drugs Act As

a. Immunomodulator: By augmenting or reducing the ability of the immune system.

b. Adaptogen: Increases the ability of an organism to adapt to environmental factors e.g., *Ashwagandha, Tulsi, haridra, Pippali, Amalaki, Guduchi, shatavari.*

c. Antioxidant: Circumvent the damage caused by oxygen free radical.

d. Nootropic: Promote intelligence and functions of brain e.g., *MedhyaRasayana* drugs (namely- *Mandookparni, Guduchi, Yashtimadhu and Shankhpushpi).*

As per Acharya Charak, *Rasayanais defined as* the means of achieving the finest quality of *rasadidhatus* (body tissues) where it increases life span, improves *medha* (intelligence), cures disease, stabilizes youthfulness, improves luster, complexion, voice and makes body and senses strong and healthy etc.

Oxidative Stress and Anti-oxidant: The most glaring example of understanding disease at the molecular level is the damage done by reactive oxygen species and reactive nitrogen species (RNS) through free radicals. Free radicals have several important physiological functions including microbicidal activity, regulation of cell proliferation and growth through apoptosis (programmed cell death) and regulation of vascular tone (through NO). The cells have protective Enzymatic and non enzymatic mechanisms to quench free radicals as soon as they are produced in the mitochondria during biological oxidation. These are superoxide dismutase, catalase, glutathione peroxidase, Glutathione (GSH) and anti-oxidants Vitamin E (tocopherol and tocotrienol), Vitamin C, Vitamin A (Carotinoid) and flavonoids.

This protective mechanism is overwhelmed in many pathological processes increasing oxidative stress. The nervous system has maximum oxidative stress and cumulative effect over decades underlies neurodegenerative disorders such as Parkinson's Disease and Alzheimer's disease. Human plasma has many antioxidants: albumin, bilirubin, ceruloplasmin, transferrin, haptoglobin, hemopexin, uric acid etc. which protect the vascular endothelium from oxidative stress. evasagayam's group at BARC have shown the effectiveness of 10 Ayurvedic anti-oxidants at various levels : prevention of radical formation, scavenging of primary and secondary radical, breaking chain initiation &propagation, repair of lipid membrane and repair of DNA and other cellular constituents. [4] Guggulsterone, the active principle of Guggul (*comifera mukul*), has properties similar to probucol in reducing oxidized LDL by 40%. This property is more crucial than the cholesterol lowering property.

Unique Molecules from Ayurvedic Herbal Drugs: The most important single event that aroused the interest of modern medicine in Ayurvedic drugs [5]. In *British Heart Journal* on the usefulness of serpina (whole extract of Sarpagandha (*Rauwolfia serpentina*) in the treatment of hypertension. Its pharmacological properties had been investigated earlier. Not only demonstrated antihypertensive effects but also noted certain side effects such as depression, parkinsonism, gynecomastia, dyspeptic symptoms etc. The active principal of *sarpagandha*, reserpine, was identified in 1978. Transporters for biogenic amines: norepinephrine (NE), dopamine, and serotonin were discovered in the 1990's. Abbreviated as NET, DAT and SERT, these transporters are of particular clinical interest since they are the molecular targets of many antidepressants, as well as drugs of abuse such as cocaine and amphetamine. The vesicular monoamine transporters (VMATs) were discovered in 1998. VMAT1 localises in endocrine tissue and VMAT2 localises in neuronal tissue. VMATs play major role in packaging neurotransmitters into distinct secretary vesicles in preparation for subsequent exocytotic release thus controlling the optimal size of each release. Reserpine today is a unique molecule that blocks both VMAT1 and VMAT2, thereby exposing biogenic amines to degradation by MAO. Another molecule tetrahydrobenazine, inhibits VMAT2 but not VMAT1. According to Braunwald (Heart, 6th ed. 2001) “a single daily dose of 0.05 mg reserpine (which is as effective as higher doses 0.125 or 0.25 mg) is the most inexpensive and effective single drug for the control of hypertension but is ignored as it has no commercial sponsors”. Here is an opportunity for Ayurvedic drug companies who make *Sarpagandha ghanavati* to answer 2 crucial questions thet how much watery extract is required to be given orally to match 0.05 mg reserpine and what is the bioavailability. Some other unique molecules from Ayurvedic herbs are Forskolin (which directly activates cell membranebound adenelyl cyclase and cAMP), Boswellic acid (LOX inhibitor).[6]

Nutrition and Immune Response: Calder (2000) has given an excellent review of inflammation in health and disease [7]. He has emphasized the important role of dietary omega-3 polyunsaturated fatty acids namely eicosapentaenoic acid (PUFA-EPA) and docosahexaenoic acid (DHA) in the suppression of pro-inflammatory cytokines, and the need and scope for dietary modification of inflammation.

Increased EPA/DHA in cell membrane phospholipids reduced production of prostanoid (PGI 2, TXA 2, PGD 2, PGE 2, PGF 2α) while increasing the production of prostacyclin and TXA 3, which inhibit platelet aggregation and inflammation.

Conclusion: The very core of Ayurveda is formed from some very basic concepts e.g. panchabhautic theory, the prakriti concept which is used to describe the predisposition to and prognosis of disease as well as governs the choice of the therapy, balance and imbalance of the three dosha (vata, pitta and kapha) in the development of disease. Interestingly, Ayurveda

further expands on these theories to plan interventions that would correct the imbalance. The actions of medicines are described through their various properties (like rasa, guna, veerya, vipaka,and prabhava) based inherently on their elemental composition. It is the need of the hour to use modern technology to explore the relevance of these concepts, so that they may be interpreted in light of contemporary scientific language to offer modern health care.

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