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Introduction :

It is a great honour to be asked to deliver NAMS Golden Jubilee Lecture. I will introduce the subject with a quote from Pandit Jawaharlal Nehru, India's first Prime Minister (who was also the first Honorary Fellow of NAMS India). After visiting the Central Institute of Research in Indigenous System of Medicine at Jamnagar on 2nd November 1955, he observed:

"A fascinating inquiry is going on in this research institute and it may well lead to very fruitful results. The only right approach has to be one of Science, that is of experiment, trial and error. In whatever type of medicine we may deal with, we cannot profit by its study unless we apply the method of Science. Nothing should be taken for granted. Every thing should be tested and proved and then it becomes a part of scientific medicine - old and new."

Charak states "The Science of life shall never attain finality. Therefore, humility and relentless industry should characterize your every endeavour and approach to knowledge. 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". Charak Samhita Viman Sthan 8, 14.

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 (1).

Correspondence : Dr. R.D. Lele, 102, Buena Vista, Gen. J Bhosle Marg, Mumbai-400021. NAMS GOLDEN JUBILEE LECTURE delivered at MLT Seth GSMC & KEM Hospital, Mumbai on November 18, 2011.

Molecular Biology and Molecular Medicine : *21st Century Paradigm :*

The union of biology with physics, chemistry, mathematics and computer science 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, electron microscopy, 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 three dimensional structure 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 that 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). All cells have receptors (on the cell membrane, in the cytoplasm, in the nuclear membrane) which recognize the signalling molecules, whose binding to the receptors trigger signal transduction to produce a specific response. Molecular recognition is a fundamental feature of all biological processes encompassing ligand-receptor, enzyme-substrate and antigen antibody reactions. A receptor is a protein to which a legend or a drug binds to activate or suppress a signal. Thanks to recombinant DNA technology, most of the important signalling molecules and their receptors have been cloned and are now available for research using radioactive ligands (2). It is now possible to image the distribution and function of receptors in the living human body including the brain. The techniques of whole body *autoradiography, micro imaging* in small animals, and *PET* studies in humans provide direct quantitative information about the distribution and site of action of drugs. How 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.

Table 1 lists herbal drugs whose mechanism of action at the molecular level has been established only in the last 30 years. This approach will to be put on a fast track, to study 50 important Ayurvedic herbs.

Table 1 : Molecular mechanism of action of Plant –derived drugs

Drug	Plant source	Clinical observation	Molecular mechanism of action
Artemether	Qinshausu	Chloroquin 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	, 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	Salix alba 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.

The Ayurvedic Concept of Disease as Dissonance- *"Dosha Vaishamya"* due to *Atiyoga* (excessive interaction), *Ayoga* (absent interaction) and *Mithya Yoga* (erroneous interaction) sums up the entire System Biology and ligand-receptor interaction, molecular recognition and signal transduction mechanisms in health and disease.

In the second edition of my book **Ayurveda & Modern Medicine** (2001) I have stated that : 'Molecular Biology and Molecular Pharmacology provide a new interface between Ayurveda and modern medicine, since the Ayurvedic concepts of *Vata, Pitta* and *Kapha* are essentially concepts of molecular biology'.

A detailed narration which lists all known receptors and their radioactive legends and the signal transduction mechanisms provides detailed information that ultimately they all fall in *Three* categories, which conceptually, are the modern versions of *Vata, Pitta, Kapha*.

1. Stimulation or suppression of ion channels – Neurotransmission.
2. Stimulation or suppression of cAMP and cGMP – PKA-Metabolism.
3. Stimulation or suppression of IP3 / DAG and PKC – Structure.

The detailed tabulation is provided under reference no. 2.

Nitric Oxide- "Vayu" :

The role of nitric oxide in cellular signalling has become one of the most rapidly growing areas in biology in the past 3 decades. Nitric oxide (NO) is a gas and a free radical with an unshared electron that regulates an ever-growing list of biological processes, mediated through activation of cGMP dependent protein kinase (PKG). The list of effects of NO that are independent of cGMP is also growing at a rapid rate. Nitroglycerine-nitric oxide doner was used for relief of angina since 1870, over 100 years before the discovery of NO in 1977 (3). There are more than 80,000 publications in the area of NO research. NO functions as an intracellular messenger, an autacoid, a paracrine substance, a neurotransmitter or as a hormone that can be carried to distant sites for physiological effects. It is an interesting thought that NO fully vindicates the *Ayurvedic concept of Vata or Vayu* since it is indeed a *Vayu* (gas) which constitutes non-adrenergic non-cholinergic (NANC) neuronal pathway. Nitric Oxide and Carbon monoxide are two gases which have a unique two-way traffic between the pre-synaptic and post-synaptic neurons unlike other neurotransmitters which have a one-way traffic.

Both a deficiency and excess of NO are involved in several pathophysiological states.

Oxidative stress and anti-oxidant :

The most glaring example of understanding disease at the molecular level is the damage done by ROS (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 anti-oxidants : albumin, bilirubin, ceruloplasmin, transferrin, haptoglobin, hemopexin, uric acid, etc. which protect the vascular endothelium from oxidative stress.

Devasagayam'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 **(Figure 1)** (4).

Dr. Nitya Anand* has shown that 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. Unfortunately this aspect of Guggul is generally overlooked by clinicians.

Unique Molecules from Ayurvedic Herbal Drugs :

The most important single event that aroused the interest of modern medicine in Ayurvedic drugs was Dr. Rustum Jal Vakil's report in 1949 (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 by Sen and Bose (1931) and Paranjape (1942). Sen and Bose not only demonstrated antihypertensive effects but also noted certain side effects such as depression, parkinsonism, gynecomastia, dyspeptic symptoms etc.

**** Chairman, Ranbaxy Science Foundation & Former Director, Central Drug Research Institute, Lucknow.***

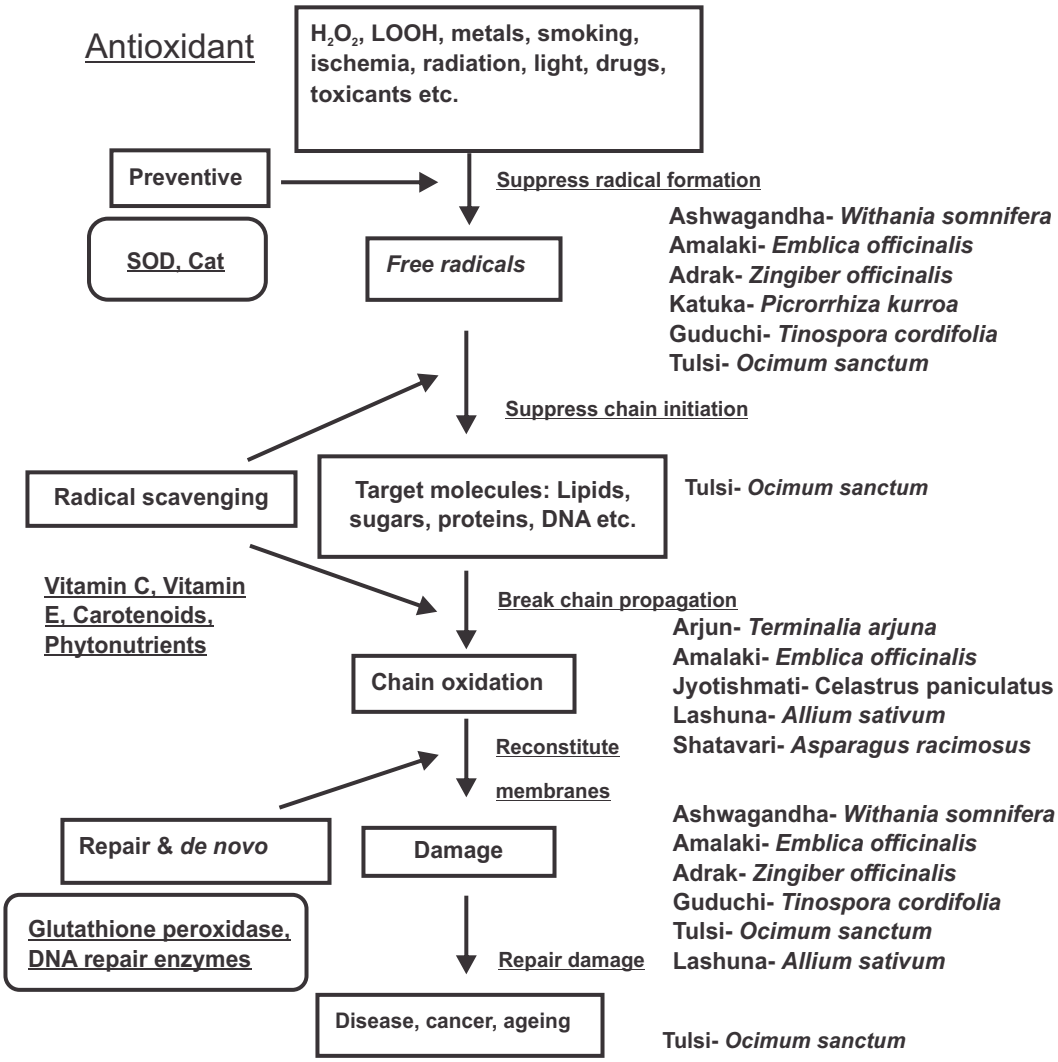

FIGURE 1 : Level of Antioxidant Action

The active principle 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 secretory 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 immediately : How much watery extract is required to be given orally to match 0.05 mg reserpine ? What is the bioavailability?

Some other unique molecules from Ayurvedic herbs are Forskolin (which directly activates cell-membrane-bound adenelyl cyclase and cAMP), Boswellic acid (LOX inhibitor).

Ayurvedic Immunomodulators :

Dahanukar SA and Thatte UM studied six Rasayanas from Ayurved selected because they were specified as ***ekadravyas*** i.e. they can be given as single entities (Gadre 1970). These were Amla: *Emblica officinale*, Ashwagnadha: *Withania somnifera*, Guduchi: *Tinospora cordifolia*, Haritaki: *Terminalia chebula*, Pippali: *Piper longum*, Shatavari: *Asparagus racemosus*.

A dose of 100 mg/kg. was selected to be given orally as total aqueous extract for one to two weeks. They showed that the aqueous extracts of *Guduchi* stimulated the phagocytic and bactericidal activity of neutrophils and macrophages. Pre-treatment with all six Rasayanas was effective in protecting the animals to a varying degree from infection. (6)

At that time not much was known about the key role of NFκB (Nuclear factor kappa B) as regulator of host inflammatory and immune response and cellular growth properties **(Figure 2)**.

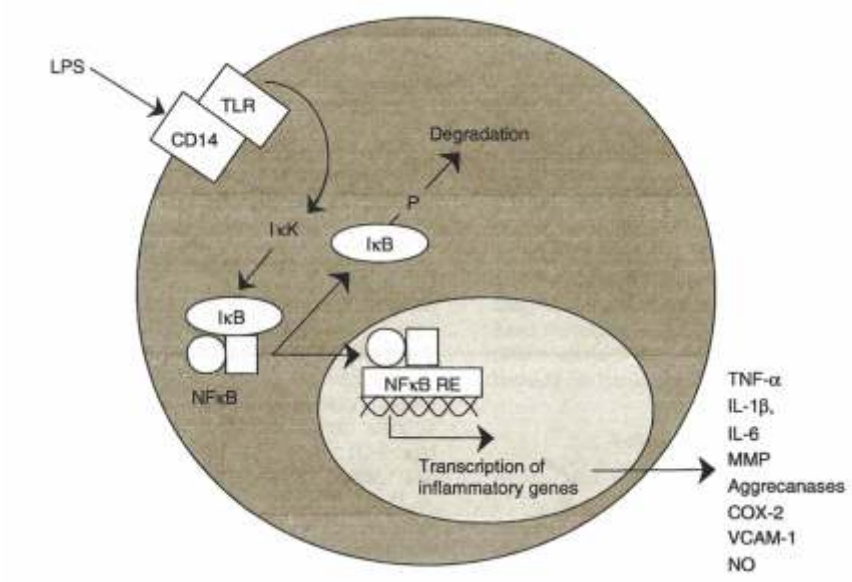

FIGURE 2 : Role of NFκB as regulator of inflammatory response

It is noteworthy that the excellent review by SS Agarwal and VK Singh on Indian Medicinal Plants as Immunomodulators (1999) (7) makes no mention of the NFκB pathway. NFκB increases the expression of specific cellular genes encoding at least 27 different cytokines and chemokines, receptors involved in immune recognition such as members of the MHC proteins involved in antigen presentation, and receptors required for neutrophil adhesion and migration. Cytokines stimulated by NFκB such as IL-1 and TNF also directly activate the NFκB pathways thus establishing a positive autoregulatory loop that can amplify the inflammatory response and increase the duration of chronic inflammation (8).

NFκB also stimulates the expression of enzymes whose products contribute to the pathogenesis of the inflammatory process (eg. iNOS which generates NO and COX-2 which generates prostanoids).

NFκB controls immune response by modulation of B lymphocyte survival, mitogen dependent cell proliferation and isotype switching which lead to the differentiation of B lymphocytes, IL-2 production which increases proliferation and differentiation of T lymphocytes.

IκB protein normally binds to NFκB thereby blocking its nuclear translocation. LPS, phorbol esters, viral infections, ultraviolet radiation and free radicals all lead to degradation of IκB and thereby release and nuclear translocation of NFκB. There is a site and event specificity of NFκB proteins. Tissue

distribution differs for various IκBs. IκB is associated with transient NFκB activation while IκB is associated with sustained NFκB activation.

Most interestingly NFκB activation is also the key pathway for carcinogenesis(9), as indicated by increased NFκB levels in the nuclei of several types of cancer : leukemia, lymphoma, solid tumours- breast, ovary, prostate & colon. There may be mutations inactivating IκB protein that activate NFκB pathway. Inhibition of NFκB pathway may enhance the efficacy of cancer chemotherapy.

The pioneering work of Dahanukar and Thatte has shown that Ayurvedic Rasayans have the capacity of regulating chronic or dysregulated NFκB pathway.

"Ahar" – Nutrition and 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.

Nutrition and immune response :

Calder (2000) has given an excellent review of inflammation in health and disease (10). 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 **(Figure 3).**

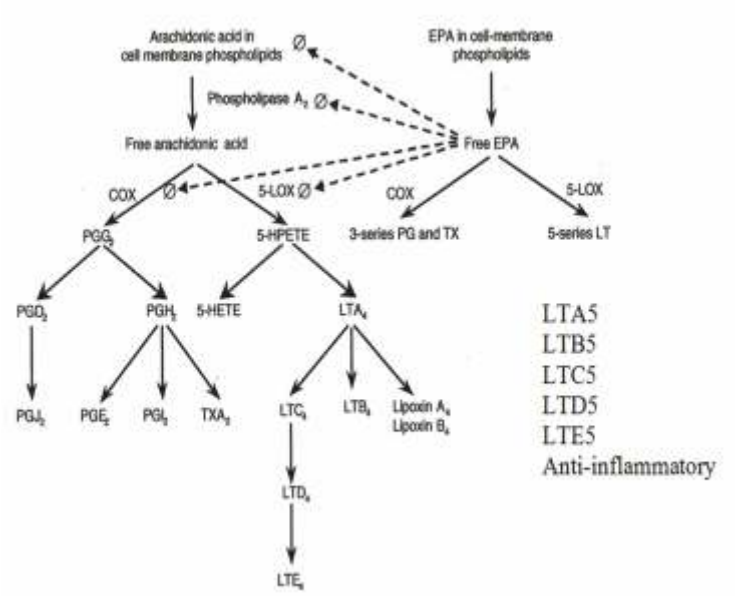

FIGURE 3 : Beneficial effects of EPA/ DHA in cells membrane phospholipids

Adequate amounts of EPA/ DHA in the cell membrane ensure the LOX-mediated production of lipoxins, resolvins (potent anti-inflammatory and immunoregulatory metabolites) and protectins (including neuroprotectins). At nanomolar and picomolar concentrations, they remove inflammatory cells and restore tissue integrity during resolution of inflammation.

Zinc, selenium, vitamins including A, B6, B12, C, E, as well as folic acid are important nutrients whose deficiency affects host immune response and thus susceptibility to infection. The important role of vitamin D has only recently been investigated. Macrophages have receptors for vitamin D, and vitamin D deficiency and vitamin D receptor polymorphism increase susceptibility to tuberculosis (11). There is a two-way interaction between nutrients and human genes (12). How genetic variations influence response to nutrients, and how nutrients influence gene expression, transcription and metabolism are the subject of Nutrigenomics. The effect of maternal malnutrition on fetal insulin–IRS-PI3K AKT pathway is well known to be a basis for insulin resistance and metabolic syndrome.

Cancer Chemoprevention by dietary phytochemicals :

Carcinogenesis is a multi-step process the initiation of which can be blocked or suppressed by dietary phytochemicals. They can also halt or retard the progression of pre-cancerous cells into malignant cells. Central components of the intracellular signaling network that maintains homeostasis are

MAPK, NFκB, AP1, NRF1 as well as β catenin, a component of cell to cell adhesion machinery. Extensive work has been done to elucidate the molecular mechanisms of chemoprevention by Haldi, red chilli pepper, ginger, green tea, honey, garlic, cabbage, broccoli, carrots, tomatoes, grapes, grape seeds and pine bark. These are summarised in **Table 2** (13).

Table 2 : Molecular mechanisms of Chemoprevention by dietary phytochemicals.

1.Curcumin (Haldi):	Inhibits TNFα induced COX2 gene transcription and NFκB & AP1 activation; anti-proliferative, pro-apoptotic and anti-metastatic activities via suppression of B Catenin.
2. Capsaisin (Red Chilli):	Blockade of IκBα degradation and NF κB Translocation into nucleus; induces apoptosis by activation of CJUN. NH2 terminal kinase (JNK) and p38.
3. Gingerol (Ginger):	Inhibits EGF -induced AP.1 activation and neoplastic transformation.
4. EGCG : Epigallocatechin 3 Gallate (green tea)	Blocks activation of AP 1 & NFκB, inhibits PI3K. AKT -NFκB and HER2 / NEU receptor tyrosine phosphorylation; inhibits VEGF, β catenin expression . G0/G1 phase arrest and apoptosis.
5. Caffeic acid phenethylester (CAPE) (honey):	Disrupts the NRF2 -KEAP1 complex. Decrease β Catenin expression; suppress NFκB activation.
6. Diallyl sulphide (garlic) :	Prevents mutagenesis by suppressing ROS
7. Indole -3 Carbinol (cabbage)	Decreases β catenin, inhibits adhesion, migration and invasion of cancer cells
8. Sulphoraphane (broccoli):	Directly interacts with KEPA1; stimulates nuclear translocation of NRF2 which subsequently activates ARE for expression of many anti-oxidant or detoxification enzymes.
9. β carotene (carrot):	Anti-oxidant-suppresses ROS.
10. Lycopene (tomatoes):	Anti-oxidant-suppresses ROS.
11. Resveratrol (grapes):	Inhibits PMA-induced COX-2, PKC and AP1, MMP -9 NFκB; induces apoptosis via activation of p53 via ErK and p38 Down-regulates β catenin.
12. Procyanidin (grape seeds):	Naturally occurring polyphenolic bioflavonoid in grape-seed & pine bark; powerful antioxidant.

Radiolabeling of herbal drugs :

On 25th May 2009 in my Homi Bhabha Birthday Centenial lecture at BARC in Mumbai, I pleaded the urgent need for *application of radiotracer technology for the validation of Ayurvedic Herbal drugs*. Every new molecule introduced in modern therapeutics is first labelled with C-14 to study its absorption, bio distribution & excretion in small animals. The only tritium labelling effort of a Chinese herbal drug Gensing was published in French in 1992. Haffkine Institute's new project with financial support from DST and DBT has been launched in collaboration with BRIT (Board of Research In Isotope Technology). Tritium-labeling of *Arjun Sal* an important Ayurvedic drug has been successfully accomplished as well as tritium-labelling of its active principle baicalein and it has been confirmed that labelling the whole extract also labels the active principle. Its bio-distribution in small animals is being studied by whole body autoradiography especially the brain and heart, since Baicalein inhibits fibrillation of α synuclein and disaggregates existing fibrils in neurons hence may prevent Parkinson's Disease (14).

Baicalein inhibits the binding of a number of chemokines to human leucocytes (CXC, CC, MIP-1β, MCP-1) reducing their migration capacity. This has great relevance to prevention of atherosclerosis which begins as endothelial inflammation (15).

Labeling *Tulsi* leaves with C-14 has also been achieved. Feeding C-14 urea as a manure in plants will be used as a novel approach for radiolabeling of various parts of the plant- bark, leaves, flowers etc. and the C-14 radio-labelled plant parts will be fed to small animals and whole body autoradiography will be performed to study the bio-distribution of the herbal drugs. To begin with, forty single drugs described by Vagbhata will be taken for study. Details about autoradiography will be found in Ref. 2.

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 (16). 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, Bhrughraj, 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 non-invasively shown by small animal PET/CT and optical imaging without sacrificing the animals. 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. Details of small animal PET and optical imaging will be found in Ref. 2.

High through-put screening for mechanism of action :

In my Haffkine Oration 2009, "Beyond Reverse Pharmacology-mechanism-based screening of Ayurvedic Herbal Drugs",(17) I have proposed radioligand displacement assay for mechanism based screening of Ayurvedic drugs (see details in reference no. 2). **Table 3** gives a complete list of receptors for which radiolabeled ligands are available commercially.

As an illustrative example Sukh Dev (1992) in collaboration with a group in USA studied ***Triphala*** (18). Using I^{125} cholecystokinin (CCK) as ligand and mouse pancreatic membrane as receptor they showed affinity of three Ayurvedic herbal extracts – *Termenalia Chebula* (96% ligand displacement), *Termenalia bellerica* (91%) and *Emblica officinalis* (76%) showing that ***"Triphala"*** constituents act on CCK receptors. CCK has receptors both peripheral and central, in GI tract and nervous system, and plays a major role in gut function, digestive processes, in feeding behaviour and in cognitive function. It is surprising that in the last two decades no further efforts were made in this direction. Haffkine Institute has launched a DBT – supported project of mechanisms-based screening of the 40 single drugs described by Vagbhata.

Charak States: "A single drug may have many appellations owing to its diverse actions just as a man is able to perform various actions". Many popular Ayurvedic drugs such as *Ashwagandha, Bramhi, Guduchi, Katuka, Shatavari* etc.

Table 3 : Receptors

Aceytl choline	Neuropeptide receptors
Muscarine	Neurotensin NTS1, NTS2
M1 M2 M3 M4 M5	Nuclear Receptors
Nicotinic α4 β2, α7, 8, 9	Retinoid α, , β
Adenosine A1, A2A, B, A3	Thyroid T3
Adreno receptors α1 A, B, D	Vit. D
Angiotensin AT1a, AT2	PPAR α, β, ϒ, δ
Bombesin BB1, BB2, BB3	Steroid : ER, PR, AR, MCR, GC
Bradykinin B1, B2	Opioid receptors- μ, δ, κ, ORL1
Cannabinoid CB1, CB2	Orexin receptors OX1, OX2.
Cholecystokinin CCK1 & 2	Potassium Channels 7 types
Dopamine D1, D2, D3, D4, D5	Proteinase- activated receptors
GABA A, B, C	PAR1, 2, 3, 4
Gastrin	Protein Prenyl transferases
Glutamate	FTase, GGTase I, II
Gpr. M Glu 1, 2, 3, 4, 5, 6, 7	Prostanoid EP1, 2, 3, 4, DP, FP, IP, TP
Ion ch. NMDA, AMPA, Kainate	Purinoreceptors P2X Ion Channel family
Glycine – inhibitory receptor	P2YG- protein family
Histamine H1, H2, H3, H4	Serotonin Receptors 5HT1, A, B, D, E, F
Imidazole – binding sites I1, I2, I3	Sigma σ1, σ2
Leukotriene BLT1, 2, CYSLY1, T2	Somatostatin SST1, 2, 3, 4, 5
Lysophospholipid STP1, 2, 3, 4, 5	Tachy Kinin NK1, NK2, NK3
LPA receptors LPA1, 2, 3	Vasopressin V1a, b, V2 Oxytocin OT
Melanin MCH1, 2	Vasoactive Intestinal peptide VPAC1, 2,
	PAC1
Melanocortin MT2, MT2, MT3	VECFR1, 2, 3

have multifarious properties ascribed to them. Obviously their molecular targets are shared by many cell systems and cell membrane components such as phospholipase A2, phospholipase C, adenelyl cyclase and cAMP, adenosine receptors, eicosanoids, ion channels and neuroreceptors i.e Dopamine, Serotonin, NE, GABA etc. Based on the described attributes for *Ashwagandha*, I have made a testable hypothesis that it binds to GABA and Sigma receptors which will be verified by radioligand displacement assays.

Chemoprevention of infection:

TL Lentz *et al* reported in *Science* January 1982 that muscarinic acetylcholine receptors serve as receptors for rabies virus. In my letter to the Editor *Science* (8th October 1982 p. 110), I mentioned that *Sushruta Samhita* recommended *Datura stramonium* as a prophylaxis for rabies to be given by mouth immediately after a dog bite in a dose sufficient to produce dilatation of pupils & delirium, which pass in a day or two when the next oral dose is given –

several such doses should be repeated. The treatment should be started as early as possible – once clinical symptoms manifest, the disease is fatal. The active principle of *Datura* blocks mAch R similar to atropine hence *Datura* for rabies represents the first documented example of *'Chemoprophylaxis by receptor blockade'*.

This approach should be explored for Ayurvedic drugs for their ability to provide receptor blockade. Amantadine is the modern example for prevention of influenza by this approach. Acemanaan, derived from Kumari *(Aloe Vera)* is shown to block the entry of HIV in T cells by CCX4 receptor blockade.

I suggest that Caenorhabditis elegans *(C.elegans)* is a useful laboratory nematode model for *in vivo* testing of microbial virulence, pathogenesis and innate host immune defence mechanisms. Many human pathogens affect C. elegans - Legionella pneumophila *(L.pneumophila), staphylococcus aureus, streptococcus pneumoniae & pyogenes, enterococci, salmonella yersinia pestis, pseudomonas, listeria monocytogenes, cryptococcus neoformans* etc. and hence this is a useful model to study possible receptor blockade capability of Ayurvedic herbal drugs (19).

Chemoprevention: future approach in Medicine :

Based on the vast information provided by genomics, transcriptomics, proteomics, metabolomics and epigenetics, it has become possible to determine each individual's *Prakriti* on which Ayurveda lays great stress, and provide *personalized medicine* on which Ayurveda and Homeopathy lay great stress. Promotion of positive health and chemoprevention of infection (Tuberculosis, viral infections including HIV), malignancy, neurodegenerative disorders (Alzheimer's, Parkinson's Disease), metabolic syndrome (diabetes, hypertension, atherosclerosis) should be the major focus of future Ayurvedic drug research. By scientific validation of Ayurvedic herbal drugs, apart from health benefits, a large share of global drug market will flow to India. Current global herbal market of US $ 70 billion is growing annually at 10-15%, Global nutraceutical market is US $ 142 billion. India's share in this is very low. What we need is vision and imaginative thinking and swift action as outlined in my four ongoing DBT / DST supported Research Projects to validate 50 Ayurvedic herbal drugs and to capture India's share in this huge market (20).

Far more valuable than money, for India and the world is the unique Ayurvedic emphasis on ethical conduct as a pre-requisite for health and longevity. "The wise man should control the impulses of fear, grief, anger, hatred, malice, jealousy, lust, greed and excessive attachment. These impulses are injurious to the body and to the mind."

I end up with the universal Ayurvedic prescription: "Any one who

takes proper diet and exercises regularly, who deliberates all his actions, who controls his sexual pleasures, who is just, generous, truthful and forgiving, and who can get along with his kin, is assured a long healthy and happy life".

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