Review Article

www.ijrap.net

PHYTOCHEMICALS: DO THEY HOLD THE FUTURE IN STEM CELL DIFFERENTIATION?

R. Narasimha Raghavan*[1], G. Vignesh[1], B. Santhosh Kumar[2], R. Selvaraj[1], B.J. Dare[1]
[1]Center for Lab Animal Technology and Research, Sathyabama University, Chennai, India
[2]Bioproducts Lab, CSIR-Central Leather Research Institute, Adyar, Chennai, India

Received on: 21/02/15 Revised on: 16/03/15 Accepted on: 08/04/15

***Corresponding author**
R. Narasimha Raghavan, Scientist –C, Centre for Laboratory Animal Technology and Research, Sathyabama University, Rajiv Gandhi Road, Sholinganallur, Chennai 600119 Tamil Nadu, India Email: raghav14rn@shotmail.com

DOI: 10.7897/2277-4343.06374

ABSTRACT

Since the discovery of stem cells, they have continuously intrigued scientists on the basis of differentiation to an entire plethora of lineages. The accumulated wealth of scientific data clearly shows its multi-factorial nature. Various investigators around the globe have thoroughly investigated and have established that chemical messengers, physical topography, rigidity of tissue etc. have vital roles to play. Specifically, chemical signals or "chemical cues" to stem cell differentiation has attracted wider attention due to its versatility and wide applicability. These chemical moieties are predominantly of animal origin, though species may differ. But recent reports have pointed out that phytochemicals do possess an ability to direct the differentiation pathway, analogous to the natural cues. This aspect of stem cell biology is still in its infancy and has a large scope to revolutionize medical treatments of many disorders. Since phytochemicals possess the said effect it has been looked upon as a promising approach for tissue engineering applications. This review critically analyses the current status of use of phytochemicals for stem cell differentiation for tissue engineering and regenerative medicine.

Keywords: Phytochemicals, herbs, stem cell differentiation, tissue engineering

INTRODUCTION

Herbs have been known to mankind since the beginning of history. Civilizations around the world have utilised these as prophylactic and therapeutic agents. They also form the base or prototype for many modern drugs. Recent surge in the search for newer and more effective drugs have resulted in assessment of traditional herbs by modern techniques. Its immediate sequel is the identification of effect of these phytochemicals on cells.

It is well known that cells respond to chemical signals and pathways and many such signals are well established. The receptors for such chemical messengers are also identified and regulation of their expression was well mapped for many such substances. But, when the focus turns to phytochemicals, there is a dearth in the literature. Many papers have focused on the activity of phyto-constituents on differentiated cells. For instance *Cissus quagrangularis* and *Butea monosperma* extracts show proliferative effects on bone cells.[1]It has been reported that *butea* extract has medicarpin as one of its components, known to stimulate estrogen receptor (beta) causing osteogenesis. To note, the same receptor is targeted by autologous bone morphogenetic protein.[2]Similarly, *Withania somnifera* is known to inhibit osteoclast activity, hence can be used as an adjuvant in bone regeneration. This aspect has gained momentum recently and many "phyto-drugs" are being systematically tested on relevant cell lines.[3]Nevertheless, screening for effects of such drugs on stem cells, is scantily reported.

The importance of relevance of phytochemicals in stem cell biology cannot be over stated. Till date, the cost of recombinant growth factors are too high to be afforded by common people, hence, limiting their use in therapeutic tissue engineering. It is also reported that growth factors can induce malignant transformation of cells in due course of time.[1, 4] On the other hand, "phyto-factors" are reported to have very short half-life and quick degradation periods, and malignant transformation can be avoided. Phytochemicals are easily available, accessible and do not require complex equipment to produce them.

Nevertheless, phytochemicals do have certain disadvantages. Are crude extracts beneficial or component separation is needed? This question has been answered differently by different people. Those who advocate component separation strongly point out that effects can be elucidated and studied only if the individual components are separated. On the other hand, it is shown that individual components of crude extracts do exert synergistic activity[5]. Hence, the decision entirely rests with the nature of the problem. Next major problem is the standardization of herbal derivatives. Phytochemicals are not present in uniform quantities in different batches, calling the need for thorough screening for aberrations in quantity. Possibly, this is one of the major concerns in using phytochemicals in stem cell investigations.

Though the phytochemicals can be chemically grouped like flavonoids, polyphenols etc, grouping them by their biological activity is apparently more useful. Bearing in mind the above facts, this paper exposes the recent advancements in the use of phytochemicals on stem cells. This paper is logically organized into sections based upon different lineages of differentiation and phytochemicals known to cause it. The paper discusses the phytochemicals causing osteogenic, endocrine and neural differentiation in detail, in addition to scanty reports on

other differentiation pathways.

Differentiation into osteogenic lineage

Osseous tissue forms the basic framework of the body. Though the need for bone regeneration is due to numerous reasons, certain defects cannot be regenerated by graft materials. In many such cases, recent literature has shown the benefit of stem cell therapy. In this connection, use of human recombinant bone morphogenetic protein is advocated. Recent advances have shown the effect of phytochemicals on osteogenic differentiation of stem cells.

Soumya et al., have indicated the feasibility of osteogenesis by *Cissus quadrangularis*.[6]They have observed spontaneous osteogenic differentiation of stem cells in presence of phytochemicals from *C. quagrangularis*. While Wang et al.[7] have demonstrated the effects of a Chinese herbal monomer naringin on MAPK signal pathway in rat bone marrow mesenchymal stem cells during osteogenic differentiation, Wei et al. [8] have shown that catechin can promote osteogenesis by enhancing PP2A activity in stem cells.

Flavonoids of *Herba epimediii* has been shown to induce osteogenic differentiation of rat MSCs by BMP and Wnt/β-catenin signaling pathway.[9, 10] *Aconitilateralis Preparata Radix* (ALR) promoted the proliferation rate of mouse bone marrow mesenchymal stem cells which was signaled by the bone morphogenetic protein-2/Smad-dependent Runx2 pathway.[11] Hence, till date, phytochemicals of diverse origin stimulating varied biochemical pathways are reported in the literature. However, there is still ample need for newer phytochemicals to promote osteogenic differentiation.

Differentiation into endocrine or glandular lineage

Endocrinal milieu of a living system orchestrates a huge number of changes in the body. Loss of endocrine tissues is predominantly due to pathologies resulting in their removal or damage due to side effect of other therapies say – radiotherapy. In such cases promotion of tissue specific stem cells to divide and differentiate into the lost organ in a biggest boon a person can receive.

Modern world sees diabetes mellitus as a pandemic. This disease is also caused by lowered secretion of insulin by the islets of langerhans. Drug therapy has been used as secretogogues to promote insulin secretion. Researches in the past couple of decades have shed invaluable light on the other aspects of pathogenesis and pathology of diabetes mellitus. Nevertheless, lowered insulin secretion is still the major problem. In cases of congenital or juvenile diabetes, there is a shortage of beta cells of islets of langerhans, leading to diabetes mellitus. In such cases, promotion of stem cell cells to form the insulin secreting cells will be of great advantage to the growing child. Ebrahiminia *et al* have experimented on flavonoids extracted from *Cichorium intybus* L leaf extract and have successfully induced P19 stem cells differentiation into insulin producing cells by flavonoids of methanolic extract.[12] Hence, it is clearly shown that differentiation of stem cells to insulin producing cells is feasible, but the translation to clinical usage needs lot more exploration.

Differentiation into neural lineage

Degenerative disorders of neural tissues substantially increase the burden of care for the care takers. Diseases like Alzheimer', schizophrenia etc are essentially due to degenerative pathology. Hence, differentiation of stem cells into neural pathway will be a great advantage to mankind since it can potentially improve the quality of life of the elderly.

Arai et al. have reported on neural differentiation of stem cells using phytochemicals from *Butea superba*. They have shown that Neurogenin2, an activator-type bHLH transcriptional factor, promotes differentiation of neural stem cells into neurons by transcription of pro-neural genes.[13]Xu et al, in their review have highlighted the possible role of flavonoids in neural differentiation of cells.[14] Li et al have shown that baicalin, a natural flavonoid from roots of the medicinal herb *Scutellaria baicalensis*, promotes neuronal differentiation of C17.2 neural stem cells in dose- and time-dependent manners.[15]Epimedium flavonoids have shown potential for promoting neurogenic differentiation of cells from neonatal rat hippocampi.[16] Natural cerebrolysin, a Chinese herb used for Alzheimer's disease therapy has showed potential for neurogenic differentiation of rat mesenchymal stem cells through multiple pathways.[17] While Ecdyterone is reported to cause neuronal differentiation of neural stem cells,[18]Xiehuo decoction can promote the survival and differentiation of transplanted neural stem cells, by influencing the expression of interleukin-4 mRNA and inhibiting the expression of interferon-gamma mRNA.[19]Components of specific Chinese herbs are reported to have influence on neural stem cell population. As Acanthopanax and Angelica could positively influence the survival of neural stem cells, Rhodiola, Ganoderma spore Polygala, Tetramethylpyrazine, Gardenia, Astragaloside and Ginsenoside Rg1 promoted proliferation of neural stem cells. Rhodiola and Astragaloside promoted differentiation of neural stem cell into neuron and glia in vivo. Astragalus, Safflower, Musk, Baicalin, Geniposide, Ginkgolide B, Cili polysaccharide, Salidroside, Astragaloside, Antler polypeptides, Ginsenoside Rg1, Panax notoginseng saponins promoted proliferation and differentiation of neural stem cells in vitro. Salvia, Astragalus, Ginsenoside Rg1, P. noto ginseng saponins, Musk polypeptide, Muscone and Ginkgolide B promoted neural-directed differentiation of MSCs into nerve cells.[20, 21]

Differentiation into other lineages

Reports are sparingly available to show that differentiation through other pathways is also feasible. Panax ginseng was observed to promote the differentiation of embryonic stem cells to cardiac lineage.[22] Stem cells from exfoliated deciduous teeth have been differentiated into hepatoyte like cells by extracts of liquorice.[23] Differentiation into adipocytic lineage if importance in rejuvenating fat loss in the elderly. Phytochemicals from *Portulaca grandiflora* has shown

adipocytic differentiation.[24] Chinese herb prescription called Quzhisu is shown to inhibit adipogenic differentiation of bone marrow derived MSCs from patients suffering from aplastic anemia by reducing the expression of PPARγ mRNA.[25]

CONCLUSION

The quest for using phytochemicals for stem cell differentiation is interesting and intriguing. The research involves screening of phytochemicals, determination of pathway of action and gene regulation. Literature survey showed that the science is still in its infancy and still a long way to go for elucidating the structure activity relationship of phytochemicals and stem cell differentiation. However, the existing literature clearly shows that a vista is already open to the scientific community to explore the use of phytochemicals in tissue engineering.

REFERENCES

1. Raghavan RN, Somanathan N, Sastry TP. Evaluation of phytochemical incorporated porous polymeric sponges for bone tissue engineering: A novel perspective. Proc Inst Mech Eng H 2013; 227:859-65. http://dx.doi.org/10.1177/0954411913489804
2. Bhargavan B, Singh D, Gautam AK, Mishra JS, Kumar A, Goel A, et al. Medicarpin, a legume phytoalexin, stimulates osteoblast differentiation and promotes peak bone mass achievement in rats: evidence for estrogen receptor β-mediated osteogenic action of medicarpin. J Nutr Biochem 2012; 23:27– 38. http://dx.doi.org/10.1016/j.jnutbio.2010.11.002
3. Ichikawa H, Takada Y, Shishodia S, Jayaprakasam B, Nair MG, Aggarwal BB. Withanolides potentiate apoptosis, inhibit invasion, and abolish osteoclastogenesis through suppression of nuclear factor-kappaB (NF-kappaB) activation and NF-kappa B-regulated gene expression. Mol Cancer Ther 2006; 5:1434-45. http://dx.doi.org/10.1158/1535-7163.MCT-06-0096
4. Von Marschall Z, Scholz A, Stacker SA, Achen MG, Jackson DG, Alves F, et al. Vascular endothelial growth factor-D induces lymphangiogenesis and lymphatic metastasis in models of ductal pancreatic cancer. Int J Oncol 2005; 27:669-679.
5. Harisha CR, Acharya Rabinarayan, Shukla VJ, Chauhan MG. Pharmacognostical evaluation of stem of *Cissus repanda* Vahl, A folk medicine. IJRAP 2010; 1:13-18.
6. Soumya S, Sajesh KM, JayakumarR, Nair SV, Chennazhi KP. Development of a phytochemical scaffold for bone tissue engineering using *Cissus quadrangularis* extract. Carbohydrate Polymers 2012; 87:1787–1795. http://dx.doi.org/10.1016/j.carbpol.2011.09.094
7. Tian W, Li Y, Ronghua Z. Effects of naringin on MAPK signal pathway in rat bone marrow mesenchymal stem cells during osteogenic differentiation. Zhongguo Bingli Shengli Zazhi 2012; 28:769-776.
8. Wei YJ, Tsai KS, Lin LC, Lee YT, Chi CW, Chang MC, et al. Catechin stimulates osteogenesis by enhancing PP2A activity in human mesenchymal stem cells. Osteoporosis International 2011; 22:1469-1479. http://dx.doi.org/10.1007/s00198-010-1352-9
9. Jin-fang Z, Guo L, Chu-yan C, Chun-ling M, Chia-miL M, Yang-chaoC, et al. Flavonoids of Herba Epimedii regulate osteogenesis of human mesenchymal stem cells through BMP and Wnt/β-catenin signaling pathway. Molecular and Cellular Endocrinology 2010; 314:70-74. http://dx.doi.org/10.1016/j.mce.2009.08.012
10. Dong-xiao L, Lei Z, Lan W, Xia W, Yu-mei X, Wen-long D. Effect of total flavonoids of Herba epimedii on intramuscular implantation of tissue engineered mesenchymal stem cell and osteoclast differentiation. Zhongyao Yaoli Yu Linchuang2007; 23:88-91.
11. Rim KD, Young KH, Kwang PJ, Kyu PS, Seog CM. Aconiti Lateralis Preparata Radix Activates the Proliferation of Mouse Bone Marrow Mesenchymal Stem Cells and Induces Osteogenic Lineage Differentiation through the Bone Morphogenetic Protein-2/Smad-Dependent Runx2 Pathway. Evidence-based complementary and alternative medicine eCAM2013; 2013586741.
12. Maryam E, Fariba E, Navaz K, Fariba H, Marzieh E. Effect of flavonoids of extract of *Cichorium intybus* L. leaf on induction of P19 stem-cells differentiation to insulin-producing cells Journal of Mazandaran University of Medical Sciences 2014; 23:92-100.
13. Midori AA, Kazune K, Takashi K,Thaworn K, Masami I. Naturally occurring Ngn2 promoter activators from *Butea superba*. Molecular Bio Systems 2013; 9:2489-2497. http://dx.doi.org/10.1039/c3mb70083f
14. Sherry LX, Kevin YZ, Cathy WCB, LuY, Simon WX, Tina TX, Karl WK. Flavonoids, derived from traditional Chinese medicines, show roles in the differentiation of neurons: Possible targets in developing health food products. Birth Defects Research, Part C: Embryo Today--Reviews 2013; 99:292-299 http://dx.doi.org/10.1002/bdrc.21054
15. Ming L, Sze-Ting C, Kam-Sze T, Pang-Chui S, Kwok-Fai L. DNA microarray expression analysis of baicalin-induced differentiation of C17.2 neural stem cells. Chem Bio Chem 2012; 13:1286-1290. http://dx.doi.org/10.1002/cbic.201200145
16. Ruiqin Y, Lan Z, Xiaoli L, Lin L. Effects of Epimedium flavonoids on proliferation and differentiation of neural stem cells in vitro. Neurological Research 2010; 32:736-742. http://dx.doi.org/10.1179/174313209X459183
17. Yinghong L, Zhengzhi W, Ming L, Xiuqin J, Min Y, Manyin C. Gene expression in rat mesenchymal stem cells following treatment with natural cerebrolysin-containing serum: validation of a whole genome microarray technique. Neural Regeneration Research 2010; 5:424-432.
18. Weihua C, Hua F, Zhi C, Mengxiong Z, Gang Z, Jiangkai L. Chinese herbal medicine-derived ecdysterone for inducing differentiation of mammalian neural stem cells to neuronal cells. Faming ZhuanliShenqing2008; CN 101280291 A 20081008.
19. Peng-cheng Z, Xing-qun L, Qing-hua L, Wen-fang L, Qing-er L, Jie-kun L, Tao T, Yuan L. Effects of Xiehuo Bushen Decoction on survival and differentiation of transplanted neural stem cells in brain of rats with intracerebral hemorrhage. Zhongxiyi Jiehe Xuebao2008; 6:626-631.
20. Yin-Chu S, Qiang L, Chun-EX, Xin N, Xiao-Hui X, Chang-Yuan Y. Chinese herbs and their active ingredients for activating xue (blood) promote the proliferation and differentiation of neural stem cells and mesenchymal stem cells. Chinese medicine 2014; 9:13. http://dx.doi.org/10.1186/1749-8546-9-13
21. Po-Cheng L, Li-Fu C, Po-Yen L, Shinn-Zong L, Wan-Chen W, Wuen-Shyong C, Chang-HaiT, Tzyy-Wen C, Horng-Jyh H. Botanical drugs and stem cells. Cell transplantation 2011; 20:71-83. http://dx.doi.org/10.3727/096368910X532747
22. Toshiya S, Ki-Bong O, Hideaki M, Mikako S. Effect of Panax ginseng components on the differentiation of mouse embryonic stem cells into cardiac-like cells. Yakugakuzasshi : Journal of the Pharmaceutical Society of Japan 2008; 128:461-7
23. Wen-Ta S, Xiao-Wei C. Stem cells from human exfoliated deciduous teeth differentiate into functional hepatocyte-like cells by herbal medicine. Bio-medical materials and engineering 2014; 24:2243-7.
24. Dong Uk S, Min Su N, Jung Hyeon S, Hyeon C. *Portulaca grandiflora* extracts for promoting differentiation of human mesenchymal stem cell to adipocyte. Repub. Korean Kongkae Taeho Kongbo 2012; KR 2012009183 A 20120201.
25. Jinsong Y, Zhijie W, Bing W, Zhenlan S. Interventional effect of Quzhisu on adipogenic differentiation of mesenchymal stem cells derived from aplastic anemia patients. Zhongguo Zuzhi Gongcheng Yanjiu Yu Linchuang Kangfu 2008; 12: 4873-4876.

Cite this article as:

R. Narasimha Raghavan, G. Vignesh, B. Santhosh Kumar, R. Selvaraj, B.J. Dare. Phytochemicals: Do they hold the future in stem cell differentiation?. Int. J. Res. Ayurveda Pharm. 2015;6(3):379-381 http://dx.doi.org/10.7897/2277-4343.06374

Source of support: Nil, Conflict of interest: None Declared