PROMISING GEROPROTECTIVE ROLE OF AYURVEDA INTERVENTIONS INAGEING

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Abstract:

In recent years, there has been a tremendous increase in the pace of human ageing around the world. WHO estimates that about 22% of the world's population will be over 60 years of age by 2050. Ageing is characterized by gradual loss of musculo-skeletal, sensory, cognitive, reproductive, immunological, endocrinal and psychological functions. It is a major risk factor for many non-communicable, chronic and degenerative diseases. Modern science has identified different ageing mechanisms at cellular and molecular levels such as chromosome and telomere regulation, proteostasis, insulin signaling, autophagy, oxidative stress, mitochondrial functioning, cytoskeletal integrity and hormesis. These ageing mechanisms are potential therapeutic targets to prevent and control ageing and associated diseases. The quest for blissful ageing draws our attention to affordable, accessible, safer, age-friendly and holistic approach of Ayurveda in prevention and treatment of geriatric disorders. Acharya Charaka describes health and bliss to be synonymous. For healthy ageing, classical interventions such as *mitahara* (dietary restriction), *upavasa* (fasting), *rasayana chikitsa* (rejuvenation therapy), *mahakashaya* (main decoctions), *rasaushadhi* (metal or mineral formulations), *abhyanga* (oil massage), *vyayama* (physical exercise), *achara rasayana* (rejuvenating behavioral therapies), etc. have been ascribed to improve longevity and extend corresponding health span. Recent evidence also supports the role of these classical interventions in geroprotection due to their anti-oxidant, telomerase enhancing, autophagy inducing, senolytic, hormetic and adaptogenic activities. Hence, the present article reviews classical

and contemporary information related to the geroprotective potential of Ayurveda's behavioral regimens and therapeutics at cellular levels leading to blissful ageing.

Key words: Ageing, Healthy ageing, Ayurveda, rasayana, geroprotection, telomere

Introduction:

Human ageing involves multiple physiological, psychological and social changes that cause functional impairment and disruption of homeostasis further leading to an increased susceptibility to diseases and an exponential rise in mortality. It is estimated that by 2050, 19% of Indians and 22% of the world's population will be over 60 years of age[1,2]. Ageing is a major risk factor for many cerebrovascular diseases, neurodegenerative diseases, infections, geriatric syndromes, cancer and disabilities. Today, the biggest killers of older people are heart disease, stroke and chronic lung disease[3]. Contemporary anti-ageing interventions such as hormonal therapy, rapamycin, resveratrol, etc. have detrimental side-effects. Hence, there is a global demand for safer, cost-effective and broad spectrum geroprotective interventions for healthy ageing. Such geroprotective interventions can be developed by understanding various molecular and cellular mechanisms involved in ageing process and by identifying potential anti-ageing therapeutic targets. The quest for blissful ageing draws our attention to affordable, accessible, safe, age-friendly and holistic interventions of Ayurveda, that have been ascribed to increase both lifespan and corresponding health span on the basis of Ayurveda's principles. The geroprotective potential of these classical interventions still remains untapped due to the skepticism about their classical anti-ageing claims and lack of evidence on how these interventions work. Recent researches strongly support the geroprotective role of these classical behavioral regimens and therapeutic interventions in healthy ageing and also in prevention and treatment of geriatric disorders by manipulation of multiple ageing mechanisms at cellular and molecular levels.

Ageing mechanisms:

Various theories including Programmed theory of ageing, Somatic mutation theory, Wear and Tear theory, Cross-linking theory, Free radical theory and Immunological theory explain the pathophysiology of cellular ageing[1]. Genetic and bio-chemical

researchers have identified multiple ageing mechanisms that can be optimized as potential therapeutic targets of cellular ageing and age-related disorders (Table 1).

Concept of ageing in Ayurveda:

Acharya Sharangdhara describes a sequential loss of biological features such as *balya* (childhood), *vriddhi* (growth), *chhavi* (complexion), *medha* (intellect), *twak* (dermal health), *drishti* (vision), *shukra* (reproductive function), *vikrama* (valor), *buddhi* (intelligence), *karmendriya* (physical capacity), *chetana* (liveliness) and *jivita* (life) respectively in successive decades of life since birth[13]. Ayurveda considers 'old age' above 60 years (Charaka samhita) or 70 years (Sushruta samhita)[14] and '*Jara'* (ageing) as a *swabhavikvyadhi* (natural/inevitable disease),[15]characterized by predominant *Vatadosha, dhatu-upadhatu kshaya, malakshaya, ojakshaya, vishamagni, and indriya daurbalya.* The classical texts also explain the health- and longevity-promoting properties of different dietary (*mitahara, upavasa*), pharmacological (*rasayana chikitsa, vayasthapana mahakashaya, jeevaneeya mahakashaya, rasaushadhi)* and behavioral (*abhyanga, vyayama, achara rasayana)* interventions for prevention and treatment of geriatric disorders.

Modern insights on selective anti-ageing interventions of Ayurveda:

1. *Mitahara* (Dietary restriction):

Dietary restriction (DR) without malnutrition, the best-studied longevity-promoting intervention, can increase lifespan and health benefits in diverse species from yeast to primates. DR mice were protected against multiple age-associated diseases, including cancer. DR rhesus monkeys have reduced incidence of diabetes, cancer, cardiovascular disease and brain atrophy[17]. Humans on a DR diet for a limited period of time show a decrease in risk factors associated with coronary heart disease, an improvement in glucocorticoid function and an increase in insulin sensitivity[16]. Calorie restriction increases both mean and maximum life-span in a variety of species[17]. Caloric restriction induces autophagy (Levine and Kroemer, 2008)[18], reduces the release of growth hormone, insulin and insulin-like growth factor 1 (IGF1) and also brings changes in

human transcriptome, hormonal status, oxidative stress, inflammation, mitochondrial function and glucose homeostasis (Fontana et al., 2010)[9].

2. *Upavasa* (Fasting):

Periodic fasting regimens exert anti-ageing effects, facilitate long-term memory formation in *Drosophila melanogaster* (Hirano et al., 2013), alleviate Alzheimer's, Parkinson's, Huntington's diseases and fronto-temporal dementia in mice, minimize the risk of developing age-related diseases such as neurodegeneration, cancer, or cardiovascular diseases in animal models and humans, and also increase life span by 83% in rats (Longo and Mattson, 2014)[9]. Fasting reduces oxidative stress[79], induces autophagy and increases lifespan in a TOR-independent manner[80].

3. *Rasayana chikitsa* (Rejuvenation and Anti-ageing therapy):

Rasayana chikitsa, one of the eight major clinical disciplines of Ayurveda, enhances the qualities of *rasadhatu* and helps attain longevity, memory, intelligence, health, youthfulness, luster, excellent complexion and voice, optimum physical and sensory strength, mastery over phonetics and brilliance[19]. It encompasses a plethora of herbal and metallic or mineral formulations as well as behavioral medicine.

Multiple anti-ageing pharmacological activities of classical *rasayana* herbs have been proven by modern researches (Table 2).

Amalaki rasayana, a classical herbal formulation shows effective anti-ageing effect by improving tolerance to a variety of cell stresses through reduced ROS and lipid peroxidation, enhanced SOD activity and Hsp27 and by repairing DNA damage and maintaining telomere length facilitated by an increase in telomerase activity[54,55,56]. *Triphala rasayana* shows anti-oxidant, nitric oxide scavenging, anti-cancer, immunomodulatory and anti-inflammatory activity[57].*Brahma rasayana* retards ageing process and tumor growth[19].

Natural products such as Resveratrol (*Draksha*), catechin (*Khadir, Ashoka*), epicatechin (*Vijaysara*),curcumin (*Haridra*) and quercetin (*Amalaki, Nimba, Draksha*) have been identified for their anti-ageing activity[5].

4. *Mahakashayas* (Main decoctions):

Vayasthapana drugs show significant anti oxidant activity clinically by improving body luster and relieving symptoms like joint pain, muscular cramps, loss of appetite, constipation, anxiety, stress and loss of concentration[58].Menopausal syndrome (psychological disturbances like irritability, depression, sleep disturbance, nervousness and dizziness) can be managed by *Jeevaneeya* drugs[59].

5. ***Rasaushadhi* (Metal or mineral formulations):**

Shilajit (Asphaltum punjabianum) shows anti-inflammatory, analgesic, anti-diabetic, immunomodulatory, anti-anxiety and adaptogenicproperties[60,61]. *Tamra bhasma* (incinerated copper) when given in lower doses, potentiates anti-oxidant activity in rats[61]. *Swarna bhasma* (incinerated gold) preparations have significant anti-oxidant and restorative effects in global and focal models of ischemia. *Swarna bhasma*-treated animals have shown significant increase in superoxide dismutase and catalase activity that reduces free radical concentrations in the body[61].

6. *Abhyanga* (Oil massage):

Sesame oil massage is proven to be effective in geriatric population[62]. Application of medicated oil followed by a gentle massage relaxes the tight junctions between endothelial cells in the CNS vessels, relieves stress and activates brain function[63]. Massage improves immunity and anti-oxidant activity[64], induces autophagy[65], and reduces the levels of stress-related hormones with a concomitant increase in circulating lymphocytes and regional cerebral blood[66].

7. *Vyayama* (Physical exercise):

Lifelong exercise is known to extend mean life-span[67]. Regular physical activity in older adults could maintain age-related decreases in anti-oxidant defense[68].Physical activity training augments telomerase activity in myocytes, and circulating mononuclear cells in rats and human leukocytes[69]. Exercisers have lengthened telomeres[69].Long- and short-term voluntary physical exercise up-regulates cardiac telomere-stabilizing proteins

and thereby induces anti-senescent and protective effects[70].Habitual physical exercise is associated with greater telomere length in postmenopausal women[71].

8. ***Achara rasayana*** **(Behavioral medicine):**

Successful ageing is most commonly operationalized as life satisfaction, high morale or the subjective appraisal of well-being that can be achieved by special health-promoting right conduct and behavior[72].High subjective well-being including life satisfaction, absence of negative emotions, optimism and positive emotions causes better health and longevity[73].Social and spiritual stimulations aimed at reversing age-related loss of dynamical complexity act upon even higher levels to ensure a reduced risk of social problems in ageing[12].

Discussion:

Ageing is influenced by time-progression, genetics, physical and social environments, personal characteristics and diseases. The underlying mechanisms of ageing process and age-related pathologies are identical[74]. Hence, these intricate and interrelated mechanisms controlling cellular ageing were summarized to provide deeper insights into potential therapeutic targets that may delay ageing, promote healthy longevity and also prevent and treat age-related diseases. Considering the diversity of ageing mechanisms and the rising demand for comprehensive, economical, safer anti-ageing and geroprotective interventions, modern researches on a few selected classical interventions that are described to possess anti-ageing properties in Ayurveda, were reviewed to evaluate their potential geroprotective role on cellular ageing mechanisms and associated diseases.

Dietary interventions such as *mitahara* and *upavasa* induce autophagy and regulate hormones, mitochondrial functioning and metabolic homeostasis. Pharmacological interventions including single *rasayana* herbs, herbal formulations and *mahakashayas* target multiple ageing mechanisms due to their diverse phyto-constituents. Since brain helps govern ageing of many organs[75], *medhya rasayanas (Mandukaparni, Yashtimadhu, Guduchi, Shankhapushpi)* possessing cerebroprotective and neuroprotective activities hold significance as anti-ageing medicine. Lifelong and periodic exposure in short doses to various stressors such as metal nanoparticles, physical and mental challenges, etc. may

inhibit or retard the ageing process by hormesis[9,11,12,76]. Induction of hormesis may be achieved with the help of hormetins like classical *metallic formulations*, *abhyanga*, *vyayama* and certain *rasayanas.* Daily behavioral regimens like *abhyanga*, *vyayama* and *achara rasayana* help reduce stress hormones, induce autophagy and maintain the synchrony of the circadian system that is tightly coupled to cellular metabolism[77]. *Achara rasayana* positively influences our environment, people, relationships, attitudes, values, health, social policies, support systems and their services, thus supporting and maintaining our intrinsic capacity and functional ability, which is a key to Healthy Ageing[78].

The selected interventions of Ayurveda exhibit anti-ageing effects in different laboratory organisms and humans, implying some commonalities in the underlying ageing mechanisms and universal applicability of these interventions.

Conclusion:

Acharya Charaka has rightly stated that 'health' and 'bliss' are synonymous. Ageing can be a blissful celebration only if it is coupled with optimum health. Ayurveda's dietary, pharmacological and behavioral interventions act as potent anti-oxidants, telomerase activity enhancers, calorie restriction mimetics, autophagy inducers, senolytics, hormetins and/or adaptogens, thus manipulating different cellular ageing mechanisms to maintain genomic stability as well as cellular, metabolic and protein homeostasis. Hence, the promising geroprotective role of Ayurveda's interventions in delaying and reversing ageing process, increasing lifespan, maintaining health and preventing and mitigating age-related disorders is scientifically supported by both Ayurveda and modern science. These evidence-based, accessible, affordable, safer and holistic geroprotective interventions of Ayurveda may contribute significantly in the development of WHO's global strategy and action plan for healthy ageing. Integrative approach of multidisciplinary sciences like Ayurveda, Gerontology and Biogenetics towards understanding ageing and optimizing classical anti-ageing interventions may help to reduce the age-related disease burden globally, improve the quality of life and embrace the positive perceptions of ageing. Further research on evaluation of long-term

effects of these classical geroprotective interventions, individually or in combination, on molecular and cellular ageing mechanisms is necessary.

References:

1. Mahesh Chand Gupta, et al. A critical review on commonly used Rasayana drugs in Ayurveda. Asian Journal of Multidisciplinary Studies. February 2015;3(2): 15-20.
2. Ageing and health. 5 February 2018. http://www.who.int/news-room/fact-sheets/detail/ageing-and-health
3. 10 facts on ageing and health. Updated May 2017. http://www.who.int/features/factfiles/ageing/en/
4. Di Loreto, et al. The Cell Biology of Ageing. Molecular Biology of the Cell. 2015;26(25): 4524–4531. PMC. Web. 1 Aug. 2018.
5. A Ding, et al. Current Perspective in the Discovery of Anti-Ageing Agents from Natural Products. Natural Products and Bioprospecting 7.5. 2017: 335–404. PMC. Web. 1 Aug. 2018.
6. Van Heemst D. Insulin, IGF-1 and longevity. Ageing and Disease. 2010;1(2):147-157.
7. Martinez-Lopez N, et al. Autophagy and Ageing. Advances in experimental medicine and biology. 2015;847:73-87. doi:10.1007/978-1-4939-2404-2_3.
8. Shahbaz, Kiran. Oxidative Stress Causes Ageing: Genetics and Epigenetics. Merit Research Journal of Medicine and Medical Sciences. 2017.;5: 604-610.
9. de Cabo R et al. The search for anti-ageing interventions: from elixirs to fasting regimens. Cell. 2014 Jun 19;157(7):1515-26. doi: 10.1016/j.cell.2014.05.031.
10. Payne BAI, et al. Mitochondrial dysfunction in ageing: Much progress but many unresolved questions. Biochimica et Biophysica Acta. 2015;1847(11):1347-1353. doi:10.1016/j.bbabio.2015.05.022.
11. Rattan SIS. Anti-ageing strategies: prevention or therapy? EMBO Reports. 2005;6(Suppl 1):S25-S29. doi:10.1038/sj.embor.7400401.
12. Kyriazis M. Clinical anti-ageing hormetic strategies. Rejuvenation Res. 2005 Summer;8(2):96-100. DOI: 10.1089/rej.2005.8.96

13. Prof. K.R. Srikantha Murthy. Sharangdhar samhita by Sarangdhara. Chaukhamba Orientalia, Varanasi. 2012:p 30
14. Meera E, et al. A review on ageing and anti-ageing measures in Ayurveda. IAMJ. July- August 2014; 2(4):427-432.
15. Prof. Singh R.H.. Charak Samhita – Ayurvedadipika Commentary. Chowkhamba Surabharati Publication, Varanasi. 2014: p 298.
16. Niccoli T, et al. Ageing as a risk factor for disease. Curr Biol. 2012 Sep 11;22(17):R741-52. doi: 10.1016/j.cub.2012.07.024.
17. Carter CS, et al. Molecular mechanisms of life- and health-span extension: role of calorie restriction and exercise intervention. Appl Physiol Nutr Metab. 2007 Oct;32(5):954-66.
18. Rubinsztein DC, et al. Autophagy and Ageing. Cell. 2011 Sep 2;146(5):682-95. doi: 10.1016/j.cell.2011.07.030.
19. Chulet R, et al. A review on Rasayana. Pharmacognosy Reviews. 2009;3: 229-234.
20. Shukla V, et al. Evaluation of anti-oxidant profile and activity of amalaki (Emblica officinalis), spirulina and wheat grass. Indian J Clin Biochem. 2009 Jan; 24(1): 70–75. Published online 2009 May 8. doi: 10.1007/s12291-009-0012-3
21. Rege NN, et al. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytother Res. 1999 Jun;13(4):275-91. DOI: 10.1002/(SICI)1099-1573(199906)13:4<275::AID-PTR510>3.0.CO;2-S
22. Kanive P. Guruprasad, et al. Influence of Amalaki Rasayana on telomerase activity and telomere length in human blood mononuclear cells. J Ayurveda Integr Med. 2017 Apr-Jun;8(2): 105–112. Published online 2017 Jun 9. doi: 10.1016/j.jaim.2017.01.007
23. De A, et al. Emblica officinalis extract induces autophagy and inhibits human ovarian cancer cell proliferation, angiogenesis, growth of mouse xenograft tumors. PLoS One. 2013 Aug 15;8(8):e72748. doi: 10.1371/journal.pone.0072748. eCollection 2013.

24. Kalekar, Samidha A., et al. Insulin Sensitizing Effect of 3 Indian Medicinal Plants: An in Vitro Study. Indian Journal of Pharmacology 45.1 (2013): 30–33. PMC. Web. 1 Aug. 2018.
25. Yamamoto, Hirotaka et al. Amla Enhances Mitochondrial Spare Respiratory Capacity by Increasing Mitochondrial Biogenesis and Anti-oxidant Systems in a Murine Skeletal Muscle Cell Line. Oxidative Medicine and Cellular Longevity 2016 (2016): 1735841. PMC. Web. 1 Aug. 2018.
26. SahaS et al. Anti-oxidant activity of polyphenolic extract of Terminalia chebula Retzius fruits. Journal of Taibah University for Science. November 2016; 10(6): 805-812.
27. Tayal S, et al. Cytoprotective role of the aqueous extract of Terminalia chebula on renal epithelial cells. Int Braz J Urol. 2012 Mar-Apr;38(2):204-13; discussion 213-4. PMID: 22555028
28. MinKyun Na, et al. Cytoprotective Effect on Oxidative Stress and Inhibitory Effect on Cellular Ageing of Terminalia chebula Fruit. Phytother. Res. 2004;18: 737–741. Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ptr.1529
29. Shen YC, et al. NEUROPROTECTIVE EFFECT OF TERMINALIA CHEBULA EXTRACTS AND ELLAGIC ACID IN PC12 CELLS. Afr J Tradit Complement Altern Med. 2017 Jun 5;14(4):22-30. doi: 10.21010/ajtcam.v14i4.3. eCollection 2017.
30. Kim HJ, et al. Neuroprotective Effect of Chebulagic Acid via Autophagy Induction in SH-SY5Y Cells. Biomol Ther (Seoul). 2014 Jul;22(4):275-81. doi: 10.4062/biomolther.2014.068.
31. Chandra Shekar, et al. ANTIDEPRESSANT ACTIVITY OF AQUEOUS EXTRACT OF FRUITS OF TERMINALIA CHEBULA IN RATS. Int J Pharm Pharm Sci. September 2012;4(4): 449-451
32. Gohil, Kashmira J et al. Pharmacological Review on Centella Asiatica: A Potential Herbal Cure-All. Indian Journal of Pharmaceutical Sciences 72.5 (2010): 546–556. PMC. Web. 1 Aug. 2018.

33. Joy J, et al. Protection of DNA and membranes from gamma-radiation induced damages by Centella asiatica. J Pharm Pharmacol. 2009 Jul;61(7):941-7. doi: 10.1211/jpp/61.07.0014.
34. Arora R, et al. Comparison of three different extracts of Centella asiatica for anti-amnesic, anti-oxidant and anticholinergic activities: in vitro and in vivo study. Biomed Pharmacother. 2018 Sep;105:1344-1352. doi: 10.1016/j.biopha.2018.05.156. Epub 2018 Jun 27.
35. Lokanathan Y, et al. Recent Updates in Neuroprotective and Neuroregenerative Potential of Centella asiatica. Malays J Med Sci. 2016 Jan;23(1):4-14.
36. Park JH, et al. Anti-Inflammatory Effect of Titrated Extract of Centella asiatica in Phthalic Anhydride-Induced Allergic Dermatitis Animal Model. Int J Mol Sci. 2017 Mar 30;18(4). pii: E738. doi: 10.3390/ijms18040738.
37. Shinomol GK, et al. Exploring the role of "Brahmi" (Bocopa monnieri and Centella asiatica) in brain function and therapy. Recent Pat Endocr Metab Immune Drug Discov. 2011 Jan;5(1):33-49.
38. Gray NE, et al. Centella asiatica Attenuates Mitochondrial Dysfunction and Oxidative Stress in Aβ-Exposed Hippocampal Neurons. Oxidative Medicine and Cellular Longevity. 2017;2017:7023091. doi:10.1155/2017/7023091.
39. Kulkarni R, et al. Nootropic herbs (Medhya Rasayana) in Ayurveda: An update. Pharmacognosy Reviews. 2012;6(12):147-153. doi:10.4103/0973-7847.99949.
40. Yi-Te Yo, et al. Licorice and Licochalcone-A Induce Autophagy in LNCaP Prostate Cancer Cells by Suppression of Bcl-2 Expression and the mTOR Pathway. J. Agric. Food Chem., 2009, 57 (18), pp 8266–8273. DOI: 10.1021/jf901054c. Publication Date (Web): August 27, 2009
41. Pathak P, et al. Rasayana effect of Guduchi Churna on the life span of Drosophila melanogaster. Ayu. 2016;37(1):67-70. doi:10.4103/ayu.AYU_11_16.
42. Saha S, et al. Tinospora cordifolia: One plant, many roles. Ancient Science of Life. 2012;31(4):151-159. doi:10.4103/0257-7941.107344.
43. Sharma R, et al. Antidiabetic claims of Tinospora cordifolia (Willd.) Miers: critical appraisal and role in therapy. Asian Pacific Journal of Tropical Biomedicine. January 2015; 5(1): 68-78

44. Agarwa P, et al. An update on Ayurvedic herb Convolvulus pluricaulis Choisy. Asian Pacific Journal of Tropical Biomedicine. 2014;4(3):245-252. doi:10.1016/S2221-1691(14)60240-9.
45. Jain S, et al. A Review on Phytochemical and Pharmacological Profiles of Pueraria tuberosa Linn. (Fabaceae). Asian Journal of Ethnopharmacology and Medicinal Foods. 2016;02 (03): 01-04.
46. Choudhary D, et al. A Phytopharmacological Review on Asparagus racemosus. International Journal of Science and Research (IJSR). July 2014;3(7): 742-746. Paper ID: 02014849. www.ijsr.net
47. Kuchewar VV, et al. Evaluation of anti-oxidant potential of Rasayana drugs in healthy human volunteers. Ayu. 2014 Jan;35(1):46-9. doi: 10.4103/0974-8520.141919.
48. Vasantharaja R, et al. Withaniasomnifera Root Extract Enhances Telomerase Activity in the Human HeLa Cell Line. Advances in Bioscience and Biotechnology. 2016;7:199-204. Published Online April 2016 in SciRes. http://dx.doi.org/10.4236/abb.2016.74018
49. Chandrasekhar K, et al. A Prospective, Randomized Double-Blind, Placebo-Controlled Study of Safety and Efficacy of a High-Concentration Full-Spectrum Extract of Ashwagandha Root in Reducing Stress and Anxiety in Adults. Indian Journal of Psychological Medicine. 2012;34(3):255-262. doi:10.4103/0253-7176.106022.
50. Dinesha R, et al. ANTI-OXIDANT ACTIVITIES OF PIPPALI (PIPER LONGUM) PROTEINS. International Journal of Pharmaceutics and Drug Analysis. 2014;2: 811-814. https://www.researchgate.net/publication/277324711_ANTI-OXIDANT_ACTIVITIES_OF_PIPPALI_PIPER_LONGUM_PROTEINS
51. João Pedro de Magalhães, et al. The Business of Anti-Ageing Science. Trends in Biotechnology. November 2017;35(11):1062-1073. http://dx.doi.org/10.1016/j.tibtech.2017.07.004
52. Liu J, et al. Piperlongumine restores the balance of autophagy and apoptosis by increasing BCL2 phosphorylation in rotenone-induced Parkinson disease models.

Autophagy. 2018;14(5):845-861. doi: 10.1080/15548627.2017.1390636. Epub 2018 Feb 21.

53. Aseervatham J, et al. Cytoprotective effect of Semecarpus anacardium against toxicity induced by Streptozotocin in rats. Journal of Experimental Pharmacology. 2010;2:135-143. doi:10.2147/JEP.S11466.
54. Bargale Sushant S, et al. ANTI-AGEING EFFECT OF AMALAKI RASAYANA IN HEALTHY ELDERLY SUBJECT. Journal of Ayurveda and Holistic Medicine (JAHM). 2014;2(1); 10-18. http://www.jahm.in/index.php/JAHM/article/view/104/pdf_27
55. Vishwanatha U, et al. Effect of Amalaki rasayana on DNA damage and repair in randomized aged human individuals. Randomized controlled trial. J Ethnopharmacol. 2016 Sep 15;191:387-397. doi: 10.1016/j.jep.2016.06.062. Epub 2016 Jun 27.
56. Guruprasad, Kanive P, et al. Influence of Amalaki Rasayana on Telomerase Activity and Telomere Length in Human Blood Mononuclear Cells. Journal of Ayurveda and Integrative Medicine 8.2 (2017): 105–112. PMC. Web. 1 Aug. 2018.
57. Sharma R, et al. Molecular targets of common Ayurvedic herbal anti-oxidants. J. Ayu. Herb. Med., 2017;3(1):33-37
58. Ganeshwar Reddy DV, Nisheteswar K, From 5th World Ayurveda Congress 2012 Bhopal, Madhya Pradesh, India. 7-10 Dec 2012. PA01.59. Evaluation of rasayana effect of vayasthapana drugs. Ancient Science of Life. 2012;32(Suppl 1):S109.
59. Dr. Ojha A. A CLINICAL STUDY ON THE CHARAKOKTA JEEVANIYA MAHAKASHAYA GHANVATI IN RAJONIVRITTI JANYA VIKAR W.S.R. TO MENOPAUSAL SYNDROME. World Journal of Pharmaceutical Research. 2018;7(5):1702-1711. DOI: 10.20959/wjpr20185-11378
60. Gavali, Jyoti. SHILAJIT AN UNIQUE DRUG OF AYURVEDA. International Ayurvedic Medical Journal. Vol III:1427-1430. https://www.researchgate.net/publication/276831443_SHILAJIT_AN_UNIQUE_DRUG_OF_AYURVEDA

61. Tripathi, R, et al. Concept of rasayana in Rasa shastra. International Journal of Research in Ayurveda and Pharmacy. 2012;3: 777-779. 10.7897/2277-4343.03615.
62. Wagh M, et al. EFFECT OF ABHYANGA IN GERIATRIC POPULATION. World Journal of Pharmacy and Pharmaceutical Sciences. 2017;6(8):1202-1210. www.wjpps.com/download/article/1501494568.pdf
63. V. Rao, Rammohan. Ayurveda and the science of ageing. Journal of Ayurveda and Integrative Medicine. 2017. https://doi.org/10.1016/j.jaim.2017.10.002
64. Karabulut AB, et al. The effect of regular exercise and massage on oxidant and anti-oxidant parameters. Indian J Physiol Pharmacol. 2013 Oct-Dec;57(4):378-83. https://www.ncbi.nlm.nih.gov/pubmed/24968576
65. King JS, et al. The induction of autophagy by mechanical stress. Autophagy. 2011;7(12):1490-1499. doi:10.4161/auto.7.12.17924.
66. Dr. Wankhade S, et al. SCIENTIFIC SIGNIFICANCE OF ABHYANGA (MASSAGE). DEERGHAYU INTERNATIONAL. Jan. -March - 2017;33 - 01 (129):31-35. www.deerghayuinternational.com/wp.../DI%20129%20-%20E-Book%20final.pdf
67. Carter C, et al. Molecular mechanisms of life- and health-span extension: role of calorie restriction and exercise intervention. Applied Physiology, Nutrition, and Metabolism, 2007, Vol. 32, No. 5:954-966. https://doi.org/10.1139/H07-085
68. Bouzid MA, et al. Lifelong Voluntary Exercise Modulates Age-Related Changes in Oxidative Stress. Int J Sports Med. 2018 Jan;39(1):21-28. doi: 10.1055/s-0043-119882. Epub 2017 Nov 23.
69. Puterman E, et al. The power of exercise: buffering the effect of chronic stress on telomere length. PLoS One. 2010 May 26;5(5):e10837. doi:10.1371/journal.pone.0010837.
70. Werner C, et al. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. J Am Coll Cardiol. 2008 Aug 5;52(6):470-82. doi: 10.1016/j.jacc.2008.04.034.
71. Kim JH, et al. Habitual physical exercise has beneficial effects on telomere length in postmenopausal women. Menopause. 2012 Oct;19(10):1109-15.

72. MARGRET M. BALTES M, et al. The Process of Successful Ageing. Ageing and Society. 1996 16:397-42. https://doi.org/10.1017/S0144686X00003603
73. Ed Diener. Happy People Live Longer: Subjective Well-Being Contributes to Health and Longevity. APPLIED PSYCHOLOGY: HEALTH AND WELL-BEING, 2011, 3 (1), 1–43. doi:10.1111/j.1758-0854.2010.01045.x
74. Niccoli T, et al. Ageing as a risk factor for disease. Curr Biol. 2012 Sep 11;22(17):R741-52. doi: 10.1016/j.cub.2012.07.024.
75. Guarent L, et al. Ageing Research—Where Do We Stand and Where Are We Going? Cell. 25 September 2014;159(1): 15-19. https://doi.org/10.1016/j.cell.2014.08.041
76. Iavicoli I, et al. Exposure to Nanoparticles and Hormesis. Dose-Response. 2010;8(4):501-517. doi:10.2203/dose-response.10-016.Iavicoli.
77. Cao Y, et al. Associations among Metabolism, Circadian Rhythm and Age-Associated Diseases. Ageing and Disease. 2017;8(3):314-333. doi:10.14336/AD.2016.1101.
78. What is Healthy Ageing? http://www.who.int/ageing/healthy-ageing/en/
79. Mojto V, et al. Effects of complete water fasting and regeneration diet on kidney function, oxidative stress and antioxidants. Bratisl Lek Listy. 2018;119(2):107-111. doi: 10.4149/BLL_2018_020
80. Catterson JH, et al. Short-Term, Intermittent Fasting Induces Long-Lasting Gut Health and TOR-Independent Lifespan Extension. Current Biology. 2018;28(11):1714-1724.e4. doi:10.1016/j.cub.2018.04.015.

Table 1: Important ageing mechanisms and potential anti-ageing therapeutic targets[4,5,6,7,8,9,10,11,12]

Sr. No.	Ageing mechanism	Cause of ageing	Potential anti-ageing therapeutic target
1.	**Chromosome and telomere regulation**	Shortening of telomere length	Improvement of telomerase activity and suppression of telomere shortening
2.	**Proteostasis**	Proteostasis failure	Regulation of proteostasis
3.	**Insulin signaling**	Increased insulin/ IGF-1 signaling	Reduction in insulin/ IGF-1 signaling
4.	**Autophagy**	Inhibition of autophagy	Stimulation of autophagy
5.	**Oxidative stress**	Increase in oxidative stress	Reduction of oxidative stress or anti-oxidation
6.	**Mitochondrial functioning**	Mitochondrial dysfunction	Boosting mitochondrial function
7.	**Cytoskeletal integrity**	Dysregulation of cytoskeleton	Maintenance of cytoskeletal structure
8.	**Hormesis**	Absence of hormesis	Induction of hormesis

Table 2: *Rasayana* herbs and their anti-ageing pharmacological activities

Sr. No.	Herb	Anti-ageing pharmacological activities
1.	*Amalaki, (Emblica officinalis)*	Anti-oxidant[20], adaptogenic[21], telomerase enhancing[22], autophagy inducing[23], insulin sensitizing[24], mitochondrial biogenesis enhancing[25] activities
2.	*Haritaki (Terminalia chebula)*	Anti-oxidant[26], adaptogenic[21], cytoprotective[27], oxidative stress inhibitory[28], neuroprotective[29], autophagy enhancing activities[30], inhibition of age-dependent shortening of the telomeric DNA length[28]
3.	*Bibhitaki (Terminalia bellirica)*	Anti-oxidant, anti-depressant activities[31].
4.	*Mandukparni (Centella asiatica)*	Anti-oxidant[32], DNA protective[33], anti-amnesic[34], neuroprotective[35], neuroregenerative[35], anti-inflammatory[36], nootropic[37] and mitochondrial dysfunction inhibitory[38] activities
5.	*Yashtimadhu (Glycyrrhiza glabra)*	Anti-oxidant[39], nootropic[39], adaptogenic[39], autophagy inducing[40], mitochondria protective[40]activities
6.	*Guduchi (Tinospora cordifolia)*	Anti-oxidant[39], life-span enhancing[41], nootropic[39], neuroprotective[42], hepatoprotective[42], hormone regulatory[43], anti-stress[39], immunomodulatory[39], adaptogenic[21], insulin sensitizing activities[43].
7.	*Shankhapushpi (Convolvulus pluricaulis)*	Anti-oxidant, neuroprotective, memory enhancing, anti-stress, anxiolytic, anti-depressant activities[44].
8.	*Vidari (Pueraria tuberosa)*	Anti-oxidant, immunomodulatory, adaptogenic, anti-inflammatory activities[45]
9.	*Shatavari (Asparagus racemosus)*	Anti-oxidant, adaptogenic[21], phyto-estrogenic activity[46]
10.	*Ashwagandha (Withania somnifera)*	Anti-oxidant[47], adaptogenic[21], anti-ageing[48], immunomodulatory[49], telomerase enhancing[48], neuroprotective[49], anti-stress[48] activities
11.	*Pippali (Piper longum)*	Anti-oxidant[50], adaptogenic[21], senolytic[51], autophagy promoting[52] activities
12.	*Bhallatak (Semicarpus anacardium)*	Anti-oxidant, cytoprotective, anti-inflammatory activities[53]