Journal of Functional Foods 66 (2020) 103822

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Dietary phytochemical approaches to stem cell regulation

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ARTICLE INFO

Keywords:
Differentiation
Phytochemical
Regenerative medicine
Self-renewal
Stem cell

ABSTRACT

Controlling self-renewal and lineage differentiation of stem cells (SCs) is critical for SC therapy in regenerative medicine. Multiple signal pathways such as Wnt, TGF-β and BMP are involved in modulating proliferation or specific differentiation of different types of SCs. Dietary phytochemicals, the major source of new drugs, are found to stimulate self-renewal and sub-population differentiation of SCs by activating/inhibiting the signal pathways (MAPK, canonical Wnt/β-catenin, AKT, etc.) and key transcription factors (OCT4, NANOG, Runx2, etc.). Dietary phytochemicals are important for SC therapy owing to the plethora of targets. In this review, we discussed the SC types and their regulatory mechanism. Applications of phenols, flavonoids, sterols and alkaloids chemicals from food or herbs on targeting SCs along with their molecular mechanisms are also discussed. Dietary phytochemicals are promising to enhance endogenous/exogenous SC therapy in various diseases.

1. Introduction

Mammalian tissue regeneration is restricted to the early stages of life and is progressively lost during development due to the decreasing regenerative capacities of endogenous stem cells (Porrello et al., 2011; Tsonis & Fox, 2009). In adult mammals, only a few organs such as the liver and blood can be fully regenerated after injury (Michalopoulos, 2007; Thomas, Lochte, Lu, & Ferrebee, 1957). In most other tissues, scar formation or fibrosis is the major consequence of injuries indicating the loss of regenerative capacity (Brockes & Kumar, 2008; Godwin & Rosenthal, 2014; Tanaka & Reddien, 2011). Endogenous stem cells reside inside specific tissues and they can self-renewal and differentiate into specific cell types. Moreover, endogenous stem cells have the advantage of mitigating risks of rejection and infection compared with exogenous stems cells (Squillaro, Peluso, & Galderisi, 2016). However, it is not easy to control the behaviors of endogenous stem cells due to the limited knowledge. So exogenous stems cells are widely studied for application in tissue repair and regeneration. Nowadays, the stem cells are used alone in clinical trials in many countries (https://www.clinicaltrials.gov/ct2/home). However, low survival rate and un-controlled differentiation of stem cells within the target regions hamper wound repair and limit the application of stem cell therapy and progress of regenerative medicine (Li, Li, Wei, & Ding, 2013). Therefore, the combined usage of stem cells and regulatory factors are promising for enhancing stem cell therapy.

Proliferation and differentiation of stem cells are controlled by various factors such as growth factors, bone morphogenetic protein (BMP2) and fibronectin (Busilacchi, Gigante, Mattioli-Belmonte, Manzotti, & Muzzarelli, 2013; Chatakun et al., 2014). Some key biological factors are selected to assist growth and lineage differentiation of stem cells. While these factors are generally proteins with low production and stability, and even the viral/endotoxin infection, which hampers the application of these factors in stem cell therapy (Dadashpour & Pilehvar-Soltanahmadi, 2017). In contrast, chemicals

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https://doi.org/10.1016/j.jff.2020.103822
Received 1 November 2019; Received in revised form 13 January 2020; Accepted 25 January 2020
Available online 14 February 2020

have advantages over biological factors and effectively modulate stem cell fate.

Plants provide essential nutrients for human life and also bioactive phytochemicals that contribute to disease prevention and treatment. The natural products from plants are valuable resources for marinating human health because plants are exposed to nature environmental changes and synthesize useful ingredients for acclimatization (Ashraf and Harris, 2004; Silva, Ribeiro, Ferreira-Silva, Viégas, & Silveira, 2010), which have therapeutic effects on human diseases. Plant-derived drugs contribute to human health since ancient times (Dillard & German, 2000; Yoo, Kim, Nam, & Lee, 2018). So phytochemicals are more promising than synthetic chemicals due to their generation from living organisms, potential biological actions and innate stereochemistry allowing their binding to protein pockets (Harvey, Edrada-Ebel, & Quinn, 2015). Nowadays, many phytochemicals are found to regulate specific targets involved in signaling, metabolic, or transcriptional mechanisms, which are valuable tools for probing basic stem cell biology and promoting stem cell survival, proliferation, lineage differentiation, reprogramming, homing and lineage conversion of adult stem cells (Liu, Yu, Xie, Li, & Ding, 2016; Schugar, Robbins, & Deasy, 2008; Xu, Shi, & Ding, 2008). Phytochemicals that modulate stem and progenitor cell fate and function are significant for drug development aimed at stem cell modulation.

Phytochemicals are important source of active chemicals and conceived as an appropriate alternative for recombinant factors used in stem cell regulation (Dadashpour & Pilehvar-Soltanahmadi, 2017). Nowadays, more studies focus on green alternative therapies such as food ingredients or herbal remedies with less toxic, affordable, and highly available properties (Pilehvar-Soltanahmadi et al., 2018; Udalamaththa, Jayasinghe, & Udagama, 2016). Herbal remedies have been used in traditional medicine practices for centuries and herbs are a promising source of drugs improving human health and disease (Udalamaththa et al., 2016). Investigating the proliferative and differentiation effects of phytochemicals on stem cells may provide in-depth insights into their disease-curing mechanisms.

The present report aims to provide a critical review related to the use of phytochemicals as stem cell (not cancer stem cells) regulators, to discuss the role of active compounds in food or herbs in promoting proliferation and differentiation of stem cells, and to analyze future perspectives about these natural dietary materials.

2. Literature selection

Online literature about the phytochemical effects on stem cells (exclusion of cancer stem cells) was searched and gathered using bibliographic databases including PubMed, Google Scholar and EMBASE. A large number of articles and reports were found on regulating proliferation and differentiation of stem cell by chemicals and extracts from food, plants and herbs. While only the literatures about the major phytochemicals, not extracts, were reviewed to clearly indicate their action and possible mechanism on modulating the stem cell fate.

3. Stem cells and signal regulation

Stem cells are generally classified according to their differentiation potential (Fig. 1). Totipotent cells including Zygote and early Blastomeres can generate the whole organism, while pluripotent cells such as embryonic stem cells (ESCs) and iPSCs could generate all cell types excluding extra embryonic trophoblast lineage (De Luca, Aiuti, Cossu, & Parmar, 2019; Dulak, Szade, Szade, Nowak, & Jozkowicz, 2015). Multipotent cells such as hematopoietic stem cells can differentiate into all cell types within one particular lineage (De Luca et al., 2019; Dulak et al., 2015). The unipotent stem cells generally exists in the tissue, which essentially consists of only one cell type, such as the basal cells in epidermis, satellite cells in muscle, and spermatocytes in the testis (Visvader & Clevers, 2016). Most of the studies focus on the proliferative and differentiate profiles of these stem cells.

3.1. Characters and molecular regulation of stem cells

3.1.1. Characters of stem cells

The proliferative and differentiation ability of stem cells are associated with their division patterns including asymmetric division, which yields one stem cell and one differentiated daughter cell (stem cell maintenance); symmetric commitment, which yields two differentiated daughter cells (stem cell exhaustion); and symmetric division, which yields two daughter cells maintaining stem cell properties (stem cell expansion) (Ito & Ito, 2016; Kriegstein, Noctor, & Martinez-Cerdeno, 2006). Metabolism and mitochondrial biology play important roles in division pattern decisions of stem cells. Metabolic pathways such as PI3K and PPAR signaling pathways, and the distribution of young or old mitochondria are regulators of the division balance of stem cells (Ito & Ito, 2016). Moreover, cyclins such as cyclin A, B or E are the core cell cycle proteins regulating stem cell self-renewal, differentiation and reprogramming (Liu & Michowski, 2019). Many types of stem cells majorly rely on anaerobic glycolysis. Stem cell function is also regulated by the AKT-mTOR pathway, Gln metabolism and fatty acid metabolism (Ito & Suda, 2014). Therefore, regulation of asymmetric division, symmetric commitment and symmetric division enable the manipulation of stem cell fate.

3.1.2. Signal regulation of stem-cell fate

Multiple signal molecules and pathways are involved in the regulation of stem cell proliferation and differentiation, such as BMP, Wnt and Notch pathways (Fig. 1). While wingless-type MMTV integration site (Wnt) and transforming growth factor-beta (TGF-β) signaling are most widely involved in modulating the fates of many types of stem cells (Massey et al., 2019). Wnt signaling is a conserved and ubiquitously functioning pathway that exerts great control over the self-renewal and differentiation of both ESCs and adult stem cells (Van Camp, Beckers, Zegers, & Van Hul, 2014). Wnt proteins bind to receptors of the Frizzled and LRP families or tyrosine kinase receptors on the cell surface to modulate transcription of Wnt target genes through β-catenin/TCF pathway (Nusse, 2008). In general, Wnt proteins act to maintain the undifferentiated state of stem cells, while other growth factors including fibroblast growth factors (FGFs) and EGF instruct the cells to proliferate (Nusse, 2008). Wnt signals emanating from the stem cell microenvironment can act as self-renewal factors influencing adjacent stem cells without affecting a broad field of cells due to its lipid-modified structure constraining them to act as short-range cellular signals in multiple mammalian tissues (Clevers, Loh, & Nusse, 2014). The TGF-β family is a key regulator of stem-cell status and differentiation. TGF-β and bone morphogenic protein (BMP) signaling play diverse roles in controlling both embryonic and adult stem-cell fate (Massey et al., 2019; Mullen & Wrana, 2017). TGF-β signaling is essential in maintaining the pluripotency of human pluripotent stem cells and directs lineage-specific differentiation. Inhibition of TGF-β signaling can enhance reprogramming through facilitating mesenchymal-to-epithelial transition and many chemicals can modulate somatic cell reprogramming to induced pluripotent stem cells (iPSCs) and neural induction from pluripotent stem cells by regulating TGF-β signaling (Ichida et al., 2009; Li, Wei, & Ding, 2016). Further understanding of how these signaling molecules regulates stem-cell state will help find specific targets of stem cell modulation. Manipulation of these signals carries potential for therapeutic approaches such as tissue engineering for regenerative medicine.

3.2. Types and specific regulation of stem cells

3.2.1. Pluripotent stem cells

ESCs are derived from the inner cell mass of the blastocyst and have a powerful system for generating specialized cell types of the human

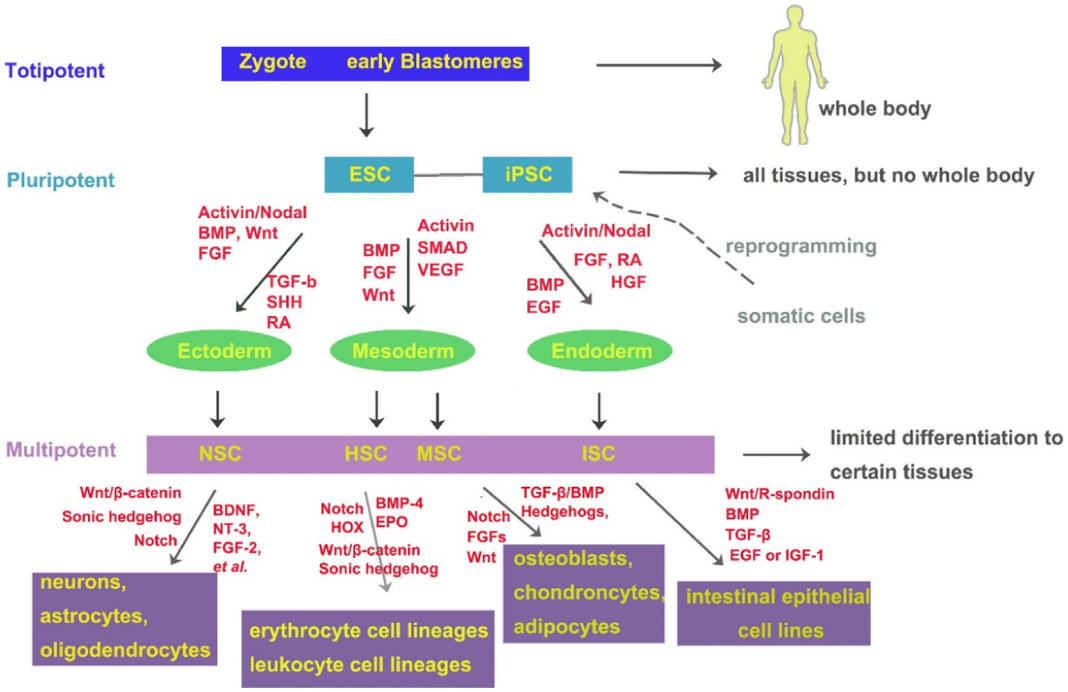

Fig. 1. Classification of stem cells and signal regulation on differentiation. ESC: embryonic stem cell, iPSC: induced pluripotent stem cell, NSC: neural stem cell, HSC: hematopoietic stem cell, MSC: mesenchymal stem cell, ISC: intestinal stem cell, BMP: Bone morphogenic protein; FGF: Fibroblast growth factor; NT-3: Neurotrophin-3; RA: Retinoic acid; SHH: Sonic hedgehog.

body, which are involved in the modulation of multiple signaling pathways, most notably the FGFs, TGF-β, BMP, and Wnt pathways (Dulak et al., 2015). Moreover, three families of growth factors including FGF, TGF-β/nodal/activin and IGF/insulin are significant to support stem cell pluripotency and expansion (Chen et al., 2011). The FGF and TGF-β/nodal/activin pathways maintain the expression of pluripotency genes such as NANOG and OCT4 (Chen, Gulbranson, Yu, Hou, & Thomson, 2012; Vallier, Alexander, & Pedersen, 2005). The FGF and IGF/insulin pathways activate cell survival signaling (Eiselleova et al., 2009; Wang et al., 2007). Klf2, Klf4, Tcfp2l1, Oct4, Nanog and Sox2 play important roles in ESC self-renewal (Chan et al., 2013; Takashima et al., 2015). The expected genes including OCT4, NANOG, SOX2, TDGF1, GDF3, NODAL, LEFTY1, ZIC2, ZIC3, THY1 and PRDM14 are all known to be associated with the undifferentiated ESC statues (Besser, 2004). Intrinsic transcription factors (OCT4, NANOG and SOX2) protect the undifferentiated status and prevent differentiation in a lineage-specific manner. Extrinsic signaling pathways including FGF/TGF-β and BMP/Wnt pathways directly impact on specific fate choices such as cardiac, skeletal muscle, neuronal and hepatocyte differentiation via regulating the gene expression of OCT4, NANOG and SOX2 (Rao & Greber, 2017). Stem cell fate is majorly determined by transcription factors and signaling receptors that define each cell type in combination with additional signals from their niches (Mullen & Wrana, 2017). So the chemicals, signaling molecules or pathways regulating OCT4, NANOG and SOX2 gene expression are important for maintaining undifferentiated status of ESCs, which is the major mechanism of reprograming somatic cells to iPSCs (Jaenisch & Young, 2008). Many chemicals have been found to promote the reprograming progress (Xu et al., 2008).

3.2.2. Multipotent stem cells

Multiple signaling pathways (Efthymiou, Chen, Rao, Chen, & Boehm, 2014; Ortmann & Vallier, 2017) are involved in pluripotent stem cells differentiation to ectodermal, mesodermal and endodermal fates (Fig. 1). The primary multipotent stem cells including neural stem cells (NSCs), hematopoietic stem cells (HSCs), intestinal stem cells (ISCs) and mesenchymal stem cell (MSC) derived from the three germ layers can further differentiate into different mature cell types through specific regulation of signal molecules. NSCs exist in the subventricular zone of the lateral ventricle and the dentate gyrus subgranular zone of the hippocampus throughout life. They can undergo self-renewal and differentiate into neurons, astrocytes and oligodendrocytes (Alvarez-Buylla & Lim, 2004; Reynolds & Weiss, 1992). NSCs are promising for treating neurodegenerative diseases, ischemia and traumatic injuries of the brain (Lee et al., 2007; Reynolds & Weiss, 1992; Yu, Ma, Kong, Shi, & Liu, 2013). So NSCs proliferation is necessary for neurogenesis (Iwai et al., 2003; Iwai et al., 2002). Wnt/β-catenin, Notch and Sonic hedgehog pathways and many factors such as BDNF, NT-3, FGF-2, IGF-1, GABA, CREB and Sox2 are involved in NSC proliferation and differentiation (Faigle & Song, 2013). HSCs, a type of adult stem cell, is the primary source of blood cell lineages. HSCs transplantation has been widely used for treating hematologic, immune and genetic diseases (Zlotoff & Bhandoola, 2011). Some important signaling pathways involved in HSC self-renewal include Notch, HOX, Wnt/β-catenin, Sonic hedgehog/BMP-4 and EPO pathways (Nakano, 2003; Tsiftsoglou, Bonovolias, & Tsiftsoglou, 2009). HSC transcriptional factors such as Ikaros, PU-1, Pax-5, C/EBPa, Notch and GATA-1/-2/-3 are involved in cell-lineage differentiation (Tsiftsoglou et al., 2009). ISCs are located at the base of the intestinal crypts where they can differentiate to multiple epithelial cells to renew the epithelium and drive mucosal regeneration (Bjerknes & Cheng, 2006). Some major signaling pathways such as Wnt/R-spondin signaling, BMP and TGF-β signaling, EGF or IGF-1 stimulated PI3K/PIP3/AKT and RAS/ RAF/MEK/ERK pathways and Notch signaling modulate ISCs fates (Holmberg et al., 2017). Adult MSCs have been identified in bone marrow, adipose tissue, dental pulp and many other organs (Crisan et al., 2008; Main, Munsie, & O'Connor, 2014). A number of critical signaling pathways are involved in regulating the lineage commitment of MSCs, including TGF-β/BMP signaling, Wnt signaling, Hedgehogs, Notch, and FGFs (Chen & Shou, 2016). The canonical Wnt/β-catenin signaling is a key regulator of MSC differentiation to the osteogenic or chondrogenic lineage through high or low Wnt canonical activity, respectively (Church, Nohno, Linker,

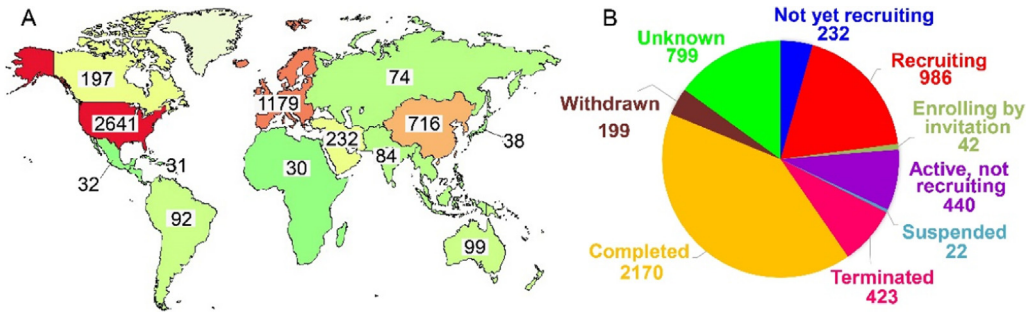

Fig. 2. The number of clinical trials of stem cell therapy. (A) The number of clinical trials in the world. (B) The number of clinical trials according to the recruitment status (clinicaltrials.gov, Jan 2020).

Marcelle, & Francis-West, 2002; Hill, Spater, Taketo, Birchmeier, & Hartmann, 2005). The absence of Wnt signaling enhances adipogenic differentiation. Activation of Notch/Hes-1, BMP/P38 MAPK/Smad and Hedgehog/Smad signaling pathways promote osteogenesis mediated by regulating transcription factors including Runx2 and Osterix (Chen & Shou, 2016). Activation of Integrin/Akt pathway can regulate PPARγ and C/EBPs to stimulate adipogenesis (Chen & Shou, 2016). So Wnt, Notch and TGF-β signaling pathways are involved in the modulation of multipotent stem cells.

3.2.3. Unipotent stem cells

In recent years, many kinds of unipotent stem cells are found in various tissues. Notch1-expressing cells reveals the existence of unipotent stem cells that retain long-term plasticity in the embryonic mammary gland (Lilja & Rodilla, 2018). In the mammary gland, limp1 expression marks a rare subpopulation of unipotent luminal stem cells that have a long-lived capacity throughout adult life (Elias, Morgan, Bikoff, & Robertson, 2017). The unipotent stem cells are important cell source for tissue maintenance and regeneration. Mammalian spermatogonial stem cells undergo unipotent differentiation in the adult male gonad and generate adult male gametes. While spermatogonial stem cells encode innate plasticity through the epigenome such as K4me3 modification, K27me3 modification and that both conversion of promoter chromatin states and activation of cell type-specific enhancers are prominent features of reprogramming (Liu & Giannopoulou, 2016). The unipotent stem cells may have advances in reprogramming and can be regulated by chemicals or biological factors.

3.3. Stem cell-derived extracellular vesicles

In recent years, stem cell-secreted extracellular vesicles can mediate cell communication in both adjacent and remote areas via paracrine and endocrine signaling, which may contribute to the therapeutic potency of stem cells (Lou, Chen, Zheng, & Liu, 2017). These vesicles includes microvesicles (0.1–1 μm in diameter) produced by shedding of the plasma membrane and exosomes (40–100 nm in diameter) derived from endocytic compartments (Phinney et al., 2015; Zomer et al., 2010). Microvesicles carry cell surface receptors, cytokines, lipids, mRNAs, noncoding RNAs and even depolarized mitochondria (Biancone, Bruno, Deregibus, Tetta, & Camussi, 2012; Phinney et al., 2015). Exosomes are natural nano-vesicles with a bi-lipid membrane and contents including functional miRNAs, small RNA, little mRNA and proteins (Zomer et al., 2010). The exosomes have high efficacy for RNA delivery to recipient cells (van den Boorn, Schlee, Coch, & Hartmann, 2011). Many studies indicate that stem cell-derived extracellular vesicles have various activities including inflammation inhibition, Immunomodulation, wound healing, tissue repair and angiogenesis regulation (Phinney et al., 2015; Vizoso, Eiro, Cid, Schneider, & Perez-Fernandez, 2017; Wen, Peng, Liu, Weizmann, & Mahato, 2016). Regulating the secretion of stem cell-derived extracellular vesicles is a novel therapeutic strategy.

Expression and release of stem cell secretome are regulated by multiple signal pathways such as PI3K/Akt, JAK-STAT and nuclear factor-κB (NF-κB) pathways. While a more comprehensive understanding of the molecular mechanism responsible for the unique stem cell secretome is still required (Ranganath, Levy, Inamdar, & Karp, 2012). Some methods including three-dimensional spheroid culture, hypoxic stimulation (oxygen concentrations of 1–5%), genetic manipulation, mechanical stimuli (fluid shear stress and compression), electromagnetic and biochemical factors stimuli can modulate the release of stem cell-derived extracellular vesicles (Phelps, Sanati-Nezhad, Ungrin, Duncan, & Sen, 2018; Teixeira et al., 2016). Another promising approach of regulating stem cell secretome release involves small molecules with the advantages of ease available, low cost, and specific actions on cellular signaling. However, there is no evidence of efficient stem cell secretome regulation by small molecules (Ranganath et al., 2012). Further research is required to fully delineate the signaling mechanisms involved in modulating the secretion and expression of stem cell secretome, and discover bioactive chemicals.

3.4. Clinical application of stem cells

Stem cells have huge potential for wound repair and tissue regeneration. Nowadays, more than 5000 clinical trials test the effects of multiple types of stem cells including HSCs, MSCs, NSCs, epidermal stem cells, endothelial progenitor cells, ESCs and iPSC on treatment of over 1000 different diseases (Fig. 2A clinicaltrials.gov). Although 2170 clinical trials have been completed (Fig. 2B), few stem cell products are approved for disease treatment (Golchin & Farahany, 2019), which suggest the frequent failure of clinical trials. Stem cells are used alone in the clinical trials. Some clinical evidences reveal the difficulty for the specific differentiation and survival of delivered stem cells (Trounson & McDonald, 2015). While the combination of endothelial stem cells and MSCs or drug is effective for vascular disease in the early clinical trials continue to evolve (Trounson & McDonald, 2015). Thus, the application of stem cells together with other cells, chemicals, biomaterials or biological factors may achieve superior quality of tissue repair and increase the number of stem cell products (Jacob, Shimomura, Krych, & Nakamura, 2019).

4. Dietary phytochemicals inducing stem cell proliferation and differentiation

The phytochemicals, also named natural compounds, can be classified into various categories according to their structure or function, such as phenolic acid, flavonoids, alkaloids and carotenoids (Cojocneanu Petric et al., 2015). These plant extracts or chemicals are widely investigated on the stimulants of proliferation and differentiation in stem cell therapy (Fig. 3), which is a cost-effective, highly available, non-toxic alternatives for therapeutic application (Udalamaththa et al., 2016). The actions and mechanism of phytochemicals on stem cells may provide more knowledge about their future

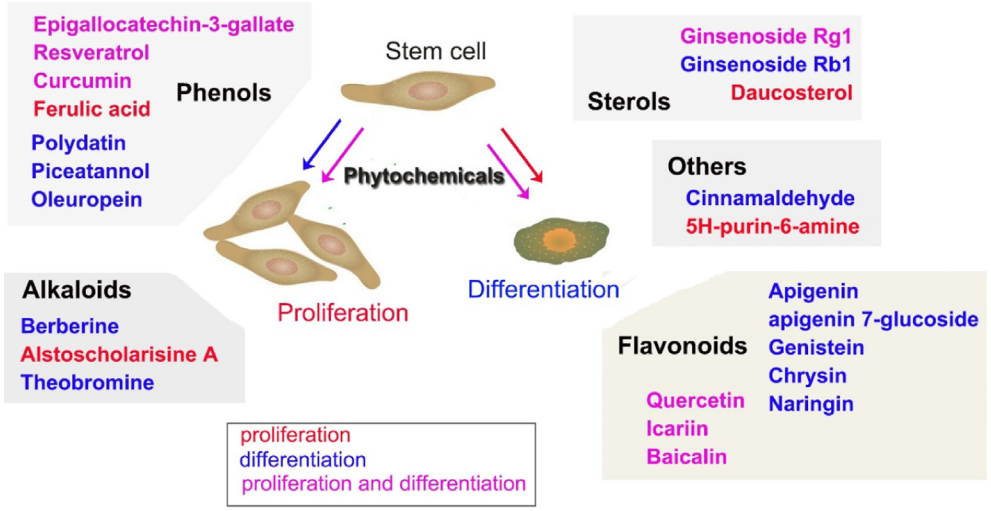

Fig. 3. Classification of dietary phytochemicals and their effects on proliferation and differentiation of stem cells.

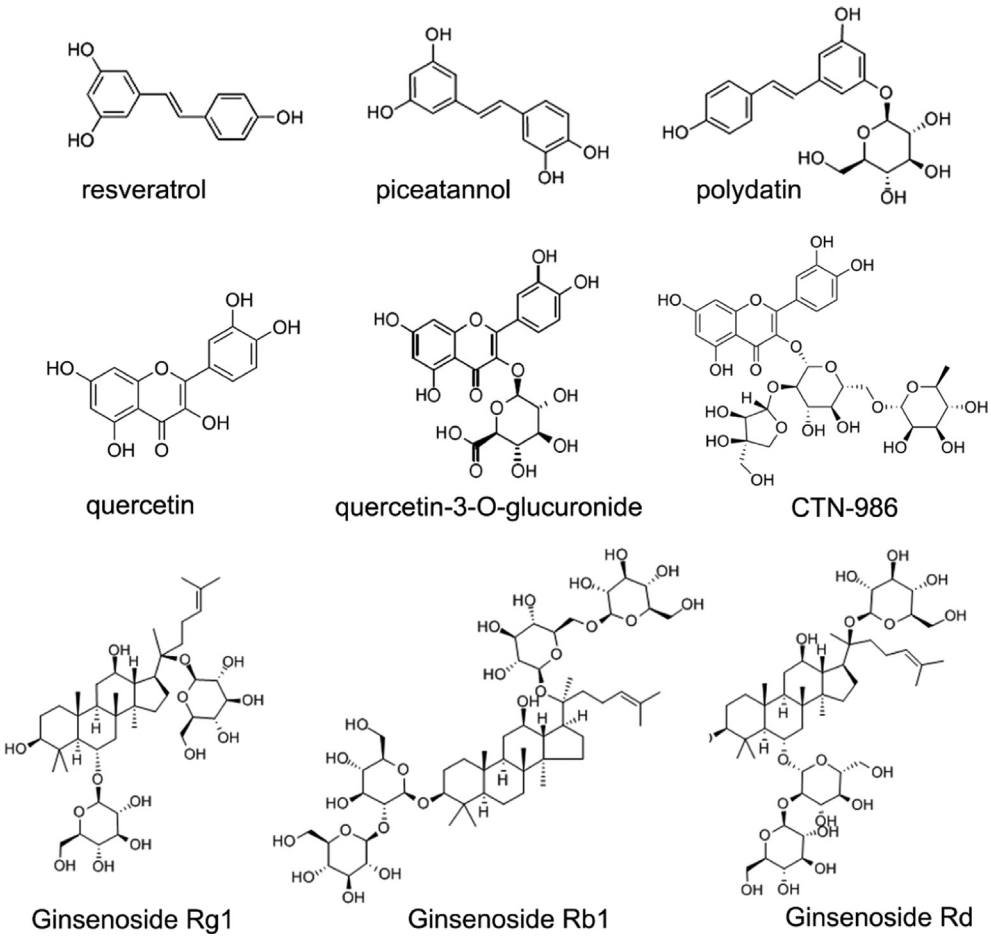

Fig. 4. Chemical structure analogs of resveratrol, quercetin and ginsenoside.

research and application in disease.

4.1. Phenolic phytochemicals

4.1.1. Resveratrol

Resveratrol, a type of natural phenol, is produced by several plants such as grapes, blueberries, raspberries, mulberries and peanuts. It increases the proliferation of bone marrow HSCs (Rimmele, Lofek-Czubek, & Ghaffari, 2014). Resveratrol enhances self-renewal of ESCs by activating JAK/STAT3, mTOR or MEK/ERK signaling pathway (Li, Du, et al., 2017; Safaeinejad et al., 2017). Furthermore, resveratrol promotes the proliferation of NSCs by upregulating the expression of Nrf2, HO–1 and NQO1, and activating ERK, p38 or sonic hedgehog signaling following oxygen-glucose deprivation/reoxygenation injury in vitro (Cheng et al., 2015; Kumar et al., 2016; Shen et al., 2016). Resveratrol (10 μM) can also improve the proliferation of porcine pancreatic stem cells (Xu et al., 2017). Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in

laminopathy-based progeria (Liu et al., 2012). These indicates that resveratrol can promote the proliferation of various stem cells.

Resveratrol has been found to enable stem cells to differentiate into cardiomyocytes, neurons, osteocytes and pancreatic beta cells. Firstly, resveratrol activates endogenous cardiac stem cells and decreases cardiomyocyte apoptosis in the ischemic myocardium by upregulating VEGF and SDF–1α expression (Ling, Gu, & Cheng, 2017). Moreover, resveratrol can direct the differentiation of ESCs into cardiomyocytes (Ding, Xu, Qin, Yang, & Feng, 2016), and promote cardiomyocyte differentiation of human iPSCs through suppressing canonical Wnt signal pathway and enhancing SRF-miR-1 axis (Liu, Zhang et al., 2016). These suggest its future applications to treat cardiovascular diseases. Secondly, resveratrol stimulates osteoblast differentiation of BMSCs, ADMSCs and iPSCs, which may be involved in upregulating RUNX2 gene expression via the SIRT1/FOXO3A axis (Dosier et al., 2012; Erdman et al., 2012; Kao et al., 2010; Ornstrup et al., 2016; Tseng et al., 2011). Resveratrol pretreatment inducing mineralization can be used for orthopaedic and dental applications for autologous stem cell therapy. Additionally, resveratrol improves the efficient differentiation of ESCs into pancreatic endoderm capable of generating β-cell-like cells and promotes the formation of β-like cells regulated by Wnt/β-catenin signal pathway (Pezzolla et al., 2015; Xu et al., 2017). Resveratrol induces a differentiation of MSCs from human umbilical cord and bone marrow into neuron-like cells at relatively high concentrations (Guo et al., 2017; Joe, Jeong, & Cho, 2015). So resveratrol has various activities to stimulate differentiation of stem cells. Resveratrol has the ability to enhance osteogenic differentiation of dental bud stem cells and its natural glycosylated precursor, polydatin (Fig. 4), is also able to stimulate the osteogenic differentiation of dental bud stem cells (Di Benedetto et al., 2018). While polydatin has better oral absorption and metabolic stability than resveratrol, and is abundant in many kinds of fruits and plants (Wang, Gao, et al., 2015). Both of them increase Sirt-1 expression in stem cells driving these cells toward osteoblast maturation through upregulating ATF-4 (Di Benedetto et al., 2018). Therefore, resveratrol is a promising inducer of stem cell differentiation.

4.1.2. Epigallocatechin-3-gallate

Green tea consumption is known to slow down the aging progress. Epigallocatechin-3-gallate (EGCG), a polyphenolic compound of green tea, increases the number of adult hippocampal NSCs and enhances adult hippocampal neurogenesis, which is associated with the sonic hedgehog signaling pathway (Wang et al., 2012). EGCG significantly increases the proliferation of NSCs and the migration of neuroblasts through the AKT signaling pathway after ischemic stroke (Zhang, Xu, et al., 2017). Additionally, EGCG promotes neuronal differentiation of NSCs and hippocampal precursor cells by activating PI3K/Akt signaling pathway (Ortiz-Lopez et al., 2016; Zhang, He, et al., 2016). While EGCG inhibits adhesion and migration of neural progenitor cells, which is initiated by EGCG binding to the extracellular matrix glycoprotein laminin, preventing its binding to β1-integrin subunits, which prohibits cell adhesion and decreases the number of migrating young neurons. So high-dose EGCG during pregnancy may disrupting neurodevelopment (Barenys et al., 2017). EGCG stimulates BMSCs towards the osteogenic lineage through the modulation of BMP-2 expression, upregulating miR-210 and downregulating the expression of miR-210-targeted EFNA3 (Jin, Wu, Xu, Zheng, & Zhao, 2014; Qiu et al., 2016).

4.1.3. Curcumin

Curcumin, a natural phenolic component of dietary spice, can significantly stimulate the proliferation of NSCs at the dose of less than 0.5 μmol/L. Curcumin activates ERKs and p38 kinases involved in the regulation of neuronal plasticity (Kim et al., 2008). Histone hypoacetylation plays an important role in controlling stem cell fate. Curcumin, as a histone acetyltransferase inhibitor, can decrease of histone H3 and H4 acetylation and induce neurogenesis, synaptogenesis and migration of brain-derived adult NSCs (Wang et al., 2019). Furthermore, curcumin stimulates the proliferation of NSCs probably by inhibiting glucocorticoid receptor and STAT3 signal pathways (Ma et al., 2018). Curcumin promotes the growth of epidermal stem cells by upregulating caveolin-1 expression and has the beneficial effect on burn wound healing in mice (Yang et al., 2018).

Curcumin induces myocardial differentiation of human ESCs at a dose of 10 μmol/L by significantly increasing the expression of cardiac specific transcription factor NKx2.5, cardiac troponin I, myosin heavy chain and endothelial nitric oxide synthase. Moreover, curcumin decreases the cAMP levels but significantly elevates cGMP contents in differentiated cells (Mujoo et al., 2012). Curcumin regulates cellular differentiation through multiple signal pathways such as JAK, STAT3, GSK-3b, b-catenin, EGFR, PI3K, Akt, mTOR, JNK, ERK, AP-1, c-Jun, c-Fos and Elk-1 (Aggarwal & Sung, 2009).

4.1.4. Ferulic acid

Ferulic acid (FA) is a plant constituent and is contained in several medicinal plants such as *Ferula assafoetida L.* and *Ligusticum*. FA, which can increase the proliferation of NSCs but do not affect either neuron- or glial- specific differentiation (Yabe et al., 2010). So FA improves functional recovery after acute spinal cord injury and prevents gentamicin-induced neuronal hearing loss by promoting NSCs survival (Gu, Cui, Wei, Yang, & Li, 2017; Li, Wang, Li, & Yuan, 2017).

4.1.5. Piceatannol

Piceatannol, a polyphenolic compound abundant in the passion fruit berries, passion fruit seeds, peanuts, grapes and wine, is a structural analogue of resveratrol but having an extra hydroxyl group at the 3′ position (Fig. 4), while piceatannol has a superior effect to resveratrol in promoting neural stem cell differentiation into astrocytes (Arai et al., 2016). An in vitro study indicates that piceatannol inhibits adipogenesis of ADMSCs and decreases glucose transport and lipogenic activities in adipocytes, which suggests the application of piceatannol in the treatment of the metabolic complications associated with obesity (Carpene et al., 2018). Therefore, finding the active groups in the chemical structure of resveratrol may provide important information for the study of stem cell regulation.

4.1.6. Oleuropein

Oleuropein is a key phenolic compound present in olive-tree leaves, fruits and olive oil. Oleuropein can increase osteoblast differentiation and inhibit the adipogenesis of human BMSCs by upregulating expression of adipogenesis-repressed genes, reducing mitochondrial activity and activating Rho and β-catenin signaling pathways (Casado-Diaz et al., 2017; Santiago-Mora, Casado-Diaz, De Castro, & Quesada-Gomez, 2011). So oleuropein can be an inhibitor of adipogenetic differentiation of MSCs.

4.1.7. Anthocyanidins

Anthocyanidins compounds belonging to the larger polyphenol class of compounds are present in many foods, fruits and vegetables, and particularly in berries (Khoo & Azlan, 2017). Delphinidin, cyanidin and malvidin are the most abundant anthocyanidins in berries with the similar core structure. While their individual structural features of anthocyanidins cause different influences on MSC differentiation including the promotion of malvidin on MSC osteogenesis, inhibition of delphinidin on MSC adipogenesis and MSC chondrogenesis stimulated by cyanidin and delphinidin (Saulite, Jekabsons, Klavins, Muceniece, & Riekstina, 2019). These suggest that the value of chemical structure modification on stem cell differentiation.

4.2. Flavonoids

4.2.1. Quercetin

Quercetin is a widely distributed natural flavonoid in many vegetables and fruits including grapes, apples and berries. Quercetin

promotes the proliferation of oligodendrocyte precursor cells under oxygen/glucose deprivation-induced injury and increases the proliferating effects on cultured chicken primordial germ cells through antioxidant action (Tang, Zhang, Zeng, Mi, & Liu, 2006; Wu et al., 2014). Furthermore, quercetin-3-O-glucuronide, the major quercetin metabolites, increases NSCs proliferation via the Akt/cyclin D1 and BDNF signaling pathway (Baral, Pariyar, Kim, Lee, & Seo, 2017). CTN-986 (quercetin 3-O-b-D-apiofuranosyl-(1→2)-.[a-L-rhamnopyranosyl-(1→6)]-b-D-glucopyranoside) dose-dependently increases the proliferation of the hippocampal neural progenitor cells, which might be closely related to the activation of the 5-HT1A receptor (Zhang, Zhang, et al., 2009). Both quercetin and its derivatives can promote stem cell proliferation, which indicates the significance of special chemical structure for finding more effective quercetin derivatives.

Quercetin can stimulate the osteogenic differentiation of BMSCs or ADMSCs mediated via Wnt/β-catenin inhibition, partially through the ERK and p38 signaling pathways or activating the MAPK signaling pathway, and not affect MSC proliferation (Casado-Diaz, Anter, Dorado, & Quesada-Gomez, 2016; Li et al., 2015; Song & Tripathy, 2018; Zhou & Lin, 2014; Zhou et al., 2015). Most of the studies confirm that quercetin can induce osteogenic differentiation of MSCs. While another report finds that quercetin has a strengthening effect on the differentiation of rat BMSCs into β-cells and increases insulin secretion in vitro (Miladpour et al., 2017). So quercetin might be beneficial in the bone tissue engineering and diabetic treatment.

4.2.2. Icaritin

Icaritin as the active compound of *Epimedium* herbs enhances MSCs proliferation by activating Wnt/β-catenin pathway and ESCs self-renewal through regulating cell cycle machinery and core pluripotency transcription factors mediated by estrogen receptor alpha (Lim, Li, Yong, & Chew, 2018; Tsang et al., 2017). Icariin, another essential bioactive component of the herb *Epimedium*, promotes the proliferation of human NSCs, adipose-derived stem cells (ADMSCs) and bone marrow-derived mesenchymal stem cells (BMSCs) by activating ERK and p38 MAPK signaling and upregulating their downstream transcription factors Elk1 and c-Myc (Fu et al., 2018; Qin, Zhou, Liu, Chen, & Wu, 2015; Yang et al., 2016). More active ingredients may also exist in the herb *Epimedium*.

Icariin promotes osteogenic differentiation of MSCs by activating the Wnt/β-catenin-/RhoA-TAZ, PI3K-AKT-eNOS-NO-cGMP-PKG signaling pathway, while inhibits adipogenic differentiation of BMSCs (Wei, He, et al., 2017; Wu, Xia, Zhou, Xu, & Jiang, 2015; Ye et al., 2017; Zhai et al., 2014; Zhang, Feng, et al., 2017). Furthermore, icariin promotes chondrogenic differentiation of BMSCs, but had no effect on hypertrophic induction (Wang et al., 2018; Wang, Sun, Li, Fu, & Liu, 2014). Icariin promotes the differentiation of ESCs into cardiomyocytes by activating mGluR5 pathway, NF-kappa B, AP-1, ERK-dependent signaling pathways and ubiquitin-proteasome system (Jin et al., 2010; Sun et al., 2011; Wo, Zhu, Yu, & Lou, 2008; Zhou et al., 2013; Zhu et al., 2011; Zhu & Lou, 2005). ROS generation and the subsequent activation of p38MAPK are essential for the inducible function of icariin on cardiomyocyte differentiation of murine embryonic stem cells (Ding, Liang, Hu, Zhu, & Lou, 2008).

4.2.3. Baicalin

Baicalin, one of the predominant flavonoid derivatives isolated from the dry roots of *Scutellaria baicalensis Georgi*, promotes the proliferation of endogenous NSCs in Alzheimer's disease model rats and stimulates hippocampal neurogenesis (Zhao, Lu, Yu, Duan, & Zhao, 2018; Zhuang et al., 2013). While 50 μM baicalin suppresses the proliferation of ESCs by down-regulating the expression of miR-294 (Wang, Masika, et al., 2015). So the dose-effect relationship is essential for consideration when evaluate the action of phytochemicals.

Baicalin can promote the neural differentiation of NSCs but inhibit glial formation, which is associated with the modulations of signal transducer and activator of transcription 3 (STAT3) and basic helix-loop-helix (bHLH) genes (Li, Zhuang, Shen, Zhang, & Shen, 2012). Baicalin promotes neuronal differentiation in human iPSCs by monitoring bHLH gene expression during neuronal differentiation (Morita et al., 2015). Baicalin induces neuronal differentiation of C17.2 NSCs mediated by activation of Erk1/2 (Li et al., 2011). Furthermore, baicalin maintains the late-stage functional cardiomyocytes in embryoid bodies derived from murine ESCs (Tang et al., 2013). These suggest that baicalin can influence the neuronal fate decision.

4.2.4. Apigenin

Apigenin, a natural flavonoid, is widely distributed in plants such as vegetable, fruits, leafs, peas and flowers (Tang, Chen, Huang, & Li, 2017). It can promote the osteogenesis of human MSCs by activating JNK and p38 MAPK signal pathways and promoting Runx2 and osterix expressions to induce bone formation (Zhang et al., 2015). Apigenin is present principally as glycosylated and apigenin 7-glucoside is the major active components in olive leaf. Treatment with luteolin 7-glucoside stimulated HSCs towards the erythroid and the myeloid differentiation, while treatment with apigenin 7-glucoside specifically induced the erythroid lineage differentiation and inhibited the myeloid differentiation by activating the JAK/STAT signaling pathway (Samet et al., 2015).

4.2.5. Genistein

Genistein, a soy isoflavone that exists in the form of an aglycone, enhances osteogenic differentiation in MSCs mainly through the BMP-dependent SMADs and RUNX2 signaling, p38 MAPK-Cbfa1 activation and NO/cGMP pathway (Dai et al., 2013; Liao, Xiao, Qin, & Zhou, 2007; Pan et al., 2005), while genistein does not influence the late osteogenic maturation markers, and suppress adipogenic differentiation via an ER-dependent mechanism involving autocrine or paracrine TGF-β signaling or downregulation of ERK1/2 activity at this early phase of adipogenesis (Heim et al., 2004; Kim et al., 2010; Liao et al., 2008).

4.2.6. Chrysin

Chrysin, a natural flavonoid, exists in various food and plants such as honey, mushroom, propolis and passion flowers. Chrysin promotes osteoblast differentiation (Yadav, Song, Huang, Chakravarti, & Jacob, 2018). Osteoblast differentiation enhanced by chrysin can be due to downregulation of the osteoblast differentiation transcription factor Runx2 and activation of ERK/MAPK pathway (Menon et al., 2018; Zeng, Yan, Zhang, Zhang, & Liang, 2013).

4.2.7. Naringin

Naringin, the main effective component of *rhizoma drynariae*, promotes the osteogenesis of stem cells from periodontal ligament, adipose, amniotic fluid and bone marrow through the upregulation of miR–20a, downregulation of PPARγ and ERK1/2 signaling pathway (Fan, Li, & Fan, 2015; Lavrador & Gaspar, 2018; Liu, Li, & Yang, 2017; Wei, Xie, et al., 2017; Zhang, Dai, et al., 2009).

4.3. Sterols

4.3.1. Ginsenoside

Ginsenoside is the major active component of ginseng. Ginsenoside Rg1 stimulates the proliferation of hippocampal progenitor cells and stem cells from adipose, periodontal ligament and dental pulp (Shen & Zhang, 2004; Wang, Wei, et al., 2014; Xu et al., 2014; Yin et al., 2015). Ginsenoside Rd can enhance the proliferation but not affect the differentiation of NSCs (Lin et al., 2012).

Many studies indicate the neuro-protective effects of ginsenoside, which may be associated with its actions on regulating stem cell differentiation. Ginsenoside promotes NSCs differentiation into neurons and astrocytes by initiating the expression of downstream VEGF after oxygen-glucose deprivation/reperfusion injury (Gao et al., 2018).

Table 1
Dietary phytochemicals control the fate of stem cells.

Phytochemicals	Food	Types of stem cells	Mechanism (signaling pathways)	References
Resveratrol	Grapes, blueberries, raspberries, mulberries, peanuts	HSCs, ESCs, NSCs, pancreatic stem cells (proliferation); ESCs, iPSCs (cardiomyocytes); BMSCs, ADMSCs, iPSCs (osteogenesis); ESCs (pancreatic β-cell-like cells)BMSCs (neuron)	JAK/STAT3, Mtor, MEK/ERK, Nrf2, HO–1, NQO1, p38, sonic hedgehog (proliferation); canonical Wnt signal pathway, SRF-miR-1 axis (cardiomyocytes); SIRT1/FOXO3A axis (osteogenesis); Wnt/β-catenin (pancreatic β-cell-like cells)	Cheng et al. (2015), Ding et al. (2016), Dosier et al. (2012), Kumar et al. (2016), Li, Du, et al. (2017), Rimmele et al. (2014), Shen et al. (2016), Xu et al. (2017)
Polydatin	A natural glycosylated precursor of resveratrol	Dental bud stem cells (osteoblast)	Sirt-1/ATF-4 (osteogenesis)	Di Benedetto et al. (2018), Wang, Gao, et al. (2015)
Epigallocatechin-3-gallate	Green tea	NSCs (proliferation); NSCs (astrocytes); NSCs (neuron); BMSCs (osteogenesis)	Sonic hedgehog, AKT signaling pathway (proliferation); PI3K/Akt (neuron); BMP-2, miR-210 (osteogenesis)	Ortiz-Lopez et al. (2016) Qiu et al. (2016), Wang et al. (2012), Zhang, He, et al. (2016)
Piceatannol	Passion fruit berries/seeds, peanuts, grapes, wine	NSCs (astrocytes); ADMSCs (inhibiting adipogenesis)		Arai et al. (2016), Carpene et al. (2018)
Curcumin	Dietary spice	NSCs (proliferation); ESCs (cardiomyocyte)	Inhibiting histone acetyltransferase, glucocorticoid receptor and STAT3 (proliferation); JAK, STAT3, GSK-3β, β-catenin, EGFR, PI3K, Akt, mTOR, JNK, ERK, AP-1, c-Jun, c-Fos, and Elk-1 (differentiation)	Aggarwal and Sung (2009), Kim et al. (2008), Ma et al. (2018), Mujoo et al. (2012), Wang et al. (2019)
Ferulic acid	Many herbs, such as: *Ferula assafoetida L.* and *Ligusticum*	NSCs (proliferation)		Gu et al. (2017), Li, Wang, et al. (2017), Yabe et al. (2010)
Oleuropein	Olive-tree leaves, fruits and olive oil	BMSCs (promoting osteogenesis, inhibiting adipogenesis)	Rho and β-catenin (promoting osteogenesis, inhibiting adipogenesis)	Casado-Diaz et al. (2017) Samet et al. (2015), Santiago-Mora et al. (2011)
Icaritin	*Epimedium* herbs	MSCs, ESCs (proliferation); MSCs (osteogenesis)	Wnt/β-catenin, estrogen receptor alpha (proliferation); Wnt/β-catenin-/RhoA-TAZ, PI3K-AKT-eNOS-NO-cGMP-PKG (osteogenesis)	Feng et al. (2019), Lim et al. (2018), Tsang et al. (2017), Zhu and Lou (2005)
Ginsenoside Rg1	Ginseng	Hippocampal progenitor cells and stem cells form adipose, periodontal ligament, dental pulp (proliferation); ESCs (neuron); ADMSCs (neuron); NSCs (glial); breast adipose-derived stem cells (chondrogenesis); periodontal ligament and dental pulp stem cells and BMSCs (osteogenesis)	GR-MEK-ERK1/2-PI3K-Akt (neurons); glucocorticoid receptor/BMP-2 (osteogenesis)	Gao et al. (2017), Gu et al. (2016), Shen and Zhang (2004), Wang, Masika, et al. (2015), Wang, Wei, et al. (2014), Wu et al. (2013), Xu et al. (2014), Xu et al. (2015), Xu et al. (2016)
Ginsenoside Rd	Ginseng	NSCs (proliferation)		Lin et al. (2012)
Ginsenoside Rb1	Ginseng	ESCs (neuron)		Hsieh and Chiang (2014)
Daucosterol	Walnut meat	NSCs (proliferation)	IGF1/AKT, RAF-MEK-ERK, PI3K/AKT (proliferation)	Jiang et al. (2014)
Icariin	*Epimedium* herbs	NSCs, ADMSCs and BMSCs (proliferation); BMSCs (chondrogenesis); ESCs (cardiomyocyte)	ERK and p38 MAPK (proliferation); mGluR5, NF-kappa B, AP-1, ERK, p38MAPK and ubiquitin-proteasome system (cardiomyocyte)	Ding et al. (2008), Fu, Yang, Hong, and Zhang (2016), Fu et al. (2018), Jin et al. (2010), Qin et al. (2015), Sun et al. (2011), Wang et al. (2018), Wang, Sun, et al. (2014), Wei, He, et al. (2017), Wo et al. (2008), Wu et al. (2015), Yang et al. (2016), Ye et al. (2017), Zhai et al. (2014), Zhang, Feng, et al. (2017), Zhou et al. (2013), Zhu et al. (2011), Zhu and Lou (2005)
Apigenin	Vegetable, fruits, leafs, peas, and flowers	MSCs (osteogenesis)	JNK/p38 MAPK (osteogenesis);	Tang et al. (2017), Zhang et al. (2015)
Apigenin7-Glucoside	olive leaf	HSCs (promoting erythroid lineage and inhibiting the myeloid differentiation)	JAK/STAT	Samet et al. (2015)
Luteolin 7-glucoside	Olive leaf	HSCs (erythroid and myeloid differentiation)		Samet et al. (2015)
Genistein	Soy	MSCs (osteogenesis)	BMP/SMADs, RUNX2, p38 MAPK-Cbfa, NO/cGMP (osteogenesis)	Dai et al. (2013), Heim et al. (2004), Kim et al. (2010), Liao et al. (2008), Liao et al. (2007), Pan et al. (2005), Rao et al. (2002), Zhang, Xue, Chen, Chai, and Ni (2016)
Quercetin	Vegetables and fruits including grapes, apples and berries	NSCs (proliferation); BMSCs, ADMSCs, MSCs (osteogenesis); BMSCs (β-cells)	Akt/cyclin D1 and BDNF (proliferation); Wnt/β-catenin I, ERK, p38, MAPK (osteogenesis)	Casado-Diaz et al. (2016), Li et al. (2015), Miladpour et al. (2017), Srivastava, Bankar, and Roy (2013), Tang et al. (2006), Wu et al. (2014), Zhou et al. (2015)
Baicalin	Dry roots of *Scutellaria baicalensis Georgi*	NSCs (proliferation); NSCs, iPSCs (neuron)	Signal transducer and activator of transcription 3 (stat3) and basic helix-loop-helix (bHLH), Erk1/2 (neuron)	Li et al. (2011), Li et al. (2012), Morita et al. (2015), Tang et al. (2013), Wang, Masika, et al. (2015), Zhao et al. (2018), Zhuang et al. (2013)
Chrysin	Honey, mushroom, propolis and passion flowers	MSCs (proliferation); MSCs (osteogenesis)	Runx2, activation of ERK/MAPK (osteogenesis)	Menon et al. (2018), Zeng et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Phytochemicals	Food	Types of stem cells	Mechanism (signaling pathways)	References
Naringin	*rhizoma drynariae*	Stem cells from periodontal ligament, adipose, amniotic fluid and bone marrow (osteogenesis)	miR–20a, PPARγ, ERK1/2 (osteogenesis)	Fan et al. (2015), Lavrador and Gaspar (2018), Liu et al. (2017), Wei, Xie, et al. (2017), Zhang, Dai, et al. (2009)
Cinnamaldehyde	*Cinnamon* trees	ADMSCs (promoting osteogenesis, inhibiting adipogenesis)		Absalan et al. (2016), Wu et al. (2018), Zhu et al. (2017)
Berberine	Medicinal plants such as *Berberis aristata, Berberis aquifolium*, and *Coptis chinensis*	MSCs, periodontal ligament stem cells (osteogenesis)	Runx2, p38 MAPK, canonical Wnt/β-catenin, EGFR, ERK, FOS (osteogenesis)	Imenshahidi and Hosseinzadeh (2016), Lee et al. (2008), Liu et al. (2018), Tao et al. (2016)
5H-purin-6-amine	*Sedum sarmentosum*	spermatogonial stem cells (proliferation)	Hedgehog pathway	Jung and Kim (2017)

Ginsenoside Rg1 possesses the effects on inducing differentiation of mouse ESCs into neurons via the GR-MEK-ERK1/2-PI3K-Akt signaling pathway (Wu et al., 2013). Ginsenoside Rg1 also promotes neural differentiation of human ADMSCs in vitro and glial–like–directed differentiation of cortical NSCs (Gao et al., 2017; Xu et al., 2014). Moreover, ginsenoside Rg1 obviously stimulates the cell proliferation of human breast adipose-derived stem cells at earlier stages in vitro and promotes the chondrogenic differentiation of breast adipose-derived stem cells at later stages in vitro (Xu et al., 2015), and ginsenoside Rg1 can enhance osteogenic differentiation of human periodontal ligament and dental pulp stem cells and BMSCs by activating the glucocorticoid receptor/BMP-2 signaling pathway (Gu, Zhou, Wang, Fan, & Yin, 2016; Wang, Wei, et al., 2014; Yin et al., 2015). Ginsenoside Rb1 is capable of up-regulating neurotrophin expression and inducing midbrain dopaminergic neurons differentiation of human ESCs (Hsieh & Chiang, 2014). Ginsenoside Rb1 and ginsenoside Re enhance the differentiation of ESCs into cardiomyocytes (Kim et al., 2014).

4.3.2. Daucosterol

Walnut meat is considered as a food nourishing brain cells and increasing intelligence. Daucosterol, a component of walnut meat, has the activity of promoting the proliferation of NSCs by increasing IGF1 expression and activating IGF1-AKT pathway (Jiang et al., 2014). IGF1 is mediated by the IGF receptor-I, activating two main downstream signaling pathways including the RAF-MEK-ERK phosphorylation cascade and the PI3K-AKT pathway (Russo, Gluckman, Feldman, & Werther, 2005), which may contribute to the neurogenetic action of daucosterol.

4.4. Alkaloids

4.4.1. Berberine

Berberine is an isoquinoline alkaloid plant extract from numerous medicinal plants such as *Berberis aristata*, *Berberis aquifolium* and *Coptis chinensis* (Imenshahidi & Hosseinzadeh, 2016). Berberine can stimulate osteogenic differentiation of MSCs by enhancing Runx2 expression and activating p38 MAPK or canonical Wnt/β-catenin signaling pathway (Lee et al., 2008; Tao et al., 2016; Zhang et al., 2019). A recent study further confirms the osteogenic differentiation of human periodontal ligament stem cells induced by berberine via binding to EGFR on the cell membrane and activating the intracellular ERK signaling pathway and nuclear-related genes of FOS change (Liu et al., 2018).

4.4.2. Alstoscholarisine a

Total alkaloids from the leaves of *Alstonia scholaris* promotes NSC proliferation and five alstoscholarisine chemicals isolated from the total alkaloids all exhibit the action of neurogenesis (Yang et al., 2014). Alstoscholarisine A is found to have the highest effects on increasing NSC growth (Mason & Weinreb, 2018; Yang et al., 2014).

4.4.3. Theobromine

Theobromine is one of the major xanthine-like alkaloids found in cacao plant, tea leaves guarana and cola nuts (Smit, 2011). It is reported that theobromine may have osteogenic bone forming properties due to their effects on stimulating tooth development (Tetsuo Nakamoto, Falster, & SimmonsJr, 2016). Further research indicates that theobromine increases the mineralization of MSCs and promotes osteogenesis (Clough et al., 2017).

4.5. Others

Cinnamaldehyde, one of the active components derived from *Cinnamon* trees, is a natural flavorant (Zhu et al., 2017). Cinnamaldehyde enhanced the osteogenesis and decreased the adipogenesis of human ADMSCs (Absalan, Mesbah-Namin, Tiraihi, & Taheri, 2016). Cinnamaldehyde inhibits osteoclastogenesis and promotes osteoblastogenesis differentiation of MSCs, which can be used for the

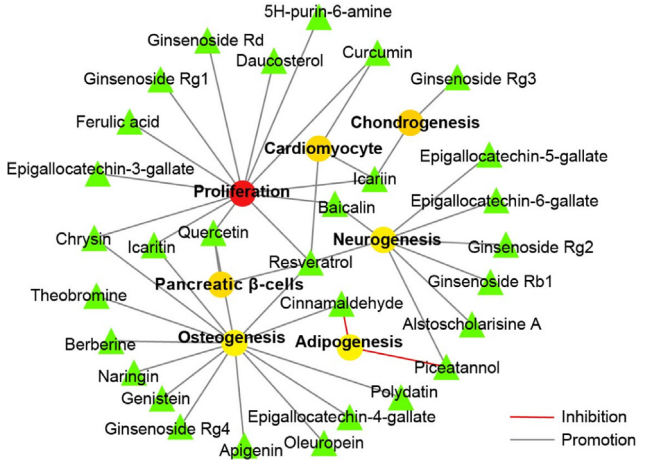

Fig. 5. Network of phytochemicals and their effects on stem cells.

treatment of osteoporosis (Wu et al., 2018).

Sedum sarmentosum, as an herb, has been traditionally used for the treatment of disease in Asian countries (Kang et al., 2000). *Sedum sarmentosum* extract can suppress the proliferation of cancer cells through the down-regulation of Hedgehog signaling pathway (Bai et al., 2016). While Hedgehog pathway plays an important role in promoting self-renewal of germline stem cells (Sahin et al., 2014). 5H-purin-6-amine originated from *Sedum sarmentosum* is a very effective compound increasing the activity and proliferation of spermatogonial stem cells (Jung & Kim, 2017).

5. Conclusion

Phytochemicals have the benefits of being safe, affordability, easy acquisition and convenient to use compared with biological factors. Multiple plant extracts such as phenols, flavonoids, sterols, alkaloids and aldehyde could control stem cell fate. Many bioactive compounds from plants are found to precisely regulate the self-renewal or lineage-specific differentiation of stem cells through different signal pathways. Additionally phytochemicals may have broad-spectrum effects by targeting multiple pathways and controlling several types of stem cells (Table 1). Therefore, the combined application of phytochemicals with stem cells is promising to improve proliferation and linear differentiation potential of stem cells and offers new avenues for regenerative medicine.

6. Future perspective

Despite the hopeful bioactivity of phytochemicals for stem cell modulation, some issues still need to be addressed in the future studies. (1) Administrative route and dosage of phytochemicals should be optimized when using stem cells in disease treatment. The combined manners of phytochemical and stem cells, such as in vitro induction, in vivo application at the same time or different times, should be considered. (2) Clinical trials are required to approve the regulatory efficacy of phytochemicals on stem cells. (3) One type of phytochemical may not be sufficient to have the maximal effect, but require others to corporately assist stem cell therapy. Thus, formulation of phytochemicals need to be tested to improve the therapeutic possibilities of stem cells. The possible combination of phytochemicals is shown in Fig. 5. (4) Some structural analogs of resveratrol and ginsenoside (Fig. 4) can affect stem cell regulation, which implies the important structure-activity relationship for further research of new chemicals. So the structural modification of phytochemicals facilitates the discovery of new drugs with strong efficiency on modulating stem cell fate. (5) Phytochemical-dependent mechanism will be helpful to understand the profiles of stem cells regulation. (6) Regulating the secretion of stem cell-derived vesicles may be also the novel mechanism of phytochemical-mediated stem cell effects, which needs to be further studied. Thus, more comprehensive studies related to these plant-derived compounds will enhance pharmaceutical exploration in the field of stem cell therapy.

7. Ethics statement

This work did not use any human or animal subjects.

Funding

This work was financially supported by grants from Innovation and Technology Support Programme, Government of Hong Kong (Project code: UIM/321), and Seed Fund for Basic Research (Project code: 201611159232), University of Hong Kong.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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