

Insights from Ayurveda for translational stem cell research

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ABSTRACT

Ayurveda, the traditional Indian system of medicine has given great emphasis to the promotion of health. Ayurveda therapies are based on restoration of body balance and nourishment of dhatus or tissues. Rasayana concept of Ayurveda explains tissue regeneration and cell renewal. The drugs and therapies explained as rasayana provide research opportunities for biology of regeneration. Specific rasayana stimulate and nourish respective dhatus. Interpretation of this description offers clues for specific differentiation of stem cells with appropriate extract. The preliminary experiments on Medhya drugs suggest neuronal stem cells differentiation. Authors highlight the potential of Ayurveda and its possible contributions in regenerative medicine. Authors propose a protocol based on integrative approach derived from Ayurveda concepts and current understanding of regenerative medicine. The advanced understanding about adult and embryonic stem cells along with concepts of regeneration in Ayurveda has immense potential in the development of regenerative medicine.

Key words: Ayurveda, rasayana, stem cells

BACKGROUND

Ayurveda physiology explains a dynamic exchange between in terms of continuous regeneration of tissues. The tissues undergo continuous process of destruction and regeneration. The homeostasis is maintained by Doshas, those regulate all the metabolic processes. Vata regulates the catabolic activity (tissue wear and tear), Kapha stimulates synthesis of newer tissues, and Pitta governs the process of nutrients assimilation into tissues. Dosha act through body tissue, Ayurveda terms those as Dhatus (Sanskrit meaning to hold or withstand). Ayurveda recommends several dietary, lifestyle, and herbomineral interventions for

Dosha balance and Dhātu nourishment resulting in healthy long life. Traditionally therapies such as Panchakarma and Rasayana are used in Ayurveda for rejuvenation. Current knowledge on adult and embryonic stem cells if used along with concepts of regeneration in Ayurveda can contribute to the development of regenerative medicine with integrative approach.

TRADITIONAL MEDICINE AND REGENERATION

Ayurveda, the traditional Indian medicine (TIM), and traditional Chinese medicine (TCM) remain the most ancient yet living traditions.^[1] Scientific studies on Ayurvedic botanicals and Chinese herbs have shown to be effective in degenerative diseases such as arthritis, Parkinson's disease, and Alzheimer's disease.^[2-4] The tissue protective effects of Rasayana herbs are known. For example, chondroprotective activity of *Phyllanthus emblica* inhibiting the activities of hyaluronidase and collagenase type 2 *in vitro*.^[5]

Phyllanthus emblica fruits, *Shorea robusta* resin, and *Yashada bhasma* have shown activities in wound healing, fractures, anemia, corneal ulcers, brain, and deoxyribonucleic acid (DNA) damage in experimental models.^[6] Amalaki Rasayana (a preparation of Amla fruits-*Phyllanthus emblica*) has effectively demonstrated reduction in DNA damage in brain cells demonstrating its genomic stability in neurons and astrocytes.^[7] The same formulation demonstrated increase in median lifespan and starvation resistance

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in *Drosophila melanogaster* mode.^[8] Several formulations of Ayurveda are used for growth, healthy aging, and arresting degeneration. A recent study on one of such formulations, Dhanvantar Kashaya (a decoction of herbs having regeneration property) has demonstrated activity on Wharton jelly mesenchymal stem cells (WJMSCs). The decoction increased the proliferation rate, decreased the turnover time, and also delayed senescence. Ayurvedic formulation, Dhanwantram Kashaya, used as a growth enhancer, is able to improve the yield and quality of stem cells *in vitro* and could be an effective nontoxic supplement for culturing WJMSCs for clinical applications.^[9]

Curcumin had been demonstrated to stimulate developmental and adult hippocampal neurogenesis, and a biological activity that may enhance neural plasticity and repair.^[10]

Traditional Chinese medicinal composition for promoting bone marrow-derived MSC survival *in vivo* is reported. This composition is shown to promote differentiation into cardiomyocytes lineage.^[11] Zuo *et al.*,^[12] has reported that *Panax ginseng* induced K562 cells to differentiate into erythrocytes. In addition, other groups demonstrated that treatment with herbal extract enhanced the contractility of embryonic stem cell-derived cardiomyocytes. Sasaki *et al.*,^[13] demonstrated that treatment with a *Panax ginseng* compound promoted the differentiation of mouse embryonic stem cells into cardiomyocytes. Lam *et al.*,^[14] described in detail the mechanisms by which a four-herb Chinese medicine formula reduces chemotherapy-induced gastrointestinal toxicity. This formula acts at the level of the gastrointestinal progenitor and stem cells. The herbal compound PHY906 appeared to be responsible. It induced the expression of the stem cell markers CD44, Lgr5, Ascl2, and Olfm4 and increased the expression of Wnt signaling components 4 days after CPT-11 chemotherapy. These results suggest that PHY906 may promote progenitor cell regeneration after CPT-11 treatment by stimulating Wnt signaling.

Sheng *et al.*,^[15] reported that the novel semisynthetic molecule icaritin, based on a common metabolite of seven flavonoid glycosides derived from herb *Epimedium* could stimulate osteogenic differentiation and inhibit adipogenesis of MSCs, which was associated with the suppression of GSK3 β and PPAR γ .

Ginkgo biloba extract was shown to promote proliferation of endogenous neural stem cells in vascular dementia rats.^[16] Natural compounds from traditional Chinese herbal medicines, which are extensively used in China to treat stroke clinically and tested their proliferation-inducing activities on neural stem/progenitor cells (NSPCs). The screening results showed that salvianolic acid B (Sal B)

displayed marked effects on the induction of proliferation of NSPCs.^[17]

Baicalin, a flavonoid compound isolated from *Scutellaria baicalensis*. The effect of baicalin was observed in E15–16 embryonic neural precursor cells (NPCs), in which it promoted neural differentiation but inhibited glial formation by regulating expression of stat3 and bHLH.^[18] Chen *et al.*,^[19] observed the effect of (+)-cholesten-3-one, which was purified from *Plastrum testudinis* in TCM. (+)-Cholesten-3-one can effectively promote the activity of tyrosine hydroxylase (TH) promoter of P19 cells depending on bone morphogenetic protein (BMP) signaling. Phenotypic cellular analysis also indicated that it induces differentiation of NSCs to dopaminergic neurons with increased expression of TH, dopamine transporter (DAT), dopamine decarboxylase, and higher level of dopamine secretion.

STEM CELL BIOLOGY

Stem cell research is being pursued in the hope of achieving major medical breakthroughs in treatment of diseases. Stem cells are self-renewing, unspecialized cells that can give rise to multiple cell types of all tissues of the body. Somatic or adult stem cells typically generate the cell types of the tissue in which they reside. For example, a blood-forming adult stem cell in the bone marrow normally gives rise to the many types of blood cells. It is generally accepted that a blood-forming cell in the bone marrow—which is called a hematopoietic stem cell—cannot give rise to the cells of a very different tissue, such as nerve cells in the brain. Experiments over the last several years have purported to show that stem cells from one tissue may give rise to cell types of a completely different tissue, a phenomenon known as plasticity. Examples of such plasticity include blood cells becoming neurons, liver cells that can be made to produce insulin, and hematopoietic stem cells that can develop into heart muscle. Therefore, exploring the possibility of using adult stem cells for cell-based therapies has become a very active research area.^[20]

In recent years, several lines of evidence have suggested that adult stem cells are multipotent and can differentiate into different cell lineages. Adult bone marrow, brain, skeletal muscle, liver, pancreas, fat, skin, and skeletal muscle, have all been shown to possess stem or progenitor cells with the capacity to differentiate into cell types other than their tissue of origin.

Studies with bone marrow stromal or MSCs, a subset of cells that can be separated by plastic adherence, have shown differentiation into various cell types, including

bone,^[21,22] tendon, cartilage, and fat.^[23] Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.^[24]

AYURVEDA AND REJUVENATION

Rasayana is one of the eight branches of Ayurveda which refers to rejuvenative therapy and immunomodulation. Rasayana therapy (also known as *Jarabhikitsa*) encompasses the health management, delay aging, and diseases also offers treatment of ageing through rejuvenation. The enhancement of *Rasa* (essence) is the quintessential quality that all Rasayana medicines possess, ultimately helping to promote health and vigor of the tissues. They have a characteristic tendency to improve the nutritional status of the body and alleviate symptoms of stress through three basic mechanisms—*Rasa* (nutrient effect), *Agni* (digestion and metabolism), and *Srotas* (microcirculation and tissue perfusion). As the essence of digested and assimilated food or drug reaches to respective Dhātu (tissues), they are nourished well to perform respective functions in optimum capacity. *Panchakarma* therapies and *swasthavritta* (daily routine as suggested by Ayurveda) have tissue strengthening and rejuvenative potential. The *panchakarma* procedures followed by Rasayana drugs improve metabolic functions at *Dhātu* level and facilitate elimination of wastes (*Malas*) formed in metabolic processes, elimination of wastes improves *Dosha*, and *Dhatus* functions reducing the rate of catabolic processes leading to strengthening effects on body. However, in this article our major focus is on Rasayana drugs.

Thus, the Rasayana herbs have many targets and activities. Those drugs are effective in treatment of diseases, especially for aging, degenerative, autoimmune, and metabolic diseases. All Rasayana are unique formulations of a specific combination and number of plants, herbs, and spices.^[25]

In Ayurveda literature, over 200 Rasayana drugs are indicated in several specific indications. Though Rasayana term covers a broad spectrum of activity, each Rasayana has a specific tissue affinity and target action. The specific affinity for a tissue is termed as *Gamitva* in Ayurveda that literary mean 'reaching the target'. The tissue specific action of various botanical drugs is helpful in selection of appropriate Rasayana for a particular patient. The activity of Rasayana again depends on several variables like method of extraction, formulation type, dosage schedule, and metabolic status of the patient. There are certain organ and

tissue specific Rasayana such as *Medhya* Rasayana for the brain, *Hridya* Rasayana for the heart, *Tmachya* Rasayana for the skin, and *Chakshusyaya* Rasayana for the eyes. Similarly, they may be age specific as they promote nutrition relevant to natural bio-losses occurring at different phases of human life. Rasayana drugs are rich in antioxidants and are good hepatoprotective, nephroprotective, and immunomodulating agents.^[26]

It has also been reported that Rasayanas have immunomodulatory, antioxidant, and antitumor functions.^[27,28] However, the ability to differentiate stem cells through modulating expression of genes has not been evaluated. Thus, there exists a need to evaluate the ability to differentiate stem cells through modulating expression of genes using Rasayana herbs.

Regeneration of tissues after the disease condition like osteoarthritis, age related macular degeneration (AMD), Alzheimer's, injuries, trauma, heart attack, stroke, accident, or aging remains a challenge to modern medicine. Tissue-specific Rasayanas could be tried for differentiation of stem cells and regenerate specific tissue of choice.

BIOMEDICAL INTERPRETATION OF DHATU

Ayurveda mentions about emergence of various Dhatus in a sequence such as "Rasa, Rakta-Mamsa, Meda, Asthi, Majja, and Shukra".^[29] These Dhatus develop sequentially and nourish further Dhatus. For example, Rakta Dhatus plays important role in formation of Mamsa, which further nourishes Meda. The concept of Dhatus from Ayurveda and that of modern biology are different, but can be interpreted according their descriptions and functions. These Dhatus cannot be directly equated to various tissues; however, each tissue is formed by composition of many Dhatus. Respective Dhatus are dominant in specific tissues. There is a possibility that there is presence of stem cells in a particular tissue (Dhatu) giving rise to the next Dhatus in sequence.

Adult bone marrow stromal cells are shown to differentiate into neural cells *in vitro* by treating them in presence of epidermal growth factor (EGF) or brain-derived neurotrophic factor (BDNF), expressed the protein and mRNA for nestin, a marker of neural precursors.^[20] Human adipose tissue obtained from liposuction procedures has also been used to isolate a fibroblast-like cell population, called processed lipoaspirate (LPA) cells. *In vitro* studies with LPA cells demonstrated differentiation into adipogenic, chondrogenic, myogenic, and osteogenic cells.^[30] Ayurvedic concept of Dhātu needs to be explored

on this background. The focus of Ayurveda intervention is to protect and nourish Dhatus to form healthy body is similar that of modern medicine. Unlike Prakriti, which is permanent composition of Doshas, Dhātu concept is dynamic and changes according to diet and drugs. The quality and quantity of Dhatus can change with Rasayana and the depleted Dhatus could be nourished. Thus, the Dhātu concept is the foundation of Rasayana therapy and regeneration of tissues. It is interesting to note that the description of Dhatus from Rasa to Shukra require different dosage forms ranging from aqueous to medicated oils or ghee.

We propose specific Rasayana with appropriate extract and formulation for its effects on stem cells. The experiment can also consider the variations of extracts according to the nature of Dhatus (cell type).

AYURVEDA AND TRANSLATIONAL STEM CELLS RESEARCH: EXPERIMENTAL APPROACH

Stem cells are considered a valuable cellular resource for tissue replacement therapies in several degenerative disorders. They have the ability to self-replicate and differentiate into numerous cell types, including adipocytes, chondrocytes, osteocytes neurons, astrocytes, cardiomyocytes, etc. As a result, stem cells have been considered the “holy grail” of modern medicine. Despite their tremendous therapeutic potential, little is known about the mechanisms that regulate their differentiation into various lineages. Substances like vitamin C, retinoic acid, insulin transferring, selenium, and activin are known differentiating agents.^[31]

Rasayanas known for their tissue specificity could also be tested in stem cells to reveal their differentiation inducing activity. Stem cell could possibly form a right kind of platform for testing potency of specific Rasayanas.

Stem cells, particularly adult stem cells, have shown promising results in both translational and clinical applications. Stem cells are known to play in key role in healing wounds, diabetic foot management, burn injuries, corneal opacity as well as breast reconstruction after mastectomy. However, major limitation of stem cell therapy is their poor survival after transplanting into the host.

This limitation could be overcome by enhancing the potency of stem cells by treating them with vitamins and antioxidants thus making them fit to survive under adverse *in vivo* disease conditions. Recent studies show that reprogramming of pluripotent stem cells is enhanced when vitamin C is present.^[32] It has been shown that umbilical cord blood (UCB) derived MSCs, on prolonged exposure

to L-ascorbic acid have been successfully differentiated into osteoblasts (bone forming cells) without altering the phenotype of the cells. Thus vitamin C can regulate proliferation as well as differentiation of stem cells depending upon its concentration.^[33] In our earlier work we have shown chondroprotective potential of fruit extracts of *Phyllanthus emblica* in osteoarthritis.^[5] Amla is rich source of vitamin C and may be acting through similar pathways. Ayurvedic preparations like Rasayanas could be explored for their role in potentiating stem cells for clinical applications.

Self-renewal and multipotent differentiation are two hallmarks of stem cells. Wound healing, self-renewal, and differentiation potential can be proved with various assays.

It is possible to test the wound healing potential of Ayurvedic compounds by using *in vitro* scratch assay on MSCs. This is a standard proven technique used for demonstrating proliferation and migrating of cells to close the wound under influence of drug/soluble factors, etc. Presentation of the scratch assay is a convenient and inexpensive *in vitro* tool used for demonstrating proliferation and migration of cells to close the wound under influence of drug or soluble factors.^[34] Wound healing potential of plant extracts and natural compounds has been studied using scratch assay.^[35]

The basic steps involve creating a “scratch” in a cell monolayer, capturing the images at the beginning and at regular intervals during cell migration to close the scratch, and comparing the images to estimate the migration rate of the cells. The *in vitro* scratch assay is highly suitable for studies on cell migration, as it mimics *in vivo* cell migration during wound healing *in vivo* and are compatible with imaging of live cells during migration to monitor intracellular events if desired.

The self-renewal ability can be proven by comparing cell counts at every 24 h interval in presence of test extracts and untreated cells by obtaining population doubling time. Moreover, MSCs are known for their self-renewing potential and their ability to differentiate into different cell lineages.

Clinical potential of mesenchymal stem cell is well-established^[36] MSCs are tissue resident stem cells found in almost all the postnatal human tissues. These are able to differentiate into bone, cartilage, muscle, neurons, glia, tendon-ligament, fat, and other connective tissues. MSCs, in addition to their multipotency, are easy to isolate and culture *in vitro* and they do not apparently represent an ethical issue based on their source of origin unlike embryonic stem cells (ESCs). Moreover, these are HLA DR negative and

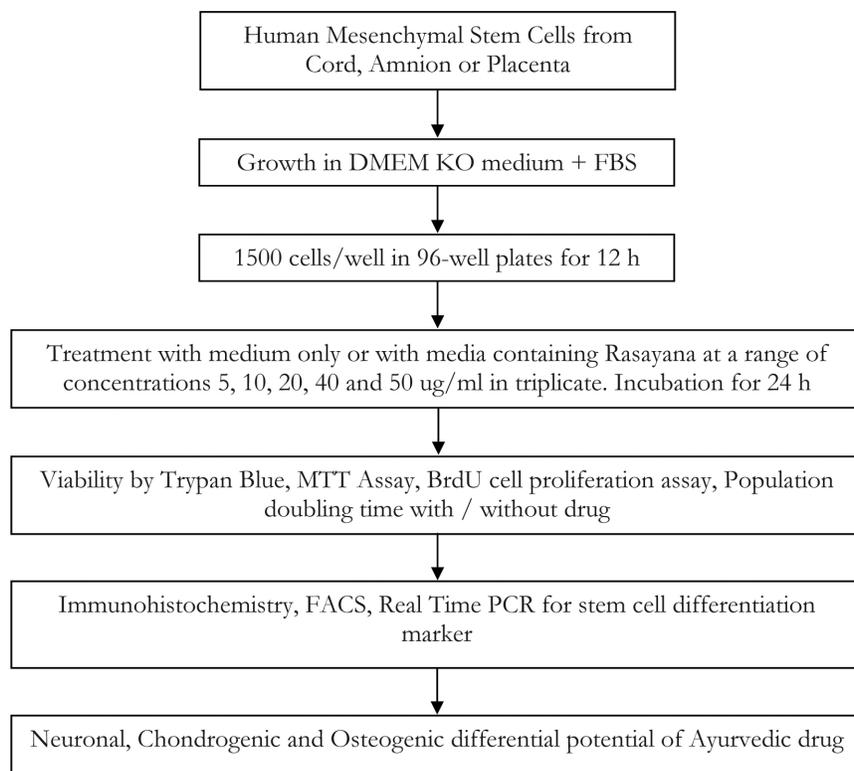


Figure 1: Flow chart of the experimental procedure

Table 1: Rasayanas and Dhatu

Specific Rasayana	Dhatu	Corresponding biological expression	Appropriate dosage form
<i>Tinospora cordifolia</i>	Rasa	The nourishing food portion absorbed after digestion, plasma	Decoction
<i>Piper longum</i>	Rakta	Blood	Decoction, Asava
<i>Asparagus racemosus</i>	Mamsa	Muscles	Medicated ghee, avaleha
<i>Terminalia chebula</i>	Meda	Adipose tissue	Decoction, Asava, avaleha
<i>Commifora mukul</i>	Asthi	Bones	Medicated ghee/oil, medicated milk, avaleha
<i>Bacopa monnirei</i>	Majja	Marrow and nervous system	Medicated ghee, avaleha
<i>Withania somnifera</i>	Shukra	Interstitial cells, epithelial lining, sperm, ovum	Medicated ghee, avaleha

hence not recognized as foreign cells. Therefore, the MSCs can be used for allogeneic cell transplantation without immunosuppression. We propose to use MSCs to study Rasayanas for their role in potentiating stem cells at for clinical applications [Figure 1].

Ayurveda describes numerous Rasayana plant drugs and a variety of health benefits [Table 1]. However, scientific studies on Rasayanas are concentrated on merely testing them for selected pharmacological activities leading

to superficial correlations. Deciphering deeper into Ayurvedic concept behind Rasayana therapy can help identify better candidates and models for study. For example, it is indicated that Rasayana drugs act through nutrition dynamics, for example, improving the quality of plasma (Rasa enhancing), normalizing the digestion and metabolism (*Agni*), and improving tissue perfusion of nutrients (*Srotas*) at molecular level.^[37] This gap provides an opportunity for further research on Rasayanas at *Dhatu* level using stem cells.

In our preliminary experiments on Medhya Rasayana, we found expression of nestin an early marker of neuronal stem cells differentiation when stem cells were treated with Rasayana extracts. We present that Ayurveda has potential to contribute to steering cellular differentiation pathways in a predictable manner.

CONCLUSIONS: THE OUTLOOK FOR RESEARCH

It is time to harness regenerative potential of Rasayana drugs from Ayurveda. A great deal of adult stem cell research has focused on investigating their capacity to divide or self-renew indefinitely and their potential for differentiation.^[38] Directed differentiation of human pluripotent stem cells into organ

pluripotent stem cells into organ and tissues *in vitro* remains a major challenge for translational studies.^[39] There is a need to undertake research on effect of *Dhatu* (tissue) specific Rasayanas on adult or embryonic stem cells or stem cells lines. Systems approach needs to be followed by stem cell biologists and Ayurveda experts to understand complex molecular pathways through which Rasayanas act and contribute to steering cellular differentiation pathways in a predictable manner.

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