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Rasayana - A therapeutic approach for longevity through maintenance of homeostasis, Immunity and Rejuvenation

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ABSTRACT

Human beings are longing for a healthy long life in terms of physical, spiritual and psychological parameters from time immemorial. However aging is a natural inevitable phenomenon associated with adverse progressive changes leading to decline in vigor etc, as a result human body is vulnerable to many diseases. Many factors accelerate this universal phenomenon like malnutrition, emotional conflicts, mental imbalances due to current hectic life schedule, chemical and radiological hazards followed by trauma and various diseases. Moreover, towards middle age, the rate of catabolic events happening in the body increases considerably to a higher extent. These in turn cause digestive and metabolic disturbances somehow linked with stress and anxiety. These interfere with the production of proper quantity and quality of Agni (bio-digestive fire) resulting quantitative and qualitative depletion in *Ojas* (essence of all tissue elements) along with its distribution to various *Dhatus* (tissues) and *Avayavas* (organs). *Rasayana chikitsa* (Rejuvenation therapy) is one of the most indispensable branches of Ayurveda which enhances rasa (digestive end products) and thereby helps to attain longevity, immunity etc. The *Rasayana* therapy maintains the balance between anabolism and catabolism in the body in the form of anti-oxidants, immune-modulators and as anti-aging agents. It is a blessing for the management of multidrug drug resistant cases as well as immune-compromised patients in addition to routine disease management. In this article author tried to elaborate various ancient *Rasayana* methods mentioned in the Indian traditional system of medicine for the preserve the healthiness specifically substantiated basis of current clinical research outcome in respect to organ wise, age wise & disease wise.

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Keywords: Anti-aging, *Ayurveda*, Immunity, Immunomodulators, *Rasayana*, *Vyadhikshamathwa*

1. INTRODUCTION

Homeostasis is the concept explains how an organism can maintain more or less constant internal conditions that allow it to adapt and to survive in the face of a changing and often hostile external environment. Homeostasis is the result of the complex interaction and competition between multiple negative and positive feedback systems and provides the basis for physiological regulation.[i] The disruption of homeostatic mechanisms leads to disease, and effective therapy must be focused toward reestablishing these homeostatic conditions. The role of immune system is to protect the organism from the alterations inside the body and against the agents penetrating from outside (bacteria, viruses, and protozoa). The remodeling of the immune system, which can be observed in elderly people, is undoubtedly not a cause of aging, but a consequence of it, which helps to suit immunity to the requirements.

According to the current theories of oxidation-inflammation to describe the aging process, the immune system seems to be involved in the chronic oxidative and inflammatory stress conditions of aging. Many diseases are due to “oxidative stress” that results from an imbalance between formation and neutralization of free radicals. Free radicals are produced in the body as byproducts of normal metabolism, as a result of exposure to radiation and some environmental pollutants. Because they are highly reactive, they can damage cellular components and are implicated in a variety of diseases.

Free radicals are normally neutralized by efficient systems in the body that include the antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and the nutrient-derived antioxidant small molecules (vitamin E, vitamin C, carotenes, flavonoids, glutathione, uric acid, and taurine). In healthy individuals, a delicate balance exists between free radicals and antioxidants. In some pathologic conditions such as diabetes and in critically ill patients, oxidative stress causes the level of antioxidants to fall below normal. Antioxidant supplements for such conditions are expected to be of benefit. As a preventive measure against

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certain diseases, the best approach for healthy individuals is to regularly consume an adequate amount of antioxidant-rich foods or herbs.[ii]

Rasayana Chikitsa (therapy) is a unique branch of Ayurveda which is aiming at rejuvenation and geriatric care. *Rasayana Chikitsa* has importance from both the preventive and curative aspect of the disease. *Rasayana Chikitsa* benefits can be achieved through drugs, diets, behavior and regimens which rejuvenate the body and psyche by delaying aging and preventing diseases and thereby promote longevity.

Indian traditional system of medicine has elaborately mentioned about *Rasayana Chikitsa* specifically in Ayurveda main commentary *Charaka Samhita* described a comprehensive chapter on *Rasayana* therapy dealing with the physiological, behavioral, pharmacological, therapeutic aspects of the *Rasayana* therapy.

2. Benefits of *Rasayana* therapy

Basis of recent published clinical researches and review of meta-analysis of various journals authors tried here to compare and highlight therapeutic approach of *Rasayana* therapy for maintenance of homeostasis, Immunity and Rejuvenation basis of their pharmacological actions (Table 1)

Pharmacological effects	**Drugs**	**Botanical Name**	**Mode of action**	**Reference**
Anti-ageing	*Amalaki*	Phyllanthus emblica	• Increase in telomerase activity* with no discernible change in telomere length	iii
	Aswagandha	Withania somnifera	• Enhance telomerase activity • Anti-genotoxic effects** against H2O2-induced DNA damage in human peripheral blood lymphocytes	iv v

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Memory & Intelligence	*Brahmi*	Bacopa monniera	• Bacosides A and B- induce membrane dephosphorylation, with concomitant increase in protein and RNA turnover in specific brain areas • Enhance protein kinase# activity in hippocampus which contribute to nootropic action • Reverse the depletion of acetylcholine, the reduction in acetyl cholinesterase activity and the decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus, induced by neurotoxin, colchicines	vi vii viii
	Sankha pushpin	Convolvulus pluricaulis	• Phytonutrients like Scopoline ß-Sitosterol,Convolvidine, Subhirsine, Convolvine,Convoline and Confoline improving memory	ix
	Mandukaparni	Centella asiatica	• Inhibit the memory impairment induced by scopolamine through the inhibition of AChE. • DNA damage protection activity	x xi
	Guduchi	Tinospora cordifolia	• Mechanism of cognitive enhancement is by immunostimulation and increasing the synthesis of acetylcholine, this supplementation of choline enhances the cognition.	xii
	Jatamamsi	Nardostachys jatamamsi	• Rhizomes contain a terpenoid ester, nardostachysin, which is proven to improve learning and memory	xiii
Anti-oxidant	*Amalaki*	Phyllanthus emblica	• Potent scavenger of hydroxyl and superoxide radicals in vitro • Enhanced GSH levels in cells at higher concentrations of E. officinalis, suggesting its potency to increase the antioxidant molecule. • E. officinalis exerts significant antioxidant effect in HepG2 cells by reducing generation of ROS and LHP and enhancement of reduced GSH levels, which may be effective under pro-oxidant exposure conditions in the cell.	xiv xv xvi
	Ashvagandha	Withania somnifera	• Methanolic extract of the plant exhibited significant free radical scavenging potential	xvii

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			and protected DNA damage induced by hydrogen peroxide	
	Guduchi	Tinospora cordifolia	• Myriad actions of Guduchi may be attributed to its antioxidant	xviii
	Jyotishmati	Celastrus paniculata	• Antioxidant activity by decreasing the lipid peroxidation	xix
	Kushmanda	Benincasa hispida	• ROS scavenger ##	xx
	Tulsi	Ocimum sanctum	• Increasing the body's levels of anti-oxidant molecules such as glutathione and enhancing the activity of anti-oxidant enzymes such as superoxide dismutase and catalase, which protect cellular organelles and membranes by mopping up damaging free radicals caused by lack of oxygen and other toxic agents.	xxi xxii xxiii
Immunomodulation	*Guduchi*	Tinospora cordifolia	• Rich source of trace elements (Zinc and Copper) which act as antioxidants and protects cells from the damaging effects of oxygen radicals generated during immune activation. • The active phytoconstituents, Tinocordioside, Cordifolioside A, Magnoflorine, and Syringin are known for its immunomodulatory effect	xxiv xxv
	Tulsi	Ocimum sanctum	• Bioactive principle of leaf extract of O. sanctum, like ursolic acid, oleanolic acid and salrigenin possess immunomodulatory potential which is indicated by % increase in neutrophil and lymphocyte and enhanced activity of the phagocytosis of the PMN cells in the bovine mammary gland and resulted in the reduction of TBC. • Enhanced cell mediated immunity and lymphoproliferation in poultry infected with IBD virus by the use of O. sanctum.	xxvi xxvii
	Yashtimadhu	Glycyrrhiza glabra	• Reduced plasma levels of TNF-α and IL-6, and increased IL-10 production in LPS-treated mice • Purified polysaccharides obtained from G. glabra was found to modulate macrophage immune functions • Polysaccharides from G. glabra decreases	xxviii xxix xxx

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			TNFα and enhance the levels of IL-2, IL-6, IL-7 and serum antitumor cytokines	
	Amalaki	Phyllanthus emblica	• Corilagin - Inhibits MPO, MDA, and translocation of NF-κB and inhibits ROS and NO production. Inhibits fMLP-induced chemotaxis in human PMN cells • Geraniin - Inhibits production of ROS and NO Inhibits pro-inflammatory cytokine release, Inhibits PHA-induced lymphocyte proliferation in human PBMCs • Gallic acid - Inhibits production of ROS and NO Inhibits pro-inflammatory cytokine release Inhibits PHA-induced lymphocyte proliferation in human PBMCs • Ellagic acid - Inhibits fMLP-induced chemotaxis in human PMN cells Inhibits PMA and zymosan-induced ROS release and LPS-induced NO release in macrophages Reduces phagocytic activity of human PMN cells	xxxi
	Ardrak	Zingiber officinale	• Gingerols have been shown to inhibit protein kinase B (Akt) and nuclear factor kappa B (NF-κB) activation, thus causing an increase in anti-inflammatory cytokines and a decrease in proinflammatory cytokines • 6-gingerol is effective in reducing high NO affords protection against host cell death • 6-gingerol have the capacity to increase lymphocyte proliferation	xxxii xxxiii xxxiv
	Nimba	Azadirachta indica	• Neem oil is shown to selectively activate the cell-mediated immune mechanisms that elicit an enhanced response to subsequent mitogenic or antigenic challenges by acting as a non-specific immunostimulant	xxxv
	Ashvagandha	Withania somnifera	• A mixture of sitoindosides IX, X, glycol, and anolides isolated from the plant statistically enhanced the immunomodulatory effect by activation of macrophages and lysosomal enzymes	xxxvi

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Strengthens the sense organs	*Triphala*	*Amalaki (Phyllanthus emblica)* *Bibhitak (Terminalia belerica)* *Haritaki (Terminalia chebula)*	• Triphala churna significantly reduced oxidative stress in lens homogenate. • Triphala churna significantly delayed the progression of diabetic retinopathy in STZ induced diabetic rats. • Triphala significantly restored glutathione levels in eye lenses. Triphala prevents selenite-induced experimental cataractogenesis in vitro and in vivo.	xxxvii xxxviii xxxix
Adaptogenic action	*Shatavari* root	Asparagus racemosus	• A. racemosus is known to have adaptogenic properties by regulating the stress-induced modulation in neurotransmitters like 5-HT, DA, and NA • Extracts of A. racemosus decreased the stress-induced increase in the tribulin, an endogenous marker for stress	xl xli
	Aswagandha	Withania somnifera	• WSG (bioactive glycowithanolides) induced an anxiolytic effect and antidepressant effect • The role of the plant for synergistic activation of the differential gamma-aminobutyric acid receptor as a potential pathway for the adaptogenic and neurological disorders (anxiety, nervous exhaustion, insomnia, etc.) in mice was investigated and found to be prominent	xlii xliii
	Kalamegha	Andrographis paniculata	• Andrographolide, a diterpene lactone from Andrographis paniculata, could be a promising stress trigger thermoregulatory agent	xliv
	Brahmi	Bacopa monniera	• Cognitive adaptation to stress was due to the normalization of monoamine and corticosterone levels in the hippocampus and cortex which were induced by Bacopa monnieri (L.)	xlv
	Kuberaksha	Caesalpinia bonduc Roxb	• Caesalpinia bonduc Roxb. (Caesalpiniaceae) seed extracts shown adaptogenic activity in cold stress model and swim endurance model, the seed coat as well as kernel extracts showed significant antistress activity when administered orally at a dose of 300 mg/kg.	xlvi
	Haridra	Curcuma	• Administration of curcumin (25 and 50	

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		longa L.	mg/kg) significantly attenuated chronic stress and chronic unpredictable stress-induced alterations in corticosterone, glucose, cholesterol and creatine kinase levels. • Administration of curcumin attenuated chronic stress and chronic unpredictable stress-associated increases in oxidative stress in terms of reduction in TBARS and elevation of glutathione levels, suggesting that the free radical scavenging property of curcumin may also be playing a key role in its adaptogenic and anti-amnesic activity.	xlvii xlviii
Anti-microbial	*Kantakari*	Solanum xanthocarpum	• The antimicrobial activity of AgNP (silver nanoparticles) was explored against multidrug-resistant (MDR) Gram-negative clinical isolates including Escherichia coli, Shigella spp., Aeronomonas spp. and Pseudomonas spp. • Extracts of Solanum xanthocarpum contains alkaloids and flavonoids which showes high sensitivity to Klebsilla pneumoniae and Salmonella typhi, moderate sensitivity to Escherichia coli and less sensitivity and resistant to Bacillus cereus	xlix l
	Ashvagandha	Withania somnifera	• Monomeric glycoprotein isolated from root tuber of the plant inhibited the growth of fungi such as Fusarium oxysporum, Aspergillus flavus, and Fusarium verticilloides, and bacterium such as Clvibacter michiganensis subsp. • Butanolic sub-fraction of methanolic root/leaf extract of the plant exhibited significant antibacterial potential against Salmonella typhimurium while oral administration of aqueous leaf/ root extract of W. somnifera exhibited bacteriostatic effect against S. typhimurium similar to chloramphenicol, the standard drug	li lii
	Nimba	Azadirachta indica	• The fungicidal potential of the tree is due to the presence of azadirachtin and nimbin. • The antimalarial activity of the limonoids	liii

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			(meldenin, isomeldenin, nimocinol, and nimbandiol) isolated from the ethanolic extract of fresh neem tree was reported to be active against chloroquine-resistant P. falciparum strain K1 • An acetone-water extract of neem leaves was found to prevent the invasion of human lymphocytes by human immunodeficiency virus (HIV), thereby protecting the target cells without any adverse effects • Mahmoodin, a novel limonoid, isolated from neem oil, showed significant antibacterial activity against various Gram-positive and Gram-negative bacteria • Crude aqueous extract of neem leaves was reported both in vitro and in vivo to display antiviral activity against the replication of Dengue virus type-2	liv lv lvi lvii
	Amalaki	Phyllanthus emblica	• The essential oil contain β-caryophyllene, β-bourbonene, 1-octen-3-ol, thymol, and methyleugenol showed a broad spectrum of antimicrobial activity	lviii
	Tulasi	Ocimum sanctum	• Ocimum sanctum essential oil have significant antifungal activity against Candida, including azole-resistant strains	lix
	Vasa	Adhatoda vasica	• Rich source of quinazoline alkaloids, such as vasicine, vasicinone, deoxyvasicinone, vasicol, and adhavasicinone. Studies have shown that plant secondary metabolites have antimicrobial activity against hazardous pathogens • Ethanolic extracts exhibited antimicrobial activity against E. coli and S. aureus	lx lxi
	Ardrak	Zingiber officinale	• Ginger extract (10 mg/kg) intraperitoneally had a dose-dependent anti-microbial activity against Pseudomonas aeruginosa, Salmonella typhimurium, Escherichia coli and Candida albicans	lxii
Anticancerous action	*Tulsi*	Ocimum sanctum	• Prevent cancers caused by toxic compounds by reducing DNA damage and inducing apoptosis in precancerous and cancerous cells, thereby reducing the	lxiii lxiv lxv

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			growth of experimental tumors and enhancing survival.	
	Yashtimadhu	Glycyrrhiza glabra	• Ability of the polysaccharides to up-regulate anticancer cytokine IL-7, which is important in proliferation and maturation of immune cells and it is associated with better prognosis in cancer.	lxvi
	Ardrak	Zingiber officinale	• 6-gingerol inhibits anchorage-independent cancer cell proliferation in HCT116 colorectal cancer cells by reducing leukotriene A4 hydrolase (LTA4H) activity	lxvii
	Amalaki	Phyllanthus emblica	• tannins from Phyllanthus emblica have been demonstrated to prevent mutagenesis and lipid peroxidation in response to carcinogens and reactive oxygen species • P. emblica exhibits its anticancer activities through inhibition of AP-1 and targets transcription of viral oncogenes responsible for development and progression of cervical cancer thus indicating its possible utility for treatment of HPV-induced cervical cancers.	lxviii lxix
	Nimba	Azadirachta indica	• Azadirone, a limonoidal constituent isolated from methanolic extract of neem flowers, was found to be a potent cytotoxic agent with good in vitro and in vivo activities • Pre-treatment with ethanolic neem leaf extract significantly lowered the concentration of lipid peroxides and increased antioxidant levels on induced oxidative stress by the potent gastric carcinogen N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) in male Wistar rats suggesting its chemoprotective effects • Nimbolide, a triterpenoid extracted from the flowers of the neem, was found to have antiproliferative activity and apoptosis-inducing property against U937, HL-60, THP1, and B16 cancer cell lines • Neem oil limonoids were found to induce caspase-dependent and apoptosis-inducing factor-mediated apoptosis, as well as	lxx lxxi lxxii lxxiii

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			autophagy in cancer cells • Terpenoids from Azadirachta indica are potent inhibitors of Akt and hitherto demonstrate anticancer potentials.	lxxiv
	Ashvagandha	Withania somnifera	• Withanolides isolated from W. somnifera inhibited the growth of cancerous cells in the central nervous system, lungs, breasts, and colon cell lines. It was investigated that withaferin A significantly reduced the growth of breast and colon cancer cell lines more effectively than famous anticancer drug doxorubicin • Withanolide D isolated from leaves of W. somnifera showed exceptional antileukemic activity. The antileukemic activity of withanolide D was mediated by ceramide accumulation after activation of N-SMase2 which in turn enhanced the apoptotic activity of neoplastic cells	lxxv lxxvi
Antiinflammatory	*Tulsi*	Ocimum sanctum	• Eugenol and linoleic acid content and the inhibition of both the cyclooxygenase and the lipoxygenase pathways of arachidonic acid metabolism.	lxxvii lxxviii
	Ardrak	Zingiber officinale	• Gingerols are very active in inhibiting both prostaglandins and leukotrienes in RBL-1 cells, and that gingerols with long alkyl side chains are more potent inhibitors of leukotrienes synthesis than of prostaglandins synthesis	lxxix
	Ashvagandha	Withania somnifera	• Alcoholic extract of the plant leaves depicted significant anti-inflammatory activity by inhibiting tumor necrosis induced activation of Iκβ kinase responsible for activation of NFκβ.	lxxx
Cardioprotective effect	*Ashvagandha*	Withania somnifera	• The cardioprotective effect of the plant extracts at a concentration of 40 mg/kg of body weight in an isolated rat heart model was observed. It was discovered that the extract had significant cardioprotective ability in ischemia and reperfusion injuries with reduced infarct size	lxxxi
	Arjuna	Terminalia arjuna	• T. arjuna bark extract has a significant prophylactic and therapeutic beneficial	lxxxii

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			effect on protection of heart against isoproterenol (ISO)-induced chronic heart failure (CHF) through maintaining endogenous antioxidant enzyme activities, inhibiting lipid peroxidation and cytokine levels.	

Table 1; Depicting the outcome of recently published clinical researches and review of meta-analysis of various journals demonstrating the pharmacological action of various Rasayana drugs.

*Telomerase activity - Telomerase activity, the ability to add telomeric repeats to the chromosome ends, is present in germline, hematopoietic, stem, and certain other rapidly renewing cells but extremely low or absent in most normal somatic cells. ** Genotoxicity - It is the ability of different agents to produce damage to genetic material. #Protein kinases - These enzymes that regulate the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thereby inducing a conformational change from an inactive to an active form of the protein. ##ROS scavenger - A chemical substance added to a mixture in order to remove reactive oxygen species

3. Classification of Rasayana

A. Rasayana as per contents

1. *Dravyabhuta rasayana* (through pharmacological therapy)
2. *Adravyabhuta rasayana* (through non-pharmacological therapy)

B. Depending on the procedure

1. *Kuti pravesika rasayana* (Indoor method of consuming *Rasayana* by entering into an isolated and specially constructed cabin and staying therein for the purpose of providing rejuvenation)
2. *Vatatapika rasayana*(outdoor method-the person continues with his routine activities, while using Rasayana)

C. Based on diet and life style

1. *Aushadha rasayana* (*Rasayan* through pharmacological therapy)
2. *Ahara rasayana*(*Rasayan* through dietary measures)
3. *Acara rasayana*(*Rasayana* through good conduct & behavior)

D. According to Prabhava (Effect)

1. *Samsodhana rasayana*(*Rasayana* through bio-purification measures)

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2. *Samsamana rasayana*(*Rasayan* through palliative measures)

E. According to the selection of Rasayana

1. *Kamya rasayana* – *Rasayana* for Promotion of general health for enhancement of longevity
2. *Naimittika rasayana* – Disease specific *rasayana* measures
3. *Ajasrika rasayana* – *Rasayana* measures in daily routine

4. Time directions for Rasayana therapy

Sushruta and *Vagbhata* recommended the *Rasayana* therapy during early adult and middle age of one's lifetime which helps to slowdown the rate of many age related and other pathological conditions. Sharanghadhara have described age wise loss of various factors in the body.[lxxxiii] And various experts in this field have been suggested many *Rasayana* drugs which can redeem the depletion in each decade of life. Here mentioning the concept of recommended the *Rasayana* therapy authpored by *Acharya Sharanghadhara* in respect of every 10 years (Table 2)

Decades of life (In years)	**Natural decay**	**Indicated Rasayana**		**Botanical name**
1-10	*Balya* (strengthening measures)	*Vacha*		Acorus calamus
		Swarna bhasma		Gold
11-20	*Vriddhi*(vitalizing measures)	*Aswagandha*		Withania somnifera
		Bala		Sida cordifolia
21-30	*Chavi*(complexion enhancing measures)	*Amalaki*		Phyllanthus emblica
		Loha bhasma		Iron
31-40	*Medha*(wisdom promoting measures)	*Shankhapushpi*		Convolvulus pluricaulis
		Jyothishmati		Celastrus paniculatus
		Brahmi		Bacopa monniera
41-50	*Tvak*(measures to strengthen the skin)	*Bringaraja*		Eclipta alba
		Priyala		Buchanania latifolia
		Jyothishmati		Celastrus paniculatus
51-60	*Drishti*(measures to strengthen the Eyes)	*Triphala*	*Amalaki*	Phyllanthus emblica
			Bibhitak	Terminalia belerica

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			Haritaki	Terminalia chebula
		Shatavari		Asparagus racemosus
		Jyothishmati		Celastrus paniculatus
61-70	*Shukra*(measures to strengthen the sperm)	*Ashvagandha*		Withania somnifera
		Kapikacchu		Mucuna pruriens
71-80	*Vikrama*(measures to strengthen the vigor)	*Bala*		Sida cordifolia
		Amalaki		Phyllanthus emblica
81-90	*Buddhi*(measures to strengthen the brain power/ intelligence)	*Brahmi*		Bacopa monniera
		Shankhapushpi		Convolvulus pluricaulis
91-100	*Karmendriya*(measures to strengthen the organ of action)	*Ashvagandha*		Withania somnifera
		Bala		Sida cordifolia

Table 2: Age wise decay of different biological factors according to *Sharanghadhara* and useful *Rasayana* drugs.

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Organ specific action of Rasayana drugs

On the basis of analysis of various Rasayana dravyas mentioned in Ayurvedic classics, some drugs show specific action in particular organs in the body (Fig.1)

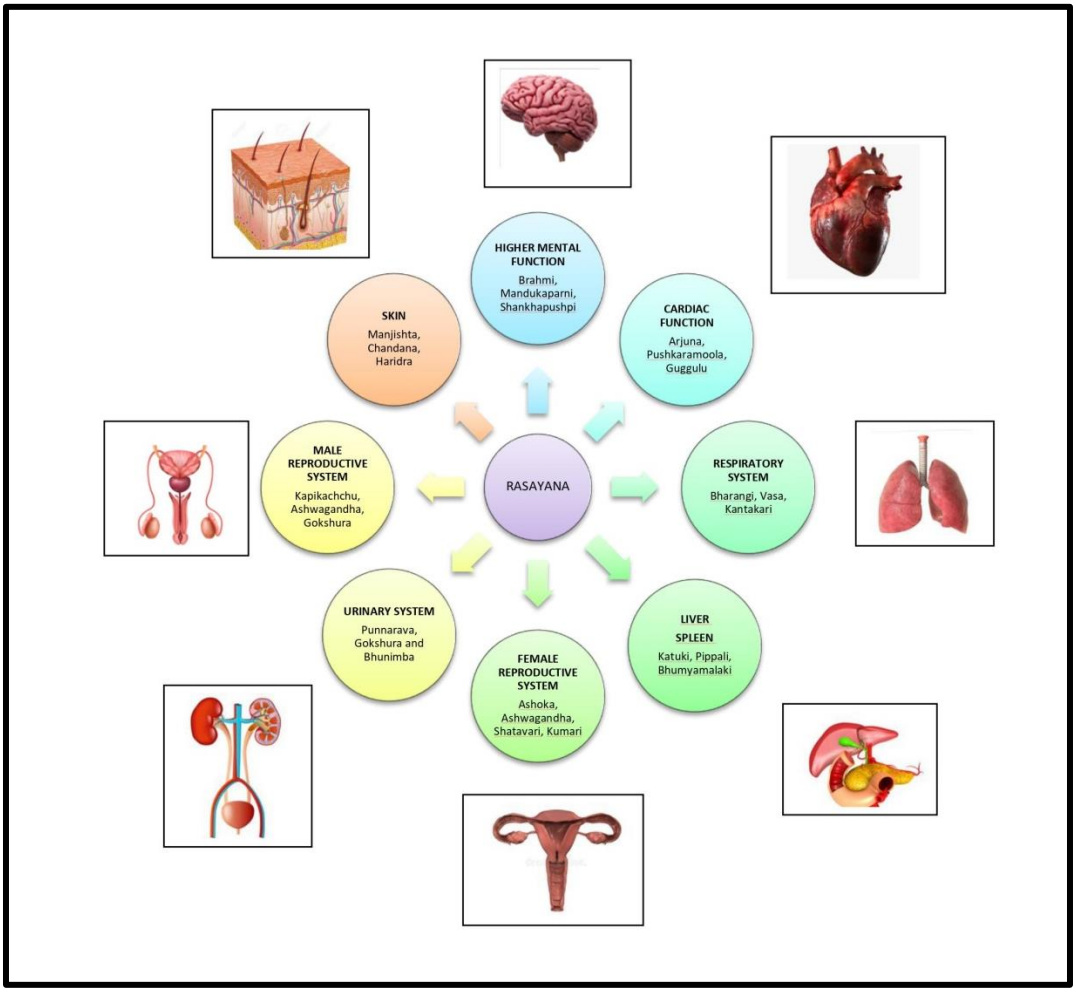

Figure 1 : Showing organ specific action of various Rasayana drugs

5. Mode of action of Rasayan Therapy

A. In respect to Ayurveda understanding

Rasayana drugs are used for preservation of positive health. *Sushruta* described that "Health is a state of homeostasis of *Doshas, Agni, Dhatus* associated with wellbeing & pleasantness of soul, the sense organs and mind". *Rasayana* is a specialized approach of treatment influencing the fundamental aspect of body i.e. *Dhatu, Agni, Ojas* and *Srotas*. It is predicted that different

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Rasayana drugs may act at different level to correct the morbidity situated at various systems. These comprehensive effects are brought about with the help of the varied Pharmacodynamic properties of *Rasayana* drugs. *Rasayana* effect is not a specific pharmacological action but is a complex phenomenon operating through a comprehensive mechanism involving the fundamental factors like *Rasa-Samvahana, Dhatus, Agni, Ojas* and *Srotas.* Considering the Ayurvedic concept of physiology it may be presumed that a *Rasayana* agents promotes nutrition through one of the following the modes.

At the level of Rasa: The *Rasayana* drugs acts at level of *Rasa* by improving specific nutritional values of *Poshaka Rasa*. Probably such type of *Rasayana* drugs are having *Madhura* (sweet), *Guru*(heavy), *Snigdha* (unctuous) and *sheeta* (cold) properties act at the level of Rasa by promoting the nutritional value of the tissue plasma, which in turn helps in obtaining the best qualities of *Dhatus*. By direct enrichment of the nutritional quality of rasa which effects *Dhatu poshana,* the drugs like *Satavari*, milk etc act facilitate *Dhatu poshana*.

At the level of Agni: Some *Rasayana* drugs have a fundamental effect at the level of Agni i.e. at the level of digestion and metabolism. The drugs which possess the *Ushna*(hot), *Laghu*(light), *Ruksha*(rough) and *Katu*(pungent), *Tikta*(bitter), *Kashaya rasa*(astringent taste) may acts at level of *Agni*, vitalizing the organic metabolism leads to an improved structural and functional pattern of tissues leading to production of the best quality *Rasayana* effects. Drugs such as *Pippali,Guggulu,Rasona, Bhallataka, Rudanti, chitraka* mainly acts at level of *Agni*, so improve the digestion and create excellence of *Saptadhatu*(seven vital tissues). The *Rasayana* drugs like *Vidanga,Chitraka,* and *Haritaki* are found to enhance *Agni* status at the level of *Jatharagni*. Similarly *Amalaki, Amrita, Pippali, Kumari* are supposed to be act at the level of *Dhatvagni*(bio-digestive fire situated at tissues) which may leads to the excellence of all *Dhatus*.

At the level of Srotas: Some *Rasayana* drugs have a fundamental effect at level of *Srotas* i.e. micro & macro channels. These drugs help the bioavailability of nutrients to all the tissues and improve tissue perfusion. The *Rasayana* drugs having *Katu*(pungent), *Tikta*(bitter), *Kashaya Rasa*(astringent); *Vishada*(clear), *Ruksha*(rough), *Laghu guna*(light properties); *Ushna virya*(hot potency) and *Katu Vipaka* (pungent digestion conversion of food into a state for assimilation)

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may leads to *Sroto-shodhana*(cleaning of channels) and may help in the evaluation of the *Rasayana* effect in the body. *Guggulu, Rasona, madhu*(honey), *Bhallathaka* are best example which acts at the level of *Srotas*.

At the level of Ojas: There are certain *Rasayana* drugs which directly influence the better formation and functions of *Oja* i.e. bio-immune strength. Drugs such as *Jivaniyagana, Svarna*(gold), *Amalaki rasayana* and *Pippali* are supposed to induce *Bala* (strength) and *Vyadhikshamatva* (immunity) in the individual.[lxxxiv]

B. In respect to contemporary concepts of understanding

i. Anti-ageing property

Aging is a natural phenomenon in which there will be unavoidable physiological, psychological, biochemical changes occurs in humans. The human being is seeking the fountain of youth that can either stop or at least stall the process of aging. Aging is the accumulation of damage in the human body which shows physical changes which reflect underlying physiological changes, like decreased pigment production in hair follicles, decreased skin elasticity etc. Functional decline reveals like reduced muscle power, vision, memory and locomotor functions, there is gradual decline in homeostasis and immune function predisposes them to infection, digestive problem and malignancy. *Rasayana* therapy prevents change in physical appearance by rejuvenating the loss of function of cells, tissues & organs.

Free radicals causes oxidative damage to various biological molecules e.g. hydroxyl radicals can damage cell membrane and lipoproteins by a process called lipid peroxidation which may contribute to aging process. Certain *Rasayana* drugs likes *Ashvagandha*, *Chyavanaprasha*, *Agastyaharitaki, Brahma Rasayana* etc best one which possess the anti-aging effect

Mitochondria, power house of the cell which produce energy. Ageing associated with decline in mitochondrial function. With advanced age, mitochondrial DNA volume, integrity and functionality decrease due to accumulation of mutations and oxidative damage induced by reactive oxygen species (ROS).[lxxxv] The mitochondrial theory of aging is based on the fact that mitochondrial DNA (mtDNA) has a higher rate of mutation and less efficient repair machinery

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compared to nuclear DNA. The mutation rate of mtDNA is up to 15-fold higher than that of nuclear DNA.[lxxxvi] *Rasayana* therapy promotes normal functioning of mitochondria as a result it performs its actions more efficiently and able to produce adequate energy.

Telomerase activity in the cells maintains telomere length and is implicated in ageing and various diseases wherein the shortening of telomere during ageing is controlled chiefly by the telomerase activity. A study have shown that maintenance of telomere length is facilitated by an increase in telomerase activity upon *Rasayana* administration in aged individuals and *Amalaki Rasayana* may prevent the erosion of telomeres over a period of time in aged individuals to promote healthy ageing.[lxxxvii]

Aging isn't deliberately programmed, but the same physiologic mechanisms that drive growth also drive aging. Aging is simply the continuation of the same growth program, and it's driven by the same growth factors and nutrients & it can be well controlled by *Rasayana* therapy. Longevity means extending youth, not extending old age. It is possible with *Rasayan* therapy.

ii. **Anti-oxidant action**

Rasayana drugs acts as antioxidants. Antioxidants are substances that reduce oxidative damage that caused by free radicals. Oxidative damage to cells is also important phenomenon in aging process. So, antioxidants are also helpful in delaying aging. Antioxidants may possibly reduce the risk of cancer and age related macular degeneration. Many *Rasayana* drugs like *Amalaki, Ashvagandha, Guduchi* etc acts as antioxidants. Withanolide in *Ashvagandha* also acts as antioxidants by increasing levels of three natural antioxidants like super oxide- dismutase, catalase, glutathione peroxidase.[lxxxviii]

Main constituents of *Amalaki* are vitamin C, carotene, and riboflavin. It is having a role in cellular oxidation reduction. They have also a role in collagen fibrin synthesis, helps the formation of fibrin & absorption of iron.

A study suggests that ascorbic acid and other polyphenols present in the natural formulation of amla show much superior antioxidant activity compared to their equivalent amounts in pure

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isolated form.[lxxxix] So *Rasayana* measures enhance the body's internal antioxidant system and do not allow the free radicals to dominate to cause diseases

iii. **Immunomodulatory action**:

Rasayana drugs perform the immunomodulator action. Certain *Rasayana* drugs such as *Guduchi, Haridra, Pippali, Shilajatu* etc performs immune-modulator functions. Strengthening of immunity is done in various ways by promoting bodily defence mechanisms by improved functions of WBC, lymphoid organs, antibodies etc.

Aqueous extract of T. cordifolia stem significantly increase INFγ and IL levels (IL-1, IL-2, IL-4) in isolated chicken peripheral blood mononuclear cells (PBMCs) against infectious bursal disease virus. Further, immune-modulatory potential via the toll-like receptor (TLR)-mediated pathway.[xc] Administration of *Brahma rasayana, Amrita prasa rasayana* and *Narsimha rasayana* were found to enhance the proliferation of lymphocytes in response to mitogens. Some were found to induce the proliferation of bone marrow cells in culture. Natural killer cell activity was also found enhanced in both normal and tumour bearing animals treated with *Rasayana*.[xci]

Macrophages are the first line of defense and constitute important participants in the bi-directional interaction between innate and specific immunity. A study has shown that, *Guduchi* (Tinospora cordifolia) act as immune-modulator for activation of macrophages.[xcii]

A study conducted on aqueous extract of Tinospora cordifolia reported that it has active immune-modulatory properties. The study of plant extracts have been mainly focused on the activation of splenocytes and lymphocytes by the Tinospora cordifolia extract through the augmentation of production of cytokines. The production of cytokine is the method to examine the augmentation activity of the immune system that have important role to control the homeostasis of whole organism.[xciii]

A study evaluated the immune-modulatory effect of *Tulasi* shown that aqueous extract resulted in increased antibody production in dose dependent manner. It enhanced the production of RBC, WBC & haemoglobin and not affected the biochemical parameters.[xciv]

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Yashtimadhu provides resistance against herpes simplex virus-1 infection and Candida albicans by IFN and Th2 cytokines secretion. Glycyrrhizic acid and its aglycone reported to modulate the function of NF-kB and IL-10 production which explains reduction of inflammation in liver.[xcv]

In a study *Adraka* is evaluated for its immunomodulatory action and resulted in suppressed lymphocyte proliferation by decrease in IL-2 and IL-10 production. Another study reported that, an aqueous ginger extract significantly increased the production of IL-1β, IL-6 and TNF-α in activated peritoneal mouse macrophages.[xcvi]

Ambwani S et.al reported that cow urine enhances both cellular and humoral immune responses. The study was done to evaluate the blastogenic activity of lymphocytes and effect of in-vivo cow urine treatment.[xcvii]

Amalaki enhanced immunity by augmenting both cell mediated and humoral response. It enhances IL-2 and gamma-IFN production and inhibits apoptosis. It also enhances NK cell activity and Antibody Dependent Cellular Cytotoxicity. It is established as a potent immune-modulator in repeated respiratory infections in human beings.[xcviii]

iv. Adaptogenic action:

Rasayana drugs of Ayurveda can be considered as adaptogenic drugs because these drugs enhance endurance and improves sustaining capacity in individuals by promoting *Dehabala* (body strength).

Shatavari root, *Haritaki* and *Amalaki* fruits extract and their fraction was studied in rat, it exhibits improvement in physical work performance and endurance in adverse stressful environment, which is an essential characteristic of adaptogen endurance to a stressful condition. Similar results were observed with *Ashvagandha* by the intake up to a period of three months stay in high mountains. *Tulasi* and Geriforte are reported to have antistress & adaptogenic property.[xcix]

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Certain experimental studies have reported few adaptogenic drugs viz., Asperagus recemosus, Bacopa monniera, Crocus sativus, Curculigo orchioides, Emblica officinalis, Ocimum sanctum, Tinospora cardifolia and Withania somnifera.[c]

v. Anabolic action:

Several epidemiological studies reveal that dairy products (*Ksiravarga*) intake is associated with a decreased incidence of colon cancer.[ci] Glycyrrhetinic acid from *Yashtimadhu*, is a proven drugs that inhibit the action of collagenase, hence it is a potent drug for the treatment of degenerative disorders of the exocellular matrix.[cii] • *Amalaki* has exhibited cell protective effect against experimentally induced acute necrotizing pancreatitis in dogs.[7]

vi. Intellect promoting & other actions:

The studies on *Medhya Rasayanas* in recent years have shown that the drugs have anxiolytic, nootropic and antiepileptic properties. *Brahmi* was proved of its anxiolytic, psychotropic, nootropic and antiepileptic effects. *Shankhapushpi* was found to have psychotropic, anticonvulsant and depressant effects. *Mandukaparni* shows nootropic effect and *Jatamansi* shows antidepressant activity were proved beyond doubt.[ciii]

Nootropics are by definition cognitive enhancers, but a cognitive enhancer is not necessarily a nootropic. These are thought to work by altering the availability of the brain's supply of neurochemicals (neurotransmitters, enzymes and hormones), by improving the brain's oxygen supply, or by stimulating nerve growth. Picrosides I and II constituents of P. kurroa, have shown to potentiate nerve growing factor in cultured PC12D cells.[civ]

Thus these drugs are still relevant and useful in the promotion of positive physical and mental health.

vii. Bactericidal and anti-microbial activity:

Several *Rasayana* drugs have been found with anti-microbial activity. The study showed that both aqueous and organic extracts of *Kantakari, Ashvagandha, Dugdhika, Nimba, Amalaki, Tulasi, Rasona* and *Vasa* have bactericidal activity against M. tuberculosis in vitro. The *Pippali*

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Rasayana showed 98% recovery of Giardia infection in mice.[cv] Alcoholic extracts of *Bhallataka* dry nuts and leaf showed bactericidal activity in three gram negative strains (E. coli, solmonella typhi and proteus vulgaris) and two gram positive bacteria (Staph. aureus and corynebacterium diphtheriae).[cvi]

6. Immunity and Rasayana Therapy

The immune system interacts with many other systems in the organism (mainly neural, metabolic, and endocrine systems) and is, therefore, one of the most ubiquitous master systems of the organism. As such, it orchestrates health when it functions well but, when maladapted, it leads to diseases in the aging organism.

i. Ageing and immunity

Age represents the primary risk factor for chronic diseases, including cardiovascular, malignant, and neurodegenerative conditions. Extremely aged individuals who survive in good health to the end of the human lifespan are rare, and a fixed limit to human lifespan may exist

ii. Innate Immune Changes

The innate immune response is the most conserved protection that allows the organism to efficiently defend against an impressive number of aggressive pathogens. This compartment is meant to recognize and react to the conserved pathogen-associated molecular patterns (external threats) and danger-associated molecular patterns (internal threats) by way of specific receptors that play a key role in elimination of the aggressors. The innate immune system influences the adaptive immune response in many ways. One of these cases is antigen presentation by dendritic cells (DCs). There are conflicting results in this domain and it seems that DCs are less able to prime CD4+ T cells in the elderly. Increased levels of pro-inflammatory cytokine production by the innate cells during aging may also influence the reactivity of the CD4+ T cells. Moreover, these cytokines may elicit increased free radical production in T cells, which will paralyze their function by increasing inhibitory events of signaling. In sum, alterations in the innate immune system may also impact adaptive immune changes with aging.[cvii]

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iii. Adaptive Immune System

The adaptive immune system is composed of the cellular and the humoral immune response. T cells are orchestrating the cellular immune responses. These cells are basically divided into CD4+ and CD8+ T cell populations, which possess very clearly defined functions. CD4+ T cells are helper cells that regulate the functions of all the other immune cells. They also possess effector functions. CD8+ T cells are effector and memory T cells responsible for clearing the aggressors. Many alterations in the adaptive immune system have been described in aging. With respect to T cell subpopulations, aging is characterized by two main changes: a decrease in naïve T cells that leads to the shrinking of the TCR repertoire and an increase in memory T cells that is primed by different aggressors.[cviii]

iv. Age-related pathologies

Aging is the predominant risk factor for most diseases and conditions that limit health span. Accordingly, interventions in animal models that end up in an extension of lifespan prevent or delay many chronic diseases. The involvement of some molecular mechanisms known to cause aging in a number of ARDs, like frailty and sarcopenia, chronic obstructive pulmonary disease (COPD), cancer, and Alzheimer and Parkinson diseases, Cardiovascular diseases and type 2 diabetes which are important pathologies that affect millions of patients and do share molecular mechanisms with aging, including inflammation and oxidative stress

The result is a low level of inflammation, which is so characteristic of aging that it's been termed inflammaging. Periodical consumption of *Rasayana* substances balances the inflammaging.

Rasayan therapy helps to attain nutrition of each and every cell and also helps to reach the immune cells in each & every part of the body. *Rasayana* therapy prevents the slow accumulation of cellular damage enhances the body ability to repair it.

7. DISCUSSION

Aging is a continuous biological process that is affected by physiological, social, psychological, and environmental factors. Aging is found to be associated with several disease conditions and

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characterized by a gradual functional decline in the body thereby significant risk for developing neurodegenerative diseases, cancers, cardiovascular diseases, and diabetes.

Ayurveda considered aging as an important health context. It is referred to as "*Jara*" (aging or declining phase) in classical Ayurveda. According to Ayurveda, aging is not a disease but a natural phenomenon like hunger, thirst or sleep. In the theory of natural destructions (*Swabhavoparamavada*), *Charaka* describes that there is a causative factor for the manifestation of a being but there is no cause for the cessation of this expression, since death following birth is a state of natural phenomenon.

The process which helps in assimilation of all pharmacological entity (*Rasa*, *guna* etc) in the body and supports for long life, provides physical strength and enhances potency by providing improved nourishment to the respective *dhatus* is known as *Rasayana*. *Rasayana* creates new tissues in the body having optimum quality and it prevent aging. The *Rasayana chikitsa* has been indicated for young and middle aged persons after prior unction and evacuation and also people, who are healthy, intelligent, having self-control over senses, a good amount of money and sufficient time, can be treated with *Rasayana Chikitsa*. *Rasayana* therapy enhances longevity, promotes memory and intelligence, prevents the development of diseases, maintains youthfulness, excellence of lusture, complexion and voice; provides optimum strength, normal coordination of sense organs, clear words, attains respect, brilliance and potency.

Rasayana therapy balances the replication process in the cells, prevents the rapid reproduction or rapid replication or excessive cell replication mechanism inside the cells, assist in the nourishment of each and every part of the cell, helps to preserve the function and morphology of cells, clears the neurovascular block in the cells, helps to maintain the homeostasis mechanism inside the cells, it assist in re-nutrition, restructuring & replenishment of each & every cells, it assist in healing and repair inside the cells, prevents the damage of the cells, prevents the senescence process etc.

Rasayana therapy is a highly dynamic, multi-step process, during which all the cells get the continuous nourishment as a result it evolve and diversify in a context dependent manner. It prevents the multiple cellular and molecular changes and distinct phenotypic alterations,

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including a stable proliferation arrest unresponsive to mitogenic stimuli. It also prevents the alterations in metabolic activity and gene expression and develops a complex senescence-associated secretory phenotype.

The regeneration capacity and rate vary in each cell. Also the replication rate is not fixed for every cell. So if a cell with slow replication rate, if undergo pathological changes which hasten the replication rate, results in the ageing of that particular cell. The mental factors like excessive emotions results in the increase of stress hormones which is also one of the root cause of ageing. *Rasayana* therapy boosts up tissue repair and regeneration, thereby contributing toward longevity & it assist in removal of senescent cells can attenuate age-related tissue dysfunction and extend health span. *Rasayana* therapy can also act as a potent anti-tumor mechanism, by preventing proliferation of potentially cancerous cells.

Rasayana medicines maintain the cellular homeostasis by improving the assimilation of nutrients and integration of metabolic products. It is a meticulous process having prior *shodhana* therapy, which provide the detoxification at cellular level and there by facilitate the adequate nourishment through *rasayana* therapy.

Immunodeficiency diseases are one of the serious global health problems leading to increased mortality and morbidity. It can be inherited, acquired or drug induced. Certain types of cancer, viral infections, AIDS, malnutrition, stress, can cause immunodeficiency conditions. An immune-compromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect everyone. Immunomodulation is an important attribute in the strengthening of immune competence in a controlled manner. Immuno-modulators are drugs enhance the immune reaction of an organism against a pathogen by nonspecifically activating the immune system. It provides a conventional chemotherapy for a variety of disease conditions of impaired immune responsiveness or when a selective immunosuppressant has to be induced in autoimmune disorders and organ transplantation. The basic concept of immunomodulation exists in *Ayurveda*. The only difference is that modern concept of immunomodulation focus only on direct attack over pathogen. It enhances cellular detoxification mechanism, repair damaged cells including cell proliferation etc. So *Rasayana*

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drugs should be used as a compulsory measure for immune deficient disorders. Besides immune-modulatory action, *Rasayana* drug act as antioxidant, anti-stress, anti-inflammatory, antimicrobial, anti-aging, anti-arthritic and anti-bacterial agent.

8. CONCLUSION

Rasayana therapy is a highly dynamic, multi-step process, during which all the cells get the continuous nourishment as a result it evolve and diversify in a context dependent manner. *Rasayana* therapy boosts up tissue repair and regeneration, thereby contributing toward longevity & it assist in removal of senescent cells can attenuate age-related tissue dysfunction and extend health span. Various kinds of *Rasayana* measures are mentioned against different conditions of the body for the healthy persons as well as diseased individuals. Periodic consumption of *Rasayana* therapies prevent the disease manifestation and help to fight against causative agents. Good conduct also provides the sustained immunological actions inside the body.

9. Conflict of Interest – Nil
10.
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