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Effects of Functional Food Ingredients on Somatic Stem Cells

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Abstract

Purpose: Somatic Stem Cells (SSCs) are capable of self-renewal and differentiate into various tissue-specific cells from which they are derived, leading to promote turnover of tissues and organ. Thus, insufficient supply and abnormal differentiation from somatic stem cells into mature cells cause to several disorders. Since functional food and dietary supplements, which contain bioactive components might be safer to use compared with other chemical reagents and substances, vigorous studies such as tissue regeneration and protection of normal tissue using functional food have been conducted. Therefore, comprehensive understanding of the influence of active ingredients in diets and supplements is very important because of their daily and long-term intake. Our aim of this review is to provide a better understanding of the effects of various dietary components on SSCs.

Methods: Information was obtained from a literature search of electronic databases such as PubMed. Somatic stem cells ',' functional food and 'nutrition' were used as keywords for search. Firstly, we described the clinical problem and application of somatic stem cells. Next, we described that each functional food was categorized together with its influence on somatic stem cells.

Results: Many functional foods such as Vitamin A and its derivatives, fatty acids, polyphenols, herbal medicine, and other antioxidants have reported protective effects on SSCs. In addition, dietary components such as tea polyphenols facilitate regeneration by directing cell differentiation.

Conclusion: Our review might contribute to basic research and clinical regenerative applications using dietary functional food.

Keywords: Functional food; Somatic stem cell; Dietary supplement

Abbreviation: ES: Embryonic Stem; iPS: Induced Pluripotent Stem; ADSC: Adipose-Derived Stem Cells; ATRA: All-Trans Retinoic Acid; PUFA: Polyunsaturated Fatty Acids; IL; Interleukin; EGCG: (-)-Epigallocatechin-3-Gallate; EGC: (-)-Epigallocatechin; ECG: (-)-Epicatechin-3-Gallate; EC: (-)-Epicatechin; ROS: Reactive Oxygen Species; BJBDT: Bonjungbangdocktang; KMKKT: Ka-Mi-Kae-Kyuk-Tang; GABA: Gamma-Amino Butyric Acid

Introduction

49% of the U.S. population currently uses dietary supplements [1], and the market continues to expand. Especially, dietary supplements are used as preventive medicine against lifestyle-related diseases including cardiovascular disease, diabetes, obesity, mental disorders, and cancer. These lifestyle-related diseases have been suggested to be associated with abnormalities of stem cell differentiation. Stem cells are defined by their self-renewal capacity and ability to differentiate into downstream progenitor cells, and contribute to maintenance and generate the cellular diversity [2]. In the last decade, active empirical studies using Embryonic Stem (ES) cells and Induced Pluripotent Stem (iPS) cells have been performed in the field of regenerative medicine. However, the use of human ES cells raises substantial ethical issues [3], and iPS cells raise oncogenic concerns despite recent technical advances techniques for generating iPS cells0 [4]. To address these problems, the biology of somatic stem cells has been investigated. Somatic stem cells are also capable of self-renewal and differentiate into various tissue-specific cells from which they are derived, leading to promote turnover of tissues, such as hair and intestinal mucosa, and enable repair of damaged tissues. Hence, insufficient supply of somatic stem cells because of exhaustion and abnormal differentiation into mature cells cause to skin ulceration, hematopoietic failure, elimination of neurogenesis in adult brains, and intestinal disorders [5]. In addition, senescence of somatic stem cells may also contribute to disequilibrium between tissue injury and repair [6], and lead to the progression of disruptive cell proliferation and carcinogenesis [7]. Recent studies demonstrated that many natural products involve in the somatic stem cell biology and several applications for the treatment of neurodegenerative diseases, muscular diseases, diabetes and many other diseases using active substances in diet [2,8]. Therefore, comprehension of the influences of dietary ingredients and supplements on somatic stem cells is very important since these are consumed daily for long periods. Moreover, the use of dietary components in regenerative medicine may be safer than using chemical reagents and other synthetic substances.

In this review, we summarize the scientific evidence of the effects of dietary components on somatic stem cell biology based on PubMed searches. The purpose of this review is to contribute to the understanding of the health effects of dietary components and to promote basic research and clinical applications.

Clinical Problems and Application of Somatic Stem Cells

Hematopoietic stem cell

Hematopoietic stem cells in bone marrow can differentiate into all mature blood cell types and have been used for the treatment of

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hematological disorders, immune system disorders, hemoglobinopathies, myeloproliferative disorders, and neoplastic disorders using bone marrow transplantations [9]. Even though chemotherapy is widely used for the treatment of cancer, long-term chemotherapy causes chronic bone marrow damage and impaired hematopoiesis [10,11]. Hence, protection of hematopoietic stem cells from damage may allow longer use of radiotherapy and chemotherapy [12].

Mesenchymal stem cell

Mesenchymal stem cells can be isolated from bone marrow, umbilical cord blood, synovial membranes, and adipose tissues and have been shown to differentiate into not only mesenchymal tissues such as bone and cartilage [13,14] but also ectodermal cells such as neurons, and endodermal cells such as hepatocytes [15-17]. Hence, mesenchymal stem cells have been widely applied in animal models and human studies of stroke and cerebral ischemia [18-20].

In recent studies, the use of adipose-tissue derived mesenchymal stem cells (ADSCs) has increased because of their abundance in adipose tissues and the ease of isolation. Furthermore, methods for differentiation of ADSCs into various cells types, such as nerve cells, chondrocytes, pancreatic β cells, myocardial cells, and hepatocytes are well established [21]. In addition, mesenchymal stem cells and ADSCs are expected to be applicable to regenerative medicine because of their multipotency. Because various functional foods influence the differentiation of these stem cells into mature cells, it is important to determine the effect of dietary ingredients on osteogenic, lipogenic, and neurogenic cell differentiation.

The effects of phytoestrogens, such as genistein, daidzein, glycitein, and phytohormones, such as kaempferol and xanthohumol phytoestrogen, on osteogenic and adipogenic differentiation of mesenchymal stem cells have been comprehensively reviewed [22]. Hence, in this review we described the effects of other nutrients.

Neural stem cell

Neural stem cells are present in developing and adult mammalian nervous systems of all mammals and have been investigated in humans [23]. Neural stem cells are located at neurogenic cerebral regions, such as the anterior sub ventricular zone and the subglandular zone, and can differentiate into nerve and glial cells (astrocytes and oligodendrocytes) [24,25], thus acting as a supply of nerve cells [23,26]. Neural stem cells are protective against neurodegenerative disease [27] and replace injured or dysfunctional neurons and glial cells in response to environmental demands and perhaps during aging [28]. Multiple investigations of regenerative biology have explored the application of neural stem cells to ameliorate memory loss, depression, and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [24,25,29,30].

Cardiac stem cell

Cardiomyocytes were previously thought to remain alive throughout life without regenerative abilities. However, in a recent study, regeneration of cardiac tissue, including cardiomyocytes, was reportedly similar to that in other organs [31], and cardiac stem cells expressing c-Kit have been identified [32]. Cardiac stem cells are classified as myogenic or vasculogenic and regulate the regeneration of cardiomyocytes or manage the turnover of coronary arteries, respectively [33,34]. Accordingly, the efficacy of myogenic cardiac stem cells on chronic ischemic heart disease was examined in an interim report of a phase I clinical trial in the US [35,36].

Hair follicle stem cell

Hair follicles grow in cycles comprising hair development (anagen), hair regression (catagen), and follicle rest (telogen). Hair follicle stem cells are located in several areas, such as bulge regions [37,38], and are marked by expression of CD34, Keratin 15 (Krt15), and integrin α 6 [39,40], and by unique gene signatures [40,41]. Hair follicle stem cells can differentiate into neural, glial (astrocyte and oligodendrocyte), keratinocyte, smooth muscle, and melanocyte cells [42,43], and reportedly lead to skin cancer upon dysregulation of STAT3 [44]. In cases of injury, hair follicle stem cells can repopulate the interfollicular epidermis during wound healing [39], and injury and subsequent inflammation in regions including hair follicle stem cells lead to permanent alopecia [45,46]. Because isolation of hair follicle stem cells is easy and safe, their clinical application to the regeneration of hair follicles and peripheral nerves is expected.

Intestinal stem cell

Intestinal epithelial cells play various important roles and are critical for absorption of nutrients and as a barrier against intestinal flora. Most functions of these cells are achieved in villi that protrude into the intestinal lumen. Whereas villi predominantly comprise differentiated cells, crypts include intestinal stem cells, which are located at the basal layer of intestinal mucosal structures. Moreover, recent reports revealed that $Lgr5^{+}$ intestinal stem cells [47] form organoids that include enterocyte, paneth, goblet, and enteroendocrine cells [48]. Unlike other somatic stem cells, Lgr^{5+} intestinal stem cells divide approximately once a day and proliferate rapidly to supply intestinal epithelial cells, which turnover every 3–5 days [47]. However, due to this rapid turnover, intestinal stem cells tend to be comparatively susceptible to damage by radiation and chemotherapy.

Muscle stem cell

Similar to skin and liver tissues, skeletal muscle has the most regenerative potential. Satellite cells are specific somatic stem cells of skeletal muscle and play important roles in the regeneration of skeletal muscle [49]. Accordingly, reductions of skeletal muscle weight with aging, also called sarcopenia, are correlated with changes in the quantity and quality of muscle satellite cells [50]. In addition, reduced regenerative capacity of skeletal muscle is related to the onset of sarcopenia [51].

Germ line stem cell

Germ line stem cells have gender-specific characteristics, including the loss of self-renewal capacity of female germ line stem cells, and reduced division has been observed with sexual differentiation, leading to decreased cell numbers after birth. In contrast, male spermatogonial germ stem cells are preserved in the testes throughout life and produce approximately 1.23×10^{8} spermatozoon cells per day [52,53]. Recently, the induction of multipotent stem cells from spermatogonial stem cells [54-56] and the differentiation from spermatogonial stem cells into mature spermatozoa [57] were reported, and the application of spermatogonial stem cells for the treatment of male infertility disorders such as azoospermia and oligospermia is expected.

Nutrients and Somatic Stem Cells

Vitamin A and its metabolites

Vitamin A and its metabolites such as retinol, retinal, and retinoic acid play important roles in hair follicle cycles, and the

overexpression of dominant negative retinoic acid receptor in the epidermis reportedly leads to aberrant skin and no hair [58]. Moreover, the vitamin A metabolite All-trans Retinoic Acid (ATRA) was shown to alter stem cells to regulate hair cycles at both telogen-anagen and anagen-catagen stages [59]. ATRA and the retinoid signaling pathway are also involved in several neurogenetic processes, including neuronal differentiation and proliferation of neurite outgrowth and synaptogenesis [60,61]. Retinoic acid receptor beta over-expression promoted neuronal differentiation and the neuronal differentiation promoting effects of ATRA on mesenchymal stem cells could be inhibited by siRNA silencing of retinoic acid receptor beta and by LE135, an inhibitor of retinoic acid receptor beta. Thus, pre-treatment with ATRA facilitated neuronal differentiation of mesenchymal stem cells and activates retinoic acid receptor β through the retinoid signaling pathway [62,63].

Retinoic acid reportedly influences hematopoietic development and embryonic stem cell differentiation *in vitro* [64,65]. Accordingly, Chanda et al. showed that activation of retinoic acid signaling dramatically enhanced hematopoietic stem cell potential, whereas conditional inactivation of the retinoic acid metabolizing enzyme retinal dehydrogenase 2 abrogated hematopoietic stem cell development in the embryonic state. Wnt signaling was also shown to completely block the induction of hematopoietic stem cells by retinoic acid modulators, whereas inhibition of this pathway promoted the development of hematopoietic stem cells in the absence of retinoic acid signaling. These data suggest that retinoic acid and Wnt signaling are key regulators of hematopoietic stem cell development [66].

Vitamin A is required for normal spermatogenesis [67,68], and nuclear receptors for retinoic acid are expressed in testes germ cells and in Sertoli and Leydig cells [69]. Houston et al. investigated the effects of a vitamin A deficient diet on testes morphology and spermatogonial stem cells in mice. Their experiments showed arrested development of germ cell differentiation, increased germ cell apoptosis, alterations of transcriptome profiles of spermatogonia, and disruption of spermatogonial stem cell organization in vitamin A deficient mice [70].

Lipids

Fatty acid: In adults, early changes of the neurogenic niches correlate with the development of diabetic complications [71]. Moreover, fat, fatty acids, their metabolites and intracellular carriers, cholesterol, and vitamins may affect proliferation and differentiation of embryonic and adult neural stem cells [72]. Accordingly, excess intake of saturated fatty acids increases the risk of impaired cognitive function [73], learning and memory performance, and the development of Alzheimer's disease-like pathophysiological changes in the brain [74]. In particular, palmitic acid causes mitochondrial dysfunction and subsequent apoptosis of various cells, including neurons and astrocytes, in the central nervous system [75,76]. In addition, treatments with palmitic acid lead to apoptosis in neural stem cells via increased protein levels of Bax and cleaved caspase 3 coupled with decreased expression of Bcl-2 [77]. In another study, toxic concentrations of palmitic acid inhibited the proliferation of neural stem cells and correlated with reactive oxygen species generation. Furthermore, nontoxic levels of palmitic acid promote astrocytogenesis in differentiated neural stem cells and are associated with Stat3 activation and altered expression of a series of basic helix-loop-helix transcription factor genes that are involved neural stem cell fate [78].

Neural stem cells express cannabinoid B1 and B2 (CB1 and CB2) receptors and enzymes for the biosynthesis and metabolism of Endocannabinoids (eCBs) [79]. Administration of CB1 or CB2 agonists affects the fate of neural stem cells [80,81], suggesting direct regulation of adult neurogenesis by the eCB system. Moreover, the n-6 PUFA precursor linoleic acid enhances eCB signaling in neural stem cells and subsequently leads to CB-1-dependent astrogliogenesis [82].

Supplementation of human diets with n-3 fatty acids reportedly impairs several aspects of neutrophil, monocyte, and lymphocyte function and selectively inhibits inflammatory responses without affecting T- and B-cell functions [83]. Melinda et al. showed that diets rich in n-3 fatty acids reduce the sizes of myeloid progenitors and then investigated the influence of n-3 and n-6 fatty acids using a hematopoietic stem cell line (EML-clone). Unexpectedly, their results indicated no differences in viability or proliferation of cells cultured in the presence of Eicosapentaenoic acid (n-3 FA) or arachidonic acid (n-6 FA), but demonstrated that arachidonic acid favors production of progenitor cells of granulocyte and macrophage lineages [84].

Saturated fatty acids reportedly promote colorectal cancer, whereas n-3 polyunsaturated fatty acids (PUFAs) are protective [85]. Accordingly, Dimantov et al. examined the effect of n-3 PUFAs on the relationship between intestinal stem cells and intestinal ontogenesis using db/db mice (insulin-resistant and obese), fat-1 transgenic mice (a transgene coding for desaturation of n-6 PUFA into n-3 PUFA), db/db crossed with fat-1 mice, and control mice. In these experiments, diabetic obesity resulted in increased colonic proliferation and dedifferentiation of epithelial colonocytes and goblet cells, with increased colonic hepatocyte nuclear factor-4α (HNF-4α) transcriptional activities. HNF-4α regulates proliferation and differentiation of adult colonocytes, and its genetic perturbation causes progression of colorectal cancer. In fat-1 transgenic mice, restrained colonic proliferation is accompanied by differentiation of intestinal stem cells into epithelial colonocytes and goblet cells by decreasing colonic expression of HNF-4α [86,87]. Taken together, these data indicate that n-3 PUFAs act as natural HNF-4a antagonists and may have potential in the treatment of colorectal cancer.

High fat diet: High-fat diets cause inflammation and neuronal damage in the hypothalamus, as indicated by decreased numbers of proliferating cells and surviving neurons [88,89], exhibiting reduced sensitivities to hormones such as insulin and leptin, leading to the onset of central insulin and leptin resistance. Accordingly, chronic high-fat diet feeding leads to the depletion and neurogenic impairment of hypothalamic neural stem cells, is associated with IKKβ/NF-κB activation, and ultimately leads to the development of obesity and pre-diabetic conditions [90].

High fat diets are also a risk factor for colon cancer [91]. Padidar et al. examined the association between intestinal stem cells and high-fat diet feeding in a mouse model of tumorigenesis using azoxymethane, which is widely used to induce aberrant crypt foci. In comparison with low-fat fed mice, the expression of IL-6, which is associated with colon cancer, and the induction of aberrant crypt foci were significantly enhanced in high-fat fed mice. Moreover, Lgr5 expression is higher in the distal colon after high fat feeding, whereas no changes are seen in low-fat fed mice during these experiments, suggesting that increases Lgr5 expression in response to diet reflects proliferative activity of stem cells in colon crypts [92,93].

In addition, other lipids, such as lipoprotein and cholesterol, have reported effects on somatic stem cells [2], and multiple functional foods have been shown to decrease lipoprotein and cholesterol levels, suggesting that these lipids interact in somatic stem cells.

Polyphenols

Resveratrol: The effects of resveratrol on cardiovascular disease are well-established and follow stimulation of endothelial nitric oxide production, reduced oxidative stress, inhibition of vascular inflammation, and prevention of platelet aggregation. In animal models of cardiovascular disease, resveratrol is protective against ischemia-reperfusion injury in the heart, reduces blood pressure and cardiac hypertrophy in hypertensive animals, and delays the progression of atherosclerosis [94]. Resveratol also suppresses cell senescence by reducing targets of rapamycin complex 1 activation, which regulates cell cycle progression [95]. Cardiac stem cells from human hearts following cardiac transplantation show features of senescence, and combinations of resveratrol and rapamycin improves the abilities of cardiac stem cell to induce cardiac repair upon injections into infarcted hearts of SCID mice. Subsequently, reduced cardiomyocyte senescence and apoptosis and increased abundance of endogenous c-Kit$^+$ cardiac stem cells are observed in the peri-infarct area [96].

Diabetes mellitus is considered an independent risk factor for cardiomyopathy, and cardiac stem cells likely play roles in diabetic cardiac dysfunction [97]. Administration of resveratrol to streptozotocin-injected diabetic rats reduces atrial cardiac stem cell loss, preserves functional abilities of cardiac stem cells and mature cardiac cells, improves cardiac environment by ameliorating inflammation, and decreases unfavorable ventricular remodeling of diabetic hearts, resulting in marked recovery of ventricular function [98].

Mesenchymal stem cells have been investigated as a treatment for severe radiation injuries with lung and salivary gland damage [99,100]. However, mesenchymal stem cells are more sensitive to radiation, warranting further exploration of strategies that protect stem cells from radiation damage. Sirtuin 1 (Sirt1) has reported anti-inflammatory properties that reflect inhibition of NF-κB signaling [101]. Resveratrol is a well-known activator of Sirt1 [102], and resveratrol pre-treatment significantly improves survival rates in irradiated mice [103]. Fu et al. examined the efficacy of resveratrol on radiation damage and showed that radiation activates IL-1β secretion and the NLRP3 inflammasome, which are required for NF-κB activation, and that resveratrol reduces these effects by up regulating Sirt1 in mesenchymal stem cells [104].

Tea polyphenol: In osteoporotic patients, the activities of mesenchymal stem cell-derived osteoblasts are inhibited and osteogenic differentiation is decreased with increasing bone marrow adipogenesis [105,106]. Mesenchymal stem cell differentiation into adipocytes or osteoblasts can be switched under several conditions, including drugs, oxidative stress, nutrient levels, hormones, and metabolic signals, and some stimuli induce differentiation in one direction at the cost of the other [107]. Recently, mesenchymal stem cells were used to treat bone fractures and osteoporotic bone defects [108], warranting enhancement of osteogenesis from mesenchymal stem cells to produce a potent therapy for bone diseases like osteoporosis [109].

Green tea has been studied extensively as a dietary supplement because it contains polyphenols such as (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC) [110]. These compounds reportedly prevent cancer [111], cardiovascular disease [112], type 2 diabetes [113], and neurodegenerative disorder [114]. Recently, beneficial effects of tea drinking on bone density in older women were reported [115]. Treatment of rat mesenchymal stem cells with 20 μM EGC stimulates ALP activity, increases extracellular matrix mineralization, and enhances the expression of osteogenic genes such as RUNX II, ALP, osteonectin, and osteopontin. In addition, EGC significantly inhibits the expression of adipogenic genes such as PPAR-γ, C/EBP-β, and FABP4 [116]. ECG and EGCG were also reported to promote osteogenesis. ECG stimulated osteoblast differentiation by activation of RUNX II in human mesenchymal stem cells [117]. EGCG was able to enhance osteogenesis in the presence of osteoinductive agents through the upregulation of bone morphogenic protein 2 expression in human bone marrow derived stem cells [118]. These observations support the potential use of green tea to protect bone against degenerative diseases such as osteoporosis. In contrast with EGC and ECG, Shin *et al*. observed that (-)-catechin stereospecifically transactivated PPAR-γ and increased the expression of the adipogenic markers FABP4 and adiponectin, leading to increased adipocyte differentiation [119]. Hence, the effects of green tea polyphenols remain controversial, and further studies of the health benefits of green tea intake are needed.

In addition to osteogenesis, EGCG is reported to be involved in the promotion of angiogenesis of mesenchymal stem cells, leading to support wound healing. Proangiogenic properties have been demonstrated in mesenchymal stem cells isolated from murine tissues, including bone marrow, white adipose tissue, skeletal muscle, and myocardium [120]. Therefore, mesenchymal stem cells-based therapies have the potential to activate a series of coordinated cellular processes, including angiogenesis. In a rat model, a single dose of EGCG at 10 mg/kg increased the efficiency of mesenchymal stem cells-induced skin wound closure. 20 days after the wound induction, mesenchymal stem cell treatment significantly enhanced the epidermal thickness, which was further increased by EGCG administration [121].

Chemicals such as β-mercaptoethanol, dimethyl sulfoxide, and butylated hydroxyanisole have been used to induce neuronal differentiation of mesenchymal stem cells [122-124]. However, because these chemicals potently cause cell death, they are not suitable for *in vivo* experiments [125,126], and non-toxic inducers of neurogenesis are required. Treatment of mesenchymal stem cells with tea polyphenol induces differentiation into neuron-like cells with similar efficacy as β-mercaptoethanol. However, the identities of the tea polyphenols used in this study were not reported [127].

Pine bark extract polyphenol: Accumulation of reactive oxygen species (ROS) has been clearly correlated with sarcopenia and may contribute to the impairment of satellite cell function via calpain (calcium-dependent protease)-dependent pathways. Moreover, calpain activity is dramatically upregulated in the muscles of old rats as compared with young rats [128], and polyphenol from pine bark extracts prevent apoptosis and calpain activation in satellite cells [129]. In addition, Poussard et al. identified several proteins that function as early regulators of ROS-mediated events in muscle satellite cells using large-scale proteomics approaches. In these studies, the stress chaperone heat shock protein beta-1 (HSPB1), which protects against muscle necrosis, was a target of pine bark extract, and levels of its phosphorylated form were increased during skeletal muscle aging. Moreover, pine bark extract polyphenol suppresses stress-induced phosphorylation of HSPB1 [130,131].

Grape seed derived proanthocyanidins: Acute skeletal muscle damage results in fiber disruption, oxidative stress, and inflammation. Satellite cells at the site of damage expand through proliferation to form

a population of myoblast precursor cells [50]. In addition, satellite cells could migrate from adjacent muscle fibers if a sufficient connection remains between the damaged and undamaged regions [132]. Grape seed extract is reported to have a high antioxidant potential such as the modulation of antioxidant enzyme expression and protection against oxidative damage in cells [133,134]. Therefore, Smith et al. examined the influence of grape seed extract on satellite sells in a contusion-induced muscle damage rat model. Grape-seed-derived proanthocyanidolic oligomers (proanthocyanidins) increase and accelerate satellite cell response, limit the induction of inflammatory cytokines, and increase free radical quenching capacity, leading to improved effective regeneration [135].

Geraniin: Geraniin is water-soluble polyphenol tannin with reported antioxidant properties [136], therefore, protects cells from radiation-induced oxidative stress and subsequent DNA damage by enhancing antioxidant enzyme activities [137]. Bing et al. demonstrated that geraniin from *Nymphaea tetragona* effectively protects intestinal stem cells against radiation toxicity by modulating p53-dependent mitochondrial signaling and reduces DNA damage and promotes proliferation in a mouse model [138], suggesting that geraniin may be a candidate non-toxic radioprotective agent.

Tart cherry: Increased intakes of anti-inflammatory polyphenols are associated with a significant reduction of cardiovascular disease incidence compared with individuals with low polyphenol intakes [139]. Tart cherry have some health effect including antioxidant [140], anti-tumorigenic [141], and anti-inflammatory properties [141,142]. Adipose tissue, and particularly adipose derived mesenchymal stem cells, secreted the highest levels of inflammatory factors [143]. Hence, Zhou et al. investigated anti-inflammatory effect of tart cherry anthocyanins on mice adipose derived mesenchymal stem cells. Tart cherry inhibit LPS-induced IL6 secretion from adipose derived mesenchymal stem cells. Importantly, its effect was synergistically enhanced by simvastatin which are used primarily for prevention of cardiovascular disease-associated event. These results suggest that combination treatment with tart cherry and simvastatin might lead to newly treatment strategies for cardiovascular disease [144].

Herbal medicine and its ingredients

Juzen-taiho-to: Several herbal medicines have reported impacts on hematopoietic stem cells. In particular, the Japanese herbal medicine Juzen-taiho-to has traditionally been administered to patients with anemia, anorexia, or fatigue, and reportedly enhances peripheral blood counts in cancer patients after chemo and/or radiation therapy [145]. Accordingly, Hisha et al. revealed that n-hexane extract fractions from Juzen-taiho-to container active components that influence hematopoietic stem cells, including the free fatty acids oleic acid and linolenic acid. Moreover, administration of oleic acid to mitomycin-C-treated mice enhances spleen colony-forming unit (CFU-S) counts, suggesting that fatty acids in Juzen-taiho-to actively promote the proliferation of hematopoietic stem cells [145].

Bojungbangdocktang: The Korean herbal medicine Bojungbangdocktang (BJBDT) reportedly prevents cisplatin-induced toxicity and apoptosis in human normal breast epithelial cells, but not in breast cancer cells [146]. Moreover, the BJBDT components *Astragalus membranaceus* and *Panax ginseng* can were shown to induce hematopoiesis [147,148]. Lim et al. investigated the influence of BJBDT on hematopoietic stem cells and showed significant increases in mRNA expression of hematopoietic cytokines such as IL-3, GM-CSF, and erythropoietin. BJBDT also enhances the phosphorylation of Janus activated kinase 2 (JAK2) and STAT5, and STAT binding to gamma interferon activated sites. These results suggest that BJBDT enhances hematopoiesis via hematopoietic cytokine-mediated JAK2/STAT5 signaling and may act as a potent cancer preventive agent [149].

Ka-mi-kae-kyuk-tang: Ethanol extracts of ka-mi-kae-kyuk-tang (KMKKT), which is an herbal formula comprising 10 Korean and Chinese herbs including *Angelica gigas*, *Panax ginseng*, *Zanthoxylum piperitum*, and *Patrinia villosa* has potent antiangiogenic, anticancer, and anti-metastatic activities *in vivo*, and no side effects have been observed [150]. Because several medicinal herbs in KMKKT have been used to treat anemia, leukopenia, and thrombocytopenia, Seo et al. examined whether KMKKT ameliorates Cyclophosphamide (CPA)-induced hematological toxicity. In this study, KMKKT mitigated hepatotoxicities such as anemia and leukopenia, and increased numbers of stem cells expressing CD34, CD117, and Sca1 in CPA-treated mice. These data indicate that KMKKT stimulates hematopoietic stem cell signaling and compensates for CPA-induced cytotoxicity in leukocytes and other cell types [151].

***Chrysanthemum zawadskii*:** *Chrysanthemum zawadskii* has been used as a Korean traditional medicine for the treatment of various diseases, including cough, common cold, bladder-related disorders, gastroenteric disorders, hypertension, and inflammatory diseases such as pneumonia, bronchitis, pharyngitis, and rheumatoid arthritis [152]. The effective constituents comprised terpenoids and essential oils, as well as flavonoids and polysaccharides. Terpenoids and flavonoids are considered the active pharmaceutical ingredients and flower extracts have been shown to have numerous pharmacological properties, including anti-allergic, anti-inflammatory and anticancer activities [153-155]. *C. zawadskii* reportedly possess hair growth activity and has been used as a treatment for hair loss. Herein, Li et al. investigated the influence of *C. zawadskii* on hair follicle cells and revealed that water fractions of *C. zawadskii* extracts stimulate differentiation and proliferation of pluripotent epidermal matrix cells in the matrix region and in epithelial stem cells of the basal layer of the epidermis [156]. *C. zawadskii* may be developed as a therapeutic agent for the prevention of hair loss.

Momordica foetida: *Momordica foetida* (Cucurbitaceae) is widely distributed in tropical Africa. Drinking of aqueous leaf extracts of t *M. foetida* to treat malaria is reported in East and Central Africa. Other medicinal uses of extracts of *M. foetida* include the treatment of hypertension, peptic ulcers, diabetes mellitus, and as a purgative [157,158]. Curcubitane triterpenoids, polyphenolic compounds, have been isolated from leaf extracts, and alkaloids and glycosides from whole plant extracts. Antidiabetic and antilipogenic activities were also reported for some Momordica species [159]. It has been suggested that increased ROS levels promote adipogenesis from ADSCs [160]. Therefore, Acquaviva et al. evaluated that the free radical scavenging capacity of different concentrations of aqueous, methanolic and dichloromethane leaf extracts of *M. foetida* by *in vitro* assays using Human Adipose Mesenchymal Stem Cell (hMSC) in order to test the hypothesis that these extracts may also affect adipocyte differentiation. Accordingly, aqueous extracts of *M. foetida* scavenge free radicals and decrease ROS levels, leading to the inhibition of adipogenesis from human ADSCs [158]. Hence, *M. foetida* might be useful in preventing metabolic syndrome.

Other functional nutrients

Oleuropein: Oleuropein is a phenolic compound that is abundant in olive oil and has powerful antioxidant and anti-inflammatory

properties and prevents the loss of bone mass in a senile rat model of osteoporosis [161,162]. Moreover, oleuropein enhances the expression of the osteoblast-correlated genes RUNX II, osterix, osteocalcin, and ALP. In contrast, oleuropein suppresses adipogenesis genes such as PPARγ, lipoprotein lipase, and FABP 4 in mesenchymal stem cells. Accordingly, it was suggested that oleuropein increases osteoblast differentiation and decreases adipocyte differentiation [163].

Astaxanthin: Astaxanthin is the principal pigment in crustaceans, salmonoids, and many other organisms [164]. Astaxanthin has antioxidant properties and enhances immune responses [165], cancer chemoprevention [166], and neuroprotective actions [167-169]. Therefore, Choi et al. isolated neural stem cells from mice and treated with astaxanthin. Astaxanthin increases the expression of the proliferation-related protein PI3K in neural stem cells, and subsequent induction of its downstream mediators such as p-MEK, p-ERK, and p-Stat3, resulting in subsequent induction of expression of proliferation-related transcription factors Rex1, CDK1, and CDK2 and the stem cell genes OCT4, SOX2, Nanog, and KLF4. Moreover, astaxanthin-treated neural stem cells showed prominent intracellular calcium deposits and fat formations, suggesting that astaxanthin also improves osteogenic and adipogenic differentiation potential of neural stem cells. These results collectively suggested that astaxanthin controls proliferation and differentiation of neural stem cells [170].

GABA: Gamma-amino Butyric Acid (GABA) is a primary inhibitory neurotransmitter in the central nervous system. In addition to traditional neurotransmission, GABA is considered to have roles in a trophic factor during both embryonic and adult neurogenesis, regulating key developmental steps, such as proliferation, differentiation and migration [171-173]. The inhibitory effect of GABA on cell proliferation is not restricted to the nervous system. GABA receptors have been identified in testis and spermatozoa [174,175]. In the male reproductive system, GABA has been shown to promote the acrosome reaction of spermatozoa [175,176]. However, the precise physiological function of GABA in germ cell development remains unclear. Du et al. demonstrated that GABA and its synthesizing enzymes are abundant in spermatogonial stem cells. Subsequently, these investigators showed that GABA reduces spermatogonial stem cell proliferation independently of apoptosis, suggesting that GABA negatively regulates spermatogonial stem cell proliferation to maintain homeostasis of spermatogenesis in the testes [177].

Sulforaphane: Myostatin is a member of the transforming growth factor-β superfamily and is a potent inhibitor of skeletal muscle growth [178], Myostatin also suppresses satellite cell activation and self-renewal of satellite cells [179]. Sulforaphane is present at high concentrations in broccoli and broccoli sprouts and acts as a histone deacetylase inhibitor. Critically, sulforaphane treatment significantly represses myostatin expression and strongly attenuates the expression of negative feedback inhibitors of the myostatin signaling pathway in porcine satellite cells via epigenetic mechanisms. Sulforaphane also reduces the expression of the myogenic marker *MyoD* and diminishes the binding of *MyoD* to the myostatin promoter and hypoacetylation of the *MyoD* binding site [180]. Hence, the biological activities of sulforaphane in satellite cells may facilitate the development of novel approaches to reducing myostatin signaling for the treatment of human skeletal muscle disorders.

Taurine: Taurine has many biological properties including antioxidation, osmoregulation, and conjugation of bile acids [181,182]. Taurine reporter was expressed in osteoblast, and taurin stimulated ALP activity and osteocalcin secretion [183]. Moreover, taurin inhibited osteoclastogenesis through the taurine transporter [184]. Zhou et al. investigated the effect of taurine on osteogenic differentiation of human bone marrow derived mesenchymal stem cells. Turine increased ALP activity, promoted mineralization, and activated extracellular signal regulated kinase (ERK) 1/2 signaling pathways which plays an important role in the osteogenic differentiation, suggesting that taurine promoted osteogeneis of mesenchymal stem cells [185].

Discussion

We have summarized the effects of various dietary ingredients that influence somatic stem cells (Table 1). Those functional ingredients have reported effects on the maintenance of somatic stem cell functions and can ameliorate inflammation, aging, and cancer. Hence, further understanding of functional ingredients that promote differentiation of somatic stem cells into mature cells might contribute to the development of regenerative medicines (Figure 1). However, the related mechanisms remain incompletely characterized. Changes in patterns of DNA methylation, histone modification, and RNA Interference (RNAi) have been reported in cancer, diabetes, and in various inflammatory disorders [186]. These epigenetic modifications may be important during differentiation of somatic stem cells [187,188]. Several studies demonstrate that natural polyphenols, such as curcumin, resveratrol, and catechins, induce epigenetic modifications [189]. In addition, among small RNA molecules with RNAi activities, micro RNA (miR) reportedly regulates gene expression in somatic stem cells via epigenetic alterations [190], and many dietary components have been shown to regulate the expression of miR [191]. Because epigenetic changes occur during initial phases of most disorders, interventional approaches that target the epigenome have been proposed as preventive and therapeutic strategies. Further studies of epigenetic regulation by dietary components are required.

In this review, we focused on scientific evidence of relationships between dietary components and several somatic stem cells. In addition to those mentioned above, other tissue-specific somatic stem cells have been reported, including in the liver [192], lung [193], and kidney [194]. Therefore, there is a possibility of finding new dietary component that affect somatic stem cells. Finally, most studies of somatic stem cells have been conducted using animal models and human cell lines due to the difficulties of isolating somatic stem cells from human samples. Thus, future clinical studies are required to confirm the benefits of functional foods in somatic stem cells.

Conclusion

The influences of various dietary ingredients on somatic stem cell biology have been summarized in the context of tissue regeneration and protection of normal tissue against disease pathogenesis and chemotherapy. Our review might contribute to basic research and clinical regenerative applications using dietary functional food.

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Author's Contributions

Hayato Urushima carried out the search of relative journals and a drafted the manuscript. Asuka Yasueda and Toshinori Ito drafted and revised the manuscript. All authors's read and approved the final manuscript.

Dietary component	Dietary component	Experimental subject	Dose	The influence on somatic stem cells
Vitamin A and its derivatives	All tans retinoid acid (ATRA)	Genetically modified mice in retinoic acid pathway		Alter HFSCs to regulate hair cycle at both the telogen to anagen and anagen to catagen
		Rat bone marrow derived mesenchymal stem cells	0.01-100 μM	Improve the neuronal differentiation efficiency of MSCs and upregulate retinoic acid receptor
		Rat bone marrow derived mesenchymal stem cells	1 μM	Improve the efficiency of neuronal differentiation of MSCs associated with activation of the retinoid signaling pathway
	Retinoic acid	Mice, Genetic modification to inactivate of the retinoic acid metabolizing enzyme retinal dehydrogenase 2	Analyse embryonic hematopoietic cell development	Promote HSCs development through the transient downregulation of Wnt signaling
	Vitamin A	Fed vitamin A deficiency diet or control diet to mice	4000 IU/kg diet vs. 0 IU/kg diet for 28weeks	The deficiency of vit A caused to arrested germ cell differentiation, increase germ cell apoptosis , alteration of transcriptome profile of spermatogonia, and disruption of SSCs organization
Lipids Fatty acid	Palmitic acid	Mice neural stem cells	50-800 μM	Lead to the apoptosis of NSCs via increase protein levels of Bax and cleaved caspase 3 coupled with decreased expression of Bcl-2 and inhibited the proliferation of NSCs, which is correlated with reactive oxygen species generation.
	Linoleic acid	Mice neural stem cells	25-400 μM	Promote astrocytogenesis
	Linoleic acid	Mice neural stem cells	0.4-2 μM	Enhance eCB signaling in NSCs and subsequently CB-1 dependent astrogliogenesis
	Omega 3 fatty acid	Fed adjustment diet to mice	Diet containing n-3 or n-6 in about 60% of fats for 14 weeks	More rapidly produce progenitors of macrophage developmental marker F4/80
	n-3 PUFA	Comparison among WT , db/db, and Fat-1 transgenic mice	Analyse colonic composition of (n-3)/(n-6) PUFA	Suppress intestinal HNF-4α activity and ameliorate diabesity-induced intestinal ontogenesis
	High Fat	Fed high fat diet to mice	45kcal% diet for 4 months	Deplete and impair neurogenesis of hypothalamic NSCs associated with IKKβ/NF-κB activation
		Fed high fat diet to azoxymethane-induced cancer model mice	60% fat by energy vs. 10% fat by energy for 16 weeks with or without carcinogen treatment	Increase activity of proliferative ISCs in the colon crypts
Polyphenols	Resveratrol	Human cardiac stem cells isolated from failing explanted heart	0.5 μM	Improve CSCs capacity to induce cardiac repair by increase abundance of c-Kit+ CSCs in the peri-infarct area
		i.p. injection to rat	2.5 mg/Kg/day for 8 weeks	Improve cardiac environment by reducing inflammatory state and ameliorate diabetic cardiac dysfunction
		Human bone marrow derived mesenchymal stem cells	50-200 μM	Protect MSCs from radiation via activation of Sirt 1 and reduction of IL-1β and NLRP3
	Tea polyphenols			
	(-)-epigallocatechin (EGC)	Rat bone marrow derived mesenchymal stem cells	2-20 μM	Enhance osteogenic gene expression such as Runx2 and osteonectin, and stimulate ALP activity Inhibit adipogenic gene expression like PPAR-γ and C/EBP-β, and FABP4
	(-)-epicatechin-3-gallate (ECG)	Human bone marrow derived mesenchymal stem cells	1-10 μM	Stimulate osteoblast differentiation by activation of RunX2
	(-)-catechin	Human bone marrow derived mesenchymal stem cells	1-10 μM	Promote adipocyte differentiation via increase the expression of adipogenic marker such as PPARγ, FABP4 and adiponectin
	Epigallocatechin-3-gallate (EGCG)	Human bone marrow derived mesenchymal stem cells	2.5-10 μM	Enhance osteogenesis in the presence of osteoinductive agents through the upregulation of BMP2 expression
		Rat model of wound healing	10 mg/kg for 20 days	Enhance the wound healing efficacy of mesenchymal stem cells
	Tea polyphenol	Mice bone marrow derived mesenchymal stem cells	10-50 μg/mL	Promote neurogenesis as similar level of stimulated by chemical inducer
	Pine bark extract	Human satellite cells LHCN-M2	Extract of pine bark (oligomeric procyanidins: 28%monomers, 18% dimers and 50% trimers up to pentamers)	Suppress the stress-induced phosphorylation of HSPB1 which correlated skeletal muscle aging
	Grape seed-derived proanthocyanidolic oligomer	Oral gavage to rat	Hydrophilic extract (contains 45% proanthocyanidins) for 28 days	Increase and accelerate satellite cell response
	Geraniin	Injected intraperitoneally twice into mice before irradiation	25 mg/kg	Protect ISCs against radiation toxicity via modulating p53, mitochondria-dependent pathway, lessening DNA damage along with promoting proliferation capacity
	Tart cherry anthocyanins	Mice adipose derived mesenchymal stem cells	125-500 μg/mL	Inhibit LPS-induced IL6 production from ADSCs

Herbal medicine	Juzen-taiho-to	Mice bone marrow derived hematopoietic cells	Water extract 10-100 μM	Promote the proliferation of HSCs
	Bo-jung-bang-dock-tang	Mice were induced aplastic anemia with or without Bo-jung-dock-tang	Once daily oral gavege of 25 or 250 mg/kg for 14 days treatment. Then, hematopoietic stem cells were analyzed	Enhance hematopoiesis via hematopoietic cytokine-mediated JAK2/ STAT5 pathway
	Ka-mi-kae-kyuk-tang	Mice were induced anemia and leukopenia with or without Ka-mi-kae-kyuk-tang treatment.	Once daily oral gavege of 25 or 250 mg/kg for 14 days	Stimulate HSCs signaling to compensate for CPA-induced destruction of leukocytes and other cell types
	Chrysanthemum zawadskii	Daily topical application to skin	Water or N-butanol fraction of 70% ethanol extract 1600 mg/ kg body weight for 30 days	Stimulate the differentiation and proliferation of HFSCs in the matrix region and basal layer of epidermis
	Momordica foetida	Human adipose derived mesenchymal stem cells	Extract of aqueous, methanolic, and dichloromethane	Inhibit adipogenesis of ADSCs by reduction of ROS
Others	Oleuropein	Human bone marrow derived mesenchymal stem cells	1-100 μM	Increase osteoblast differentiation and decrease adipocyte differentiation
	Astaxanthin	Mice neural stem cells	1-10 ng/mL	Improve the proliferative capacity of NSCs and induce the improvement of oestrogenic and adipogenic differentiation potential of NSCs
	GABA	Spermatogonial stem cells of mice	500 μM, culture for 6 days	Reduce SSCs proliferation
	Sulforaphane	Porcine muscle satellite cells	5-15 μM	Control the signaling pathway of myostatin which regulate skeletal muscle growth
	Taurine	Human bone marrow derived mesenchymal stem cells	1-10 mM	Promote the osteogenesis of hMSCs by activating the ERK pathway

Table 1: Summary of the influence of functional foods upon somatic stem cells.

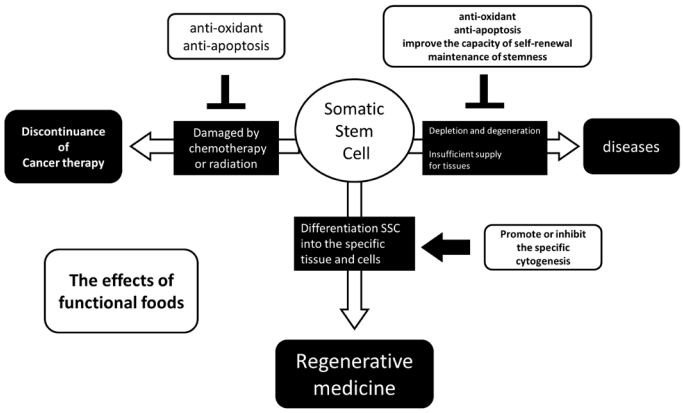

Figure 1: Differentiation of somatic stem cells into mature cells.

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