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Role of Herbal Extract in Stem Cell Development

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Stem cell research has been developed, and today we can witness some stem cell clinical trials are on going in Indonesia. To meet a successful stem cell treatment, several factors need to be considered, such as cell number. Cell number has been reported to be crucial, and therefore optimal cell number should be achieved. Meanwhile, in some circumstances, cell number is not enough, therefore cell number should be enriched in an in vitro stem cell culture setting. In an in vitro stem cell culture, besides suitable and sterile equipment, reagents such as culture medium, serum and antibiotics are all important. Although all those criteria are fulfilled, somehow stem cell enrichment cannot be achieved, cell number is still below the target. Modification of stem cell microenvironment should then be an alternative. The addition of growth factors is a part of the strategies to reach a better enrichment. So that, stem cells could later be induced to proliferate at a higher rate. This strategy was then pursued by the scientist involved in herbal medicine. Herbal extracts were now highly investigated due to its potential to induce cell proliferation. Some herbal extracts inducing proliferation and differentiation of stem cell will be shown and described.

Keywords: herbal extract, stem cell, progenitor cell, proliferation, differentiation

Introduction

Stem cells with phenomenal ability, which can regenerate, proliferate and at the same time differentiate, attract the attention of both medical and non medical sites. People are amazed with the potential usage of stem cell in many aspects. Despite the scientific aspect, the study of stem cells in various other aspects is now also a topic that is often discussed in various meetings.¹

Generally, stem cells are divided into embryonic and adult stem cells. Advancement in embryonic stem cell

methods has been widely reported, including embryonic stem cell identification, culture and differentiation^{2,3}; Somatic Cell Nuclear Transfer^{4,5}, Altered Nuclear Transfer⁶, inner cell mass selected isolation⁷. However, due to some ethical problems, human embryonic stem cells can not be investigated in some countries, including Indonesia.⁸

Meanwhile, adult stem cells are not facing such ethical problems.⁸ Moreover, adult stem cells can be found from variety of sources, including: umbilical cord blood, bone marrow, peripheral blood, fat tissue, etc.^{1,9} Adult stem cells

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are no less important than embryonic stem cells, because their numbers and functions are also very adequate and potential for the treatment of various diseases.^{1,9,10} Moreover, umbilical cord blood has shown its unique property through its low immunogenicity profile.¹¹ Since the fetomaternal tissues of cord blood, umbilical cord matrix, and placenta have been demonstrated to express Oct-4, the tissue could be a good source for both embryonic and adult stem cells.¹² Not only umbilical cord blood, fat tissue contain mesenchymal stem cells that have immunomodulatory effects.¹³

The application of stem cell therapy in the medical field are rapidly developing. Efforts to achieve the applications also vary, such as the development of stem cell and its microenvironment isolation methods^{14,15}, development of methods to increase the number of stem cells¹⁶⁻²², the development of stem cell differentiation methods²³ (including cell reprogramming)^{24,25}, stem cell storage methods^{26,27}, the development of stem cell transplantation methods^{16,28}, etc. Since then, some particular stem cell types with their potential differentiation capacities can be isolated and cultured to meet the requirement of each clinical study to be explored.^{29,30}

Stem cell research has been developed and at present we can witness some stem cell clinical trials are on going in Indonesia. To meet a successful stem cell treatment, several factors need to be considered, such as cell number. Cell number has been reported to be crucial, and therefore optimal cell number should be achieved. Meanwhile, in some circumstances, cell number is not enough, so therefore cell number should be enriched in an *in vitro* stem cell culture setting.^{16,17,19-22}

In an *in vitro* stem cell culture, besides suitable and sterile equipment, reagents such as culture medium, serum and antibiotics are all important. Although all those criteria are fulfilled, somehow stem cell enrichment cannot be achieved, cell number is still below the target. Modification of stem cell microenvironment should then be an alternative. The addition of growth factors is a part of the strategies to reach a better enrichment. So that, stem cells could later be induced to proliferate at a higher rate. This strategy was then pursued by the scientist involved in herbal medicine. Herbal extracts were now highly investigated due to its potential to induce cell proliferation.³¹⁻³⁴ The following are some potential herbal extracts in inducing stem cell proliferation.

Tea Extract

Tea as a source of flavonoids has been shown to have strong reactive oxygen species (ROS) scavenging activity and prevent low-density lipoprotein (LDL) to oxidize. Tea extract consists of epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC) and catechin (C).³¹ EGCG was reported to induce proliferation of adipose tissue-derived mesenchymal stem cells (AD-MSCs). In addition, EGCG induces differentiation of AD-MSCs into endothelial progenitor cells (EPCs) as well.³² Later, it was found that EGCG, ECG, EGC and C of tea extract could induce differentiation of peripheral blood mononuclear cells (PB-MNCs) into peripheral blood-derived EPCs (PB-EPCs).³¹ The resulted PB-EPCs were confirmed by flow cytometry to detect EPCs membrane markers expressions (CD34, CD133, VEGFR-2). Treatment of EGCG, ECG, EGC and C increased the percentages of all CD34, CD133, VEGFR-2 expressions.³¹ In addition, EGCG, ECG, EGC and C could protect PB-EPCs from oxidative damage by suppressing the intracellular ROS levels as well.³¹ Therefore tea flavonoids might be related to PB-EPCs production and protection.

Curcuma longa Extract (CLE)

CLE contains curcuminoid compounds which have high antioxidant activity. Some of the curcuminoid compounds are curcumin, demethoxy curcumin and bisdemethoxy curcumin, which have higher antioxidative activities compared with α -tocopherol. Curcumin, a pigment isolated from turmeric (*Curcuma longa* L.), has antioxidant and anti-inflammatory properties. Curcumin is able to prevent methylglyoxal-induced oxidative stress and apoptosis in mouse embryonic stem cells and blastocysts.³² Based on previous report, it is known that IC₅₀ of CLE on 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity was 7.61 μ g/mL. The highest proliferation rates were induced by CLE at concentrations of 1 μ g/mL. CLE stimulated differentiation of AD-MSCs into EPCs marked by over expression of CD34, CD133 and VEGFR-2.³²

Caffeic Acid

Caffeic acid, a major representative of hydroxycinnamic acids, is found in various green plants and is involved in food mainly as an ester with quinic acid, which is

designated as chlorogenic acid (3-O-caffeoylquinic acid). Caffeic acid found in natural resources, such as legumes, grapes and coffee. Caffeic acid has been shown to inhibit the differentiation of osteoclastic progenitor into osteoclast, known as osteoclastogenesis.^{35,36} The osteoclastogenesis induced by receptor activator nuclear factor κ B ligand (RANKL) and tumor necrosis factor alpha (TNF- α) could be inhibited by caffeic acid through the NF κ B underlying mechanism.³⁵ Later on, it was found out that caffeic acid inhibited RANKL - TNF- α - TNF receptor-associated factor 6 (TRAF6)-induced osteoclastogenesis pathway, but did not influence TRAF6 expression.³⁶

Conclusion

Herbal extract has been shown to be useful in inducing proliferation and differentiation of stem cell/progenitor cells. In the same time, the extract can also inhibit differentiation of osteoclastic progenitor. This shows that some extracts have different specific role in cell differentiation. Hence, depending on their activities, the extract can be beneficial for future use in medicine. Therefore, other potential herbal extracts in Indonesia should be further explored.

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