13 Application of Bioactive Compounds and Biomaterials in Promoting Cell Differentiation, Proliferation, and Tissue Regeneration

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Abstract

Cells, mainly stem cells, possess immense potential in regenerative medicine. Stem cells (SCs) can also play a crucial role in treating diseases due to their remarkable ability of self-renewal, proliferation, and differentiation into germ layers or gastrula (i.e., internal layer (ectoderm), middle layer (mesoderm), and outer layer (endoderm)). In this regard, pluripotent stem cells like induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) can differentiate into all three germ layers. However, targeted cellular differentiation is not possible without a suitable induction environment, microenvironment, or substrate. Based on the reports, the group of polymers or biopolymers, bioactive compounds, and biomaterials can provide such a microenvironment or substrate and lead to an increase in the interactions of cell-to-cell and cell-to-substrate, better differentiation, and secretion of growth factors to accelerate tissue regeneration. These materials can synthesize by living organisms such as animals, bacteria, fungi or algae, and plants. In this field, polysaccharides (such as hyaluronic acid, galactans, poly-galactosamine, chitosan, etc.) and proteins (such as silk fibroin, silk sericin, collagen, etc.) are known as natural biomaterials or biopolymers. Moreover, polyphenols, flavonoids, mucilage, pectin, apigenin, quercetin, galangin, curcumin, etc. obtained from medicinal herbs are

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phytochemicals and bioactive compounds which can be led to an increase in cellular proliferation and differentiation, induction of cellular signaling, promotion of regeneration rate, and immunomodulation. Hence, the present chapter is aimed to study the applications and consequences of bioactive compounds and biomaterials on stem cell proliferation and differentiation, as well as to highlight their role in tissue regeneration.

Keywords

Stem cells · Regenerative medicine · Biopolymers · Bioactive compounds · Biomaterials

13.1 Introduction

Stem cells are known as precursor biological cells that can be classified into totipotent,[1] pluripotent,[2] multipotent,[3] oligopotent,[4] and unipotent[5] stem cells, depending upon the differentiation capacities. These cells possess a high potential for self-renewal and differentiation into other cells, and as a promising resource for medicine, applications can play an important role in regenerative medicine or tissue engineering and cellular therapies (Chagastelles and Nardi 2011). However, applying stem cells to treat diseases and regenerate damaged tissues will be successful when suitable conditions are available to improve cellular interaction control and differentiate into the target cells (Izadyari Aghmiuni et al. 2021). Indeed, the creation of environments for therapeutic cloning that can well control cellular behavior can be the main factor in this regard (Fig. 13.1). Based on the reports, the use of biomaterials or biopolymers and bioactive compounds obtained from medicinal plants is considered a fundamental strategy for this purpose, due to their excellent bioactivity and role in the improvement of cellular biological response as well as in mimicking functional and structural properties of the target tissues (Yu et al. 2019). Such that, recent efforts in the design of biomaterial-based scaffolds, hydrogels, substrates, etc. (Chaudhari et al. 2016; Shafei et al. 2017; Ahmed 2013; Talebian et al. 2019; Zhao et al. 2020; Wang et al. 2018a) have provided significant opportunities to use these materials in regenerative medicine and generate novel

[1] Totipotent is embryonic stem cells of 1–3 days (e.g., zygotes)—differentiation into any cell types.

[2] Pluripotent is embryonic stem cells of 5–14 days (e.g., blastula) and induced pluripotent stem cells (iPSCs)—differentiation into cells from any of the three germ layers.

[3] Multipotent is adult stem cells—differentiation into a limited range of cell types such as neural stem cells, epithelial stem cells, hematopoietic stem cells, etc.

[4] Oligopotent is adult stem cells—differentiation into a limited number of cell types such as neural progenitor cells, myeloid stem cells, lymphoid stem cells, etc.

[5] Unipotent is adult stem cells—differentiation into single cell type such as gut cell, erythrocytes, neurons, etc.

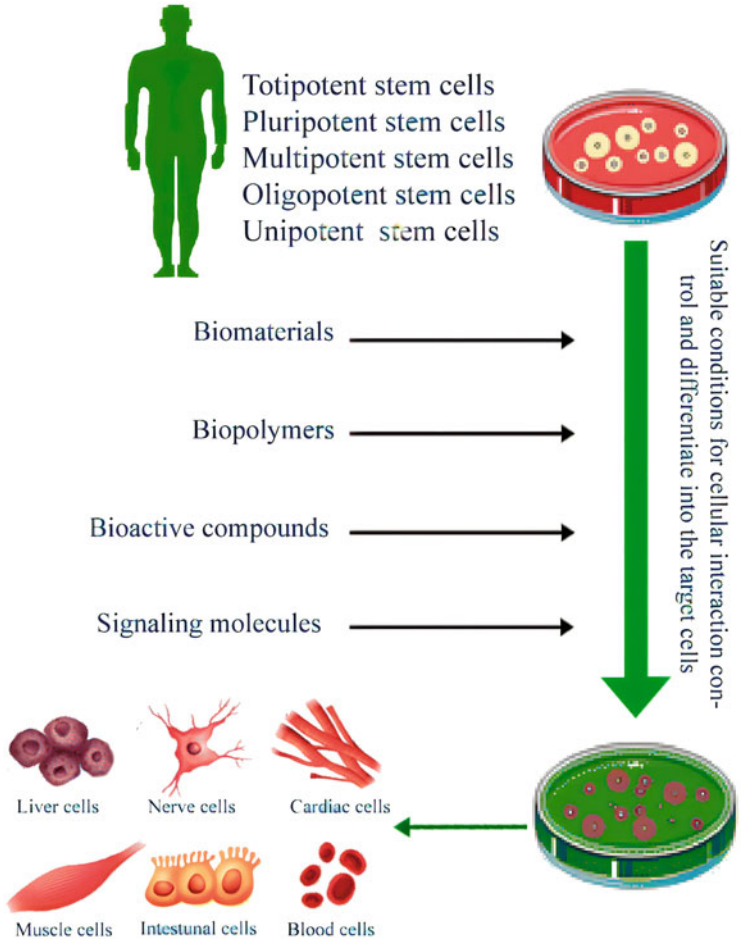

Fig. 13.1 The effective materials for the proliferation and differentiation of stem cells

substitutes for tissue engineering applications (Ramalingam et al. 2019; Aghmiuni et al. 2020).

There are biomaterials or bioactive materials with different natures which seem to be effective in targeting cell differentiation and tissue regeneration. Medicinal herbs are one of these bioactive materials gaining significant attention among researchers and scientific communities due to the promotion of cell proliferation and controlled differentiation (Izadyari Aghmiuni et al. 2020; Dey et al. 2010). The biopolymers similar to signaling molecules such as glycoproteins, proteoglycans, and glycosaminoglycans which exist in the network of the tissue extracellular matrix (ECM) are other samples from these biomaterials that can promote cell-cell signaling on the engineered substrates to modulate cellular functions (i.e., adhesion, proliferation, differentiation, and morphogenesis). Silk fibers (SF) are one of the biomaterials in this matter that owing to the amino acids of alanine and glycine can mimic the

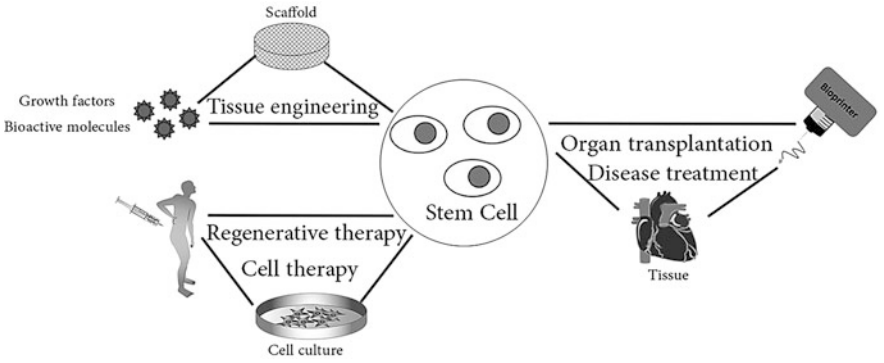

Fig. 13.2 Potential applications of stem cells

proteoglycans' behavior in the tissue ECMs (Omenetto and Kaplan 2010). Moreover, hyaluronic acid (HA), as a linear polysaccharide and signaling molecule, can act like glycosaminoglycans of the ECM (Kogan et al. 2006; Volpi et al. 2009; Petrey and de la Motte 2014) and play a crucial role in cell-cell and cell-substrate interactions via communication between cell-surface receptors (Volpi et al. 2009; Lam et al. 2014; Dicker et al. 2014). According to the importance of subject and attention to personalized therapies in tissue engineering or regenerative medicine, the present chapter is aimed to assess the association of bioactive materials and biomaterials with cellular functions (such as cell signaling, proliferation, differentiation, migration, etc.) and their role in increasing effectiveness and safety of therapeutic methods and regenerating damaged tissues.

13.2 Proliferation and Differentiation Potential of Stem Cells

Stem cells are known as cells with extensive biological functions to differentiate into cell types, as well as to enable the growth, healing, or replacement of cells (Fig. 13.2) (Zakrzewski et al. 2019). These cells are found both in embryos (uncontrolled range of differentiation) and adult or somatic cells. Although adult stem cells possess a restricted range of differentiation, however, it is possible to reprogram these cells back to their pluripotent states or improve their capacity of self-renewal (Wu et al. 2018). Therefore, to be useful in therapy and be converted into target cells, as well as avoid teratoma formation, the creation of similar body conditions or imitation of the extracellular microenvironments plays an important role in controlling cell behavior (cellular interaction, proliferation, and differentiation). In this regard, understanding signaling pathways and identifying effective substances to improve these pathways are also the main factors in successful regenerative medicine. In the following, the different materials that can bring us closer to this aim, as well as their role in inducting cell signaling and improving proliferation and differentiation, have been mentioned.

13.3 Herbal Bioactive Compounds to Induce Differentiation of Stem Cells

The tremendous differentiation of stem cells is one of the desirable properties of these cells. However, this property can act as a double-edged sword, which means an increase in the risk of tumorigenicity. Thus, therapeutic strategies which led to the complete and irreversible differentiation of stem cells play an important role in controlling differentiation.

One of these strategies includes the use of biomaterials or bioactive materials to design scaffolds, substrates, or tissue substitutes (Izadyari Aghmiuni and Heidari Keshel 2022; Aghmiuni et al. 2022). This approach can provide suitable physicomechanical properties to differentiate stem cells and lead to a sustained delivery and local of bioactive molecules for tissue regeneration. Indeed, bioactive compounds or biomaterials play the main role in providing the cell differentiation microenvironment, so that they can control cellular functions and interactions via creating an ideal substrate. In this matter, Izadyari Aghmiuni's research has shown that the phytochemical materials in herbs possess high therapeutic and regenerative effects (Izadyari Aghmiuni et al. 2020). However, their physical forms like gel, mucilage, and the extract or essential oil from different parts of the plants cannot be applied on damaged tissue (such as the bone, skin, cartilage, blood vessels, nerve, cornea, tendon, etc.) directly. This research team showed that quince seed mucilage is one of the bioactive components that can turn an engineered scaffold into a smart biological substrate. They stated that this herbal bioactive material is classified into the group of polysaccharide and composed of xylose(glucuronoxylan) and glucuronic acid; however, swell in water due to the existence of hydrophilic groups (i.e., amino, hydroxyl, amide, and carboxylic acid), unlike some of the polysaccharides such as chitosan which suspended in the acidic solvent. The results of this study indicated that quince seed mucilage-based hybrid scaffolds can create a better porous network compared to chitosan-based scaffolds. Moreover, these scaffolds support the proliferation of dermal fibroblasts and provide high water absorption capacity for the scaffold. Based on this research, the combination of quince seed mucilage and PEG leads to an increase in the transduction of mechanical force-induced signals and improves the biological signals to induce stem cell differentiation (with the same differentiation patterns) into targeted cells such as keratinocytes.

Another study in this regard is *Aloe vera*-based scaffolds that possess wide applications in biomedical and pharmaceutical sciences. The popularity of these herbal polysaccharides is inducted by their bioactive components (i.e., anthraquinones, anthrones, carbohydrates, proteins, vitamins, etc.) that lead to antimicrobial, anti-inflammatory, and antiviral properties, antioxidant effects, as well as immunomodulatory, neo-angiogenesis, and tissue repair effects (Darzi et al. 2021; Rahman et al. 2017). In this regard, Kallyanashis Paul et al. reported that *Aloe vera*-based hydrogel could alleviate maternal birth injuries (Paul et al. 2021). Based on this study, *Aloe vera*-alginate hydrogels can be an immediate treatment by delivering stem cells to regenerate damaged tissue. The results of this

research team showed that local injection of hydrogel with/without stem cells can be significantly effective in repairing birth injuries, so that it leads to the improvement of elastin content and smooth muscle. They stated that such hydrogels can be a suitable therapeutic strategy for preventing pelvic organ prolapse or healing birth injuries.

The electrospun mesh of *Aloe vera* is another sample that can act as a transdermal therapeutic factor. Suganya et al. showed that fibers of poly(caprolactone) containing *Aloe vera* powder (10 wt%) possess better hydrophilic properties along with higher tensile strength (6.28 MPa) and elastic modulus similar to skin tissue, as well as more desirable cell proliferation, secretion of collagen, and expression of F-actin compared to polycaprolactone-collagen fibers (Suganya et al. 2014a). Based on the reports of Tahmasebi et al., nanofibrous scaffolds of poly(3-hydroxybutyrate-co-3-hydroxy valerate) blended with *Aloe vera* gel can be also useful for applications of bone tissue engineering (Tahmasebi et al. 2020). The results of this study indicated the higher biocompatibility of the mentioned nanofibrous scaffold when blended with *Aloe vera*. Moreover, alkaline phosphatase activity, amount of mineralization, and expression of bone-related genes or proteins increase compared to *Aloe vera*-free nanofibrous scaffold. They stated that *Aloe vera* gel possesses the osteoinductive potential and can be used for acceleration of bone regeneration as a bio-implant.

According to the reports, the use of *Aloe vera*, along with other herbal bioactive compounds, can accelerate wound healing processes. In this matter can mention to hybrid nanofibrous scaffolds based on *Aloe vera* and curcumin were designed by Ezhilarasu et al. to increase their synergistic effects on the proliferation of fibroblasts and antimicrobial activities (Ezhilarasu et al. 2019).

The study of Oryan et al. demonstrates that adipose-derived stem cell-loaded *Aloe vera* hydrogels can be also effective in the burn wound models (Oryan et al. 2019). The results of this study showed that hydrogels containing *Aloe vera* and stem cells can significantly increase the rate of burn wound healing, lead to improvement of angiogenesis and reepithelialization, as well as decrease TGF-β_1[6] and interleukin-1β levels. *Urtica dioica* L. (nettle) is one of the other herbs in this matter that can be led to osteogenic differentiation when blended with biomaterials such as silk fibroin. Zadegan et al. indicated that silk fibroin-nettle nano-fiber possesses better water uptake and cellular attachment as well as higher cellular proliferation than that of silk fibroin nano-fiber. Moreover, nettle-based nano-fibers can express both early and late markers of osteoblast differentiation (Zadegan et al. 2019).

Urtica dioica, along with ZnO nanoparticles, can also provide the synergy effects for the increase of antibacterial activities in the electrospun scaffolds. Ghiyasi et al. stated that incorporation of *Urtica dioica* and ZnO nanoparticles to poly (caprolactone) scaffolds can be led to an increase in the tensile strength up to 2.54 MPa and improvement of water uptake ability and promotion of fibroblast L929 cell proliferation (Ghiyasi et al. 2021). Another study relates to the induction of

[6]Transforming growth factor-β_1.

periosteal cell differentiation and proliferation by *Urtica dioica* extract. According to the report of Bing et al., the extract of this herb led to an increase in alkaline phosphatase and calcium nodule levels, as well as induction of osteoblast differentiation and proliferation on the polyclonal lactone scaffolds (Xu and Liu 2018).

Moreover, the study of Hajiali et al. showed that nanofibrous dressings based on sodium alginate-lavender essential oil possess high efficacy for the treatment of UVB-induced skin burns with antibacterial activities (Hajiali et al. 2016). These dressings are also able to decrease and control the inflammatory responses induced in the skin fibroblasts due to UVB exposure. Some reports showed animal fats could also increase the differentiation and proliferation of stem cells. In this regard, the design of emu oil-based electrospun nanofibrous by Pilehvar-Soltanahmadi et al. illustrates that emu oil not only promotes differentiation and proliferation of adipose tissue-derived stem cells into keratinocytes but also can lead to increase in cell adherence and cytoprotection (Pilehvar-Soltanahmadi et al. 2017). Such that, it can be a suitable candidate to fabricate wound dressings and/or bio-engineered substitutes containing stem cells for skin tissue repair.

There are many studies on this matter and some examples are listed in Table 13.1.

Specifically, studies on herbal bioactive compounds have illustrated that herb-derived materials not only can increase the proliferation and differentiation of adult stem cells but also inhibit the proliferation of cancer cells (Saud et al. 2019; Olatunbosun et al. 2012; Kornicka et al. 2017; Potu et al. 2009; Gao et al. 2013). However, studies have shown that the proliferation and/or differentiation ability of stem cells is influenced by the doses of the stimulant compounds. It means that a specific dose of herbal extracts can promote stem cell proliferation and induce its differentiation into the targeted cell. In this regard, we can refer to Zhang's study on the effects of naringin on human bone mesenchymal stem cell proliferation and osteogenic differentiation (Zhang et al. 2009a). Zhang et al. showed that 1–100 μg/mL concentrations of extract from this citrus lead to an increase in the proliferation of human BM-MSCs and their osteogenic differentiation, while, 200 μg/mL concentration can decrease the growth of these cells. Similar research in this field is related to the study of Yu et al. They showed that naringin in 50 μg/mL concentration can activate the Notch signaling pathway and lead to stimulation of osteogenic differentiation of BMSCs.[7] However, higher concentrations than 100 μg/mL can suppress the proliferation rate of these cells (Yu et al. 2016).

Zhang et al. also reported that naringin can induce osteogenic activity and differentiation of canine bone marrow stromal cells (Zhang et al. 2021). To this end, they added different concentrations of this bioactive to the mentioned cells. Their results showed that the 10^{-6} mol/L concentration can promote cell proliferation and be led to an increase in cellular proliferation and calcium nodules, as well as induction of bone marrow stromal cell differentiation into osteoblasts.

[7] Bone marrow stromal cells.

Table 13.1 Herbs-based scaffolds, substrates, or gels for improvement of cellular interactions and functions

Herb	Scaffolds, substrates, or gels	Function	Reference
Curcumin	Collagen-alginate scaffold containing curcumin-loaded chitosan nanoparticles	Acceleration in wound closure; the complete epithelialization along with the formation of thick granulation tissue; the decrease of inflammation; regeneration of diabetic wounds	Venkata et al. (2016)
	Poly(ε-caprolactone) nano-fibers loaded by curcumin	More than 70% viability on human foreskin fibroblast cells; anti-inflammatory property; high antioxidant activity; the decrease of oxidative stress and IL-6 release; wound healing capability by increasing rate of wound closure in a diabetic mice model induced by streptozotocin	Merrell et al. (2009)
	Electrospun poly (ε-caprolactone)-poly (ethylene glycol)-poly (ε-caprolactone) fibrous mat containing curcumin	Improvement of antioxidant properties and low cytotoxicity; the increase of wound closure; suitable candidate for wound dressings	Fu et al. (2014)
	The thermosensitive hydrogel containing encapsulated curcumin	Biodegradable gel with suitable tissue adhesiveness for release of curcumin along with antioxidant and anti-inflammatory properties; accelerating agent in wound closure; improvement of collagen content, granulation, and wound maturity; reduction of superoxide dismutase; the higher thicker epidermis and tensile strength in regenerated skin; suitable for	Gong et al. (2013)

(continued)

Table 13.1 (continued)

Herb	Scaffolds, substrates, or gels	Function	Reference
		wound healing as a wound dressing	
	Nano-graphene oxide reinforced fish scale collagen-based 3D scaffold containing curcumin	No toxicity against NIH 3T3 fibroblast cells; suitable antimicrobial properties against the growth of gram-positive and gram-negative bacteria; acceleration of wound healing; suitable for skin tissue engineering applications	Mitra et al. (2015)
	Chitosan-gelatin composite sponge containing curcumin	Sponge possessed a high capacity for water absorption, antibacterial activity, and drug release; the increase of wound closure on rabbit wound model; suitable for wound healing applications	Nguyen et al. (2013)
	Collagen matrix incorporated by curcumin	Increase of cellular proliferation and wound healing; efficient free radical inhibiting and decrease of oxidative stress; suitable for supporting dermal wound healing	Gopinath et al. (2004)
	Curcumin-treated pluronic F-127 gel (25%) and curcumin (0.3%) in pluronic gel	Increase of the wound contraction; reduction in the expressions of inflammatory cytokines or enzymes such as TNF-α^a, IL-1β^b, and MMP-9^c; increase in the level of anti-inflammatory cytokines such as IL-10 and antioxidant enzymes (like dismutase, catalase superoxide, and glutathione peroxidase); promotion of fibroblast proliferation and	Kant et al. (2014)

(continued)

Table 13.1 (continued)

Herb	Scaffolds, substrates, or gels	Function	Reference
		improvement of collagen deposition; covering wound via creating a layer of thick epithelial and diabetic wound healing	
Aloe vera	Electrospun polycaprolactone mat incorporated with *Aloe vera*	The control of scaffold degradation rate; improvement of wettability behavior and increase of hydrophilicity of the substrate; promotion of fibroblast proliferation	Agnes Mary and Giri Dev (2015)
	Electrospun silk fibroin-hydroxyapatite scaffold containing *Aloe vera*	The creation of biomimicry similar to the natural bone constitution in scaffold; enhancement of osteocalcin expression and osteogenesis; increase in proliferation of human mesenchymal stem cells, mineral deposition, and osteogenic differentiation	Suganya et al. (2014b)
	Electrospun polycaprolactone-silk fibroin nanofibrous scaffolds containing *Aloe vera*	The increase of adipose-derived stem cell proliferation on scaffolds; promotion in the expression of osteogenic markers such as osteocalcin and alkaline phosphatase; enhancement of osteogenic differentiation and mineralization; suitable for bone tissue regeneration applications	Shanmugavel et al. (2014)
	Bacterial nano-cellulose-*Aloe vera* composites	Improvement of mechanical properties, suitable for biomedical application, design of engineered scaffolds or substitutes, and cell	Godinho et al. (2016)

(continued)

Table 13.1 (continued)

Herb	Scaffolds, substrates, or gels	Function	Reference
		culture substrate applications	
	Eye drops derived from *Aloe vera* gel	The decrease of the corneal epithelial defect area; no developed hypersensitivity reaction, corneal perforation or descemetocele, and limbal ischemia; control of inflammatory responses	Rezaei Moghadam et al. (2020)
	Nanofibrous poly (L-lactic acid)-collagen scaffold coated with *Aloe vera* gel and chitosan	The improvement of mouse fibroblast (L929) behaviors (adhesion, viability, and proliferation) on the scaffold and physicomechanical properties of the substrate; suitable for skin tissue engineering	Salehi et al. (2016)
	Core-shell electrospun mat containing *Aloe vera* extract	The improvement of mechanical and physicochemical properties in the substrate; the increase of cellular adhesion and growth on the mat; high potential for wound healing	Zahedi et al. (2019)
Azadirachta indica, *Indigofera aspalathoides*, *Myristica andamanica*, and *Memecylon edule*	Electrospun polycaprolactone nanofibrous scaffolds containing herbal extracts	The promotion of human dermal fibroblast proliferation; induction of epidermal differentiation of adipose-derived stem cells (both early and intermediate stages of differentiation), suitable for skin tissue engineering	Jin et al. (2013)
Cissus quadrangularis	Polycaprolactone nanofibrous scaffold containing hydroxyapatite and *Cissus quadrangularis*	The increase in osteogenic activity and bone tissue regeneration, promotion of cell	Suganya et al. (2014c)

(continued)

Table 13.1 (continued)

Herb	Scaffolds, substrates, or gels	Function	Reference
		proliferation, and mineralization	
Xylan (natural polysaccharide in plants)	Polyvinyl alcohol nano-fibers containing xylan	Promotion of fibroblast proliferation on the nanofibrous scaffold; the improvement of mechanical properties and increase in the natural biodegradable rate of the scaffold; enhancement of fibroblast adhesion; better interactions of cell-to-matrix to regenerate skin tissue	Krishnan et al. (2012)
Althea officinalis	Electrospun poly (ε-caprolactone)-gelatin scaffold containing *Althea officinalis*	Expedition of the therapy duration and acceleration of wound healing; the increase of anti-inflammatory and antimicrobial properties of the scaffold; improvement of mechanical and physicochemical properties of the scaffold; promotion of cellular proliferation	Ghaseminezhad et al. (2020)
Arnebia euchroma	The nanofibrous scaffold of polycaprolactone-chitosan-polyethylene oxide containing *Arnebia euchroma*	Scaffolds possess high potential in burn wound healing; control of biodegradation rate of the scaffold; improvement of swelling and mechanical properties of the scaffold; increase of antibacterial activity and human dermal fibroblast cell proliferation; suitable for skin tissue engineering applications	Asghari et al. (2022)
Spinacia oleracea	Alginate-carboxymethyl cellulose scaffold incorporated with	The mechanical stability of the scaffold; improvement of biocompatibility of scaffold; control of	Sharmila et al. (2020)

(continued)

Table 13.1 (continued)

Herb	Scaffolds, substrates, or gels	Function	Reference
	Spinacia oleracea extract	biodegradation rate; promotion of MG-63 human osteosarcoma cell proliferation; suitable for bone tissue engineering applications	
Angiogenin and curcumin	Polyethyleneimine-carboxymethyl chitosan-poly (D, L-lactic-co-glycolic acid)-cellulose nanocrystal electrospun nano-fiber containing angiogenin and curcumin	Nano-fibers possessed excellent biocompatibility, anti-infection, and angiogenesis properties; suitable for skin regeneration	Mo et al. (2017)
Gum tragacanth	Gum tragacanth-poly (ε-caprolactone) electrospun nano-fiber containing curcumin	High antibacterial properties against gram-positive and gram-negative bacteria; reduction of the epithelial gap; fast wound closure along with the formation of granulation tissue, hair follicles, and sweat glands; proliferation of fibroblasts; creation of collagen deposition and the layer of early regenerated epithelial completely; increase of angiogenesis number	Ranjbar-Mohammadi et al. (2016)

[a] Tumor necrosis factor-alpha
[b] Interleukin-1beta
[c] Matrix metalloproteinase-9

Beom Su Kim et al. indicated that the extract of brown algae *Laminaria japonica* (fucoidan) in 0.1–10 μg/mL concentrations can lead to JNK- and ERK[8]-dependent BMP2[9]–Smad 1/5/8 signaling and induces osteoblast differentiation of human mesenchymal stem cells (Kim et al. 2015). They also found that this osteogenesis bioactive can increase ALP activities and accumulation of calcium and leads to the expression of the osteoblast-specific gene.

[8] Extracellular signal-regulated protein.
[9] Bone morphogenetic protein.

Moreover, MaríaSatué et al. reported that some flavonoids lead to the stimulation of MC3T3-E1 cell differentiation into osteoblast and inhibition of osteoclastogenesis in RAW 264.7 cells (Satué et al. 2013). The results of this study illustrated that doses greater than 100 μM of diosmetin, galangin, and chrysin, as well as 500 μM doses of taxifolin, possess a toxic effect on cells. However, quercitrin with safe doses of 200 and 500 μM and taxifolin in safe doses of 100 and 200 μM can induce osteocalcin mRNA and bone sialoprotein expression and lead to higher osteocalcin levels. Fei Li et al. also showed that the echinacoside as phenylethanoid glycosides can promote bioactivities of cell line MC3T3-E1 (i.e., proliferation, differentiation, and mineralization of osteoblastic) (Li et al. 2012). To this end, this bioactive component isolated from Cistanches Herba stems and the amount of the secretion of osteoprotegerin, osteocalcin, and collagen I were evaluated. Based on this study's results, concentrations between 0.01 and 10 nmol/L can significantly promote cell proliferation, osteocalcin levels, and collagen I content can lead to an increase in the mineralization of osteoblastic. They stated that echinacoside possesses a stimulatory effect on the formation of osteoblastic bone and can potentially be effective against osteoporosis.

Likewise, Hui-HuiXiao et al. observed that vanillic acid isolated from *Sambucus williamsii* Hance possesses estrogen-like activity in the rat UMR 106 cells that can be due to MAP[10] kinase (MEK/ERK)-mediated specific estrogen receptor (ER) antagonist signaling pathways (Xiao et al. 2014). The results of this study showed that this phenolic acid stimulates the mentioned cell proliferation and alkaline phosphatase (ALP) activity. Vanillic acid can also increase Runx2,[11] osteocalcin, and the ratio of osteoprotegerin-receptor activator of nuclear factor kB ligand [i.e., OPG-RANKL] mRNA expression.

Kim's study is one of the other samples hereof (Kim et al. 2014). Kim et al. illustrated that kirenol extracted from Herba Siegesbeckia can promote osteoblast differentiation via activation of the BMPs and Wnt/β-catenin signaling pathways in MC3T3-E1 cells. Moreover, this natural diterpenoid compound can lead to the promotion of mineralization and ALP activity, as well as the increase in osteopontin, collagen I, and expression of OPG/RANKL. Puerarin and phytoestrogens isolated from *Pueraria mirifica* are the other bioactive compounds in this field that can lead to an increase in cellular proliferation and the expression of osteoblastic differentiation markers in osteoblast-like UMR106 cells (Tiyasatkulkovit et al. 2012). Such that, Tiyasatkulkovit et al. indicated that puerarin can increase the mRNA expression of ALP, as well as lead to a decrease in the mRNA expression of RANKL and induction of bone gain via increasing osteoblast differentiation in rat osteoblast-like UMR106 cells and suppressing osteoclast functions. They stated that puerarin can induce the differentiation of osteoblast rather than the proliferation of osteoblast in the estrogen receptor-dependent manner; hence, it can be the appropriate option to prevent and treat postmenopausal osteoporosis. Choi et al. stated that honokiol

[10] Mitogen-activated protein.

[11] Runt-related transcription factor 2.

isolated from the bark of *Magnolia officinalis* not only can stimulate osteoblast MC3T3-E1 cell function (i.e. increase in cell growth, improvement of ATP activity, promotion of collagen synthesis and glutathione content, and release of osteoprotegerin in the cells) but also decrease or inhibit the production of bone-resorbing mediators. They suggested that this phenolic compound can be effective in natural therapies for osteoporosis (Choi 2011).

There are many studies on stem cell differentiation into the progenitor cells of endothelial or vascular, cardiomyocyte, neuronal, osteogenic, neurogenic, etc. that their stimulation factor is bioactive components extracted from herbs. Indeed, these bioactive components can not only promote cellular proliferation and differentiation but also decrease the time required for tissue regeneration. Table 13.2 illustrates some effective herbs in this regard.

13.4 Biomaterials and Their Characteristic to Design Ideal Substrates and Induce Cell Differentiation

The ideal substrates possess different characteristics which originate from their materials and lead to the targeted differentiation of stem cells (Discher et al. 2005).

Regardless of the tissue type, some of the key characteristics of bio- or active material-based substrates when designing and determining the suitability of the scaffolds for regenerative medicine applications include biocompatibility, mechanical properties, biodegradability, the architecture of the scaffold, and manufacturing technology. One of the requirements of a scaffold to regenerate tissue is biocompatible properties; according to Williams, "The biocompatibility of a scaffold or matrix for a tissue engineering product refers to the ability to perform as a substrate that will support the appropriate cellular activity" (Williams 2008). Indeed, the scaffold structure must possess suitable stimuli or recognizable stimuli by cells to colonize scaffolds and regenerate (Parisi et al. 2018). In other words, the cells must first adhere to the scaffold, proliferate, differentiate, and then migrate onto the surface of the scaffold. Finally, differentiated cells should proliferate on the scaffold to create a new matrix (Fig. 13.3).

In this regard, natural polymers are considered one of the main candidates that not only can increase cell biological activities on the scaffold (i.e., adhesion or attachment, spreading, proliferation, differentiation, and migration) but also imitate the structure and function of the native extracellular matrix (ECM) and lead to controlled induction of cell functions (Izadyari Aghmiuni et al. 2020; Izadyari Aghmiuni and Heidari Keshel 2022). Indeed, biomaterials are agents that can provide an ideal microenvironment with suitable physicomechanical and physicochemical properties to mimic the structure of the ECM network and functions of targeted cells and tissues (Izadyari Aghmiuni et al. 2021; Izadyari Aghmiuni and Heidari Keshel 2022). Collagen is one of these biopolymers that is found in most soft and hard tissues such as the blood vessels, nerves, cornea, skin, tendon, cartilage, bone, etc. Given that, this biomaterial leads to maintaining the structural and biological integrity of the native ECM network and can help in the physiological functions of the

Table 13.2 The effect of herbal bioactive compounds on the cellular functions

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
Ugonin K/*Helminthostachys zeylanica* L.	Flavonoid	MC3T3-E1 mouse osteoblast-like cells	Induction of differentiation and mineralization of cells, the increases in alkaline phosphatase (ALP) activity, expressions of osteocalcin and bone sialoprotein, as well as formation of bone nodule via estrogen receptor antagonist ICI 182,780 that led to upregulation in the expressions of osterix and Runx2, increase of the phosphorylated level of c-Src, promotion of estrogen receptor-α protein level, stimulation of osteoblastic differentiation of rat primary osteoblasts and promotion of osteoblastic differentiation of human MG-63 osteosarcoma cells via estrogen receptor-dependent activation in the pathways of nonclassical signaling mediated by c-Src phosphorylation	10 μM	Lee et al. (2012a)

Icariin, baohuoside-I, epimedin-B, and sagittatoside-A/Herba epimedii	Flavonoid	Rat osteoblastic-like UMR-106 cells	The stimulation of the proliferation rate of the cells; the increase of ALP activity and osteoprotegerin (OPG)/RANKL mRNA expression in cells Sagittatoside A also possesses selectively activated ERE[a]-luciferase activity by ERα[b] Moreover, all four flavonoids can stimulate estrogen receptor-dependent osteoblastic function	10^{-8} to 10^{-10} M	Xiao et al. (2014)
Neobavaisoflavone/*Psoralea corylifolia* L.	Isoflavone	Murine calvaria-derived osteoblastic cell line MC3T3-E1	Increase of ALP activity, enhancement in the expression of bone-specific matrix proteins like collagen I, bone sialoprotein, and osteocalcin; promotion of osteogenesis in cells; formation of bone nodules; regulation of Runx2[c] and osterix expression	10–15 μM	Don et al. (2012)
Poncirin/*Poncirus trifoliata*	Flavanone glycoside	C3H10T1/2 mesenchymal stem cells and primary bone marrow mesenchymal stem cells	The prevention of adipocyte differentiation in C3H10T1/2 cells via inhibiting accumulation of cytoplasm lipid droplet and	1 and 10 μM	Yoon et al. (2011)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
			PPAR-γ[d] and protein-β (C/EBP-β) mRNA expression via binding CCAAT enhancer; promotion of osteoblast differentiation in mesenchymal stem cells; the increase in expression of the key osteogenic transcription factors, ALP, Runx2, and osteocalcin; the increase in the formation of the mineral nodule in primary bone marrow mesenchymal stem cells		
Genistein/lupin, fava beans, and soya beans	Phytoestrogen	MC3T3-E1 cells and primary rat calvarial osteoblasts	Increase of the phosphorylation of kinase 1/2 regulated with the extracellular signal; the increase of MAPK[e] activated with p38 mitogen and c-Jun N-terminal kinase 1/2; the increase in translocation of c-Jun and NF-κB; induction of ERα mRNA expression and increase of its level and content of nuclear ERα protein in rat calvarial	10 μM	Liao et al. (2014)

			osteoblast; induction of expressions of the genes related to osteoblast differentiation; increase in osteoblast mineralization		
Quercetin and rutin/fruit and vegetables	Flavonoid	Mouse bone marrow-derived mesenchymal stem cells	The increase of ATP activity and mineralization; promotion of the prominent marker expression (such as RunX2, osteopontin, osteoprotegerin, osterix, and osteocalcin) to differentiate osteoblast; effective in controlling osteodegenerative disorders and effective in bone development	50 μM for quercetin and 25 μM for rutin	Srivastava et al. (2013)
Puerarin/*Pueraria lobata* (Willd.)	Isoflavone glycoside	Human osteoblastic MG-63 cell	Stimulation of osteoblast proliferation and differentiation via both ERα and ERβ, as well as activation of estrogen receptor-dependent MEK/ERK[f] and PI3K[g]/Akt signaling (partially); opposition with apoptosis induced from cisplatin in osteoblastic MG-63 cells	0.1 μM	Wang et al. (2013)
Sweroside/Fructus corni	Iridoid glycoside	Human MG-63 cells and rat osteoblasts	Increase in osteogenic effect on the proliferation and differentiation of rat	10^{-5} and 10^{-6} g/mL	Sun et al. (2013)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
			osteoblasts and MG-63 cells; the increase of ALP activity and osteocalcin level; attenuation and inhibition of apoptosis		
Salidroside/*Rhodiola rosea* L.	Phenylpropanoid glycosides	Murine pluripotent mesenchymal cell line C3H10T1/2 and osteoblastic cell line MC3T3-E1	The increase of the ALP activity and the mRNA expressions of osteoblast marker genes; enhancement of C3H10T1/2 cell mineralization; the increase of the mRNA level in genes involved in regulating BMP^h signaling pathways (such as BMP2, BMP6, and BMP7) and regulation of bone metabolism; enhancement of the Smad1/5/8 and ERK1/2 phosphorylation; promotion of the osteoblast proliferation and differentiation	0.5–10 μM	Chen et al. (2013a)
Ginsenoside-Rb_2/ginseng	20(S)-protopanaxadiol glycoside	Osteoblastic MC3T3-E1 cells	Promotion of MC3T3-E1 cell proliferation; improvement of ALP expression; the increase of calcium mineralization and osteogenic gene expression (like	0.1–10 μM	Huang et al. (2014)

			osteopontin, Col1a1, and osteocalcin) against H_2O_2-induced oxidative damage; reduction of the RANKL and IL-6[i] expression level; inhibition of the ROS[j] production induced by H_2O_2; improvement of a micro-architecture of trabecular bone; the increase of BMD[k] of the L4[l] and distal femur		
Gastrodin/*Gastrodia elata*	Phenolic glycoside	Human bone marrow mesenchymal stem cells (hBMMSCs) and macrophage cell line (RAW264.7 cells)	Promotion of the hBMMSC proliferation; improvement of osteogenic markers; reduction of lipid generation and inhibition of mRNA expression of adipogenic genes; reduction in the number of osteoclasts, TRAP, and CTX-1 activity (serum bone degradation markers) and osteoclast-specific gene expression; suppression of the production of ROS in both studied cells; prevention and treatment of osteoporosis	0.1, 1, 10 μM	Huang et al. (2015a)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
Ophiopogonin D/*Ophiopogon japonicus* Radix	Steroidal glycoside	Mouse pre-osteoblast cell line MC3T3-E1 subclone 4 cells and a macrophage cell line RAW264.7 cells	Promotion of MC3T3-E1 cell proliferation; improvement of the osteogenic markers; reduction of TRAP and CTX-1 activities (as the serum bone degradation markers) and mRNA expression in the osteoclastic gene of RAW264.7 cell; suppression of ROS produced in both studied cells; anti-osteoporosis effect through ROS reduction by the FoxO3a-β-catenin signaling pathways	1, 10, and 100 μM	Huang et al. (2015b)
2,3,5,4′-Tetrahydroxystilbene-2-*O*-β-D-glucoside/*Polygonum multiflorum* Thunb	Stilbene glycoside oligomers	Osteoblastic MC3T3-E1 cells	Increase of cellular survival, calcium deposition; promotion of ALP activities and the expression of ALP, collagen I, and osteocalcin induced by H_2O_2; reduction of the RANKL production, IL-6, intracellular reactive oxygen species, and MDA^m of studied cells induced by H_2O_2;	1–10 μM	Zhang et al. (2012)

			protective effect on the cells through inhibiting the release of bone-resorbing mediator and cell oxidative damage		
Imperatorin and bergapten (coumarin derivatives)/ *Cnidiummonnieri* and *Angelica pubescens*	Furanocoumarin	Primary osteoblastic cell	Increase of ALP activity and collagen I synthesis; promotion of bone nodule formation; the increase of BMP-2 expression; enhancement of the phosphorylation of $SMAD^n$ 1/5/8, p38, and ERK^o and consequently increase of bone formation	0.3–10 μM	Tang et al. (2008)
Albiflorin/Paeoniae radix [root of *Paeonia lactiflora* Pallas (Paeoniaceae)]	Monoterpene	Osteoblast-like MC3T3-E1 cells	Reduction of ROS/RNS level; the decrease of apoptosis and lactate dehydrogenase release; enhancement of mineralization; reduction of cardiolipin peroxidation and mitochondrial cytochrome c loss induced by antimycin A; improvement of mitochondrial function by preserving cytochrome c and cardiolipin	0.01–1 μM	Suh et al. (2013)
Salvianolic acid B/*Salvia miltiorrhiza*	Phenolic acid	Human mesenchymal stem cells	Increase of ALP activity; stimulation of Runx2, osteopontin, and osterix expressions in studied cells; promotion of	5 μM	Xu et al. (2014)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
			mineralization and osteogenesis of cells via activating the ERK[p] signaling pathways		
Psoralen (coumarin-like derivative)/*Psoralea corylifolia* fruit (Buguzhi)	Derivative of umbelliferone (structurally)/linear furanocoumarins	Primary mouse calvarial osteoblasts	Stimulation of osteoblast differentiation via activation of BMP signaling; increase in expressions of osteocalcin, collagen I, and bone sialoprotein; improvement of ALP activity; upregulation and increase of the Bmp2 and Bmp4 expression, phospho-Smad1/5/8 level, and BMP (12xSBE-OC-Luc) activity	1–100 μM	Tang et al. (2011)
Resveratrol (3,4′,5-trihydroxystilbene)/ mulberries, peanuts, and the berry skins of most grape cultivars	Polyphenolic phytoestrogen	Human bone marrow-derived mesenchymal stem cell	The increase of cell growth/proliferation; stimulation of osteoblastic differentiation and osteoblastic maturation inducted by ALP activity; promotion of calcium deposition; the expression of osterix, osteocalcin, and RUNX2/CBFA1; rapid activation of MAPK[q] and ERK1/2 signaling at 10–6 M concentration	10^{-8} to 10^{-5} M	Dai et al. (2007)

Costunolide/*Saussurea lappa* (Compositae)	Sesquiterpene lactone	Osteoblastic MC3T3-E1 cells	Increase of MC3T3-E1 cell proliferation induced by PI3K, ER, ERK, PKC^{r}, and mitochondrial ATP-sensitive K^{+} channels; promotion of collagen content, ALP activity, and mineralization in cells	10 μg/mL	Lee and Choi (2011a)
Apocynin (4-hydroxy-3-methoxy-acetophenone)/ isolated from a variety of plant sources	Methoxy-substituted catechol	Osteoblastic MC3T3-E1 cells	Increase of collagen content, ALP activity, and mineralization; promotion of cell survival/ proliferation; the increase of calcium deposition and release of osteoprotegerin; the decrease of ROS production and TNF-α, IL-6, and RANKL expressions	0.01–1 μM	Lee and Choi (2011b)
Osthole (7-methoxy-8-isopentenoxycoumarin)/ *Cnidium monnieri* and *Angelica pubescens*	Coumarin-like derivative	Primary mouse calvarial osteoblasts	Increase in the formation of new bone via local injection of the bioactive compound; improvement of bone micro-architecture parameter, and biomechanical and histomorphometric properties; increase in upregulation of collagen I, osteocalcin, and BSP^{s}; activating Wnt/β-catenin	10–100 μM	Tang et al. (2010)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
			signaling; increase in the expression of Bmp2; stimulation of osteoblast differentiation via β-catenin-BMP signaling		
Kobophenol A/*Caragana sinica* (Buc'hoz) Rhed	Tetrameric stilbene	Human osteoblast-like MG-63 cells	Inhibition of downregulation of Bcl-XL and Bcl-2; inhibition of JNK and c-Jun phosphorylation induced by SNP; the decrease of NF-κB and AP-1 activities induced by SNP; reduction of death inducted by nitric oxide; protective effects against osteoblast apoptosis via regulating NF-κB, JNK, and AP-1 signaling pathway	25 and 50 μg/ mL	Lee et al. (2011)
Emodin/roots/bark of herbs such as the genus *Rhamnus*	Anthraquinone	Mouse osteoblastic MC3T3-E1 subclone 4 cells	The induction of ALP expression; induction of the PI3K, Akt, and MAP kinase activation; regulation of BMP-2 expression; the increase of mineralization; acceleration of osteoblast differentiation; effective on bone health	Up to 5 μM	Lee et al. (2008)

Acerogenin A/*Acer nikoense* Maxim	Diarylheptanoid	MC3T3-E1 osteoblastic cells and RD-C6 osteoblastic cells	Increase of ALP activity and mRNA expression related to osteoblast differentiation (such as primary osteoblasts, osteocalcin, Runx2, and osterix); increase of mRNA expression level of Bmp-2, Bmp-4, and Bmp-7; stimulation of the studied cell proliferation and differentiation via BMP activity	30 μM	Kihara et al. (2011)
Icariine/*Epimedium pubescens*	Flavonoid	Human marrow mesenchymal stem cells	Promotion of ALP activity and the calcified nodule level of osteoblast; enhancement of BMP-2 mRNA synthesis; increase in the human osteoblast proliferation and differentiation	20 μg/mL	Leishi (2007)
Soy peptide/*Glycine max* var.	Isoflavones	Human adipose tissue-derived mesenchymal stem cells and cord blood-derived mesenchymal stem cells as adult stem cells	Increase of TGF-β_1[t], VEGF[u], and IL-6 in the studied cells; activation of the mTOR signaling pathways and ERK; stimulation of cellular proliferation rate	Preparation of 1% medium in DMEM (serum-free)	Lee et al. (2012b)
Extracts of the leaves containing linalool, eugenol, methyl cinnamate, methyl chavicol, steroidal glycoside, ferulate, methyl eugenol, and	Natural terpene alcohol, allylbenzene, methyl ester, phenylpropene, steroidal glycoside, hydroxycinnamic acid,	Human dental pulp-derived mesenchymal stem cells and bone marrow-derived mesenchymal stem cells	Reduction of level of osteonectin; the decrease of doubling time in both cells; induction of cell proliferation; acceleration	10 μg/mL concentration	Mendi et al. (2017)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
triterpenoids/*Ocimum basilicum*	isopentenyl pyrophosphate oligomers		of the osteogenic differentiation; *O. basilicum* acts as a smart osteoinductive agent		
Hydro-alcoholic guaraná extract/*Paullinia cupana*	Rich in catechin and caffeine	Human lipoaspirate-derived senescent adipocyte stem cells	The increase of cellular proliferation; reduction in lipoperoxidation, ROS level, DNA damage, and oxidative stress marker; the increase of catalase activity/gene expression; reversion of the initial senescence processes in adipocyte-mesenchymal cells and consequently tissue regeneration	5 mg/mL	Machado et al. (2015)
Ethyl acetate extract of root containing glabridin and glabrene/*Glycyrrhiza glabra*	Rich in phytoestrogen	Human bone marrow mesenchymal stem cells	The increase in cellular proliferation; the effect on the osteogenesis via ALP activity, stimulation of estrogen receptor-mediated mechanism, and the bone-specific gene expression (like BMP-2, Runx2, and osteocalcin); promotion of calcium deposition	10–50 μg/mL	Azizsoltani et al. (2018)
Seed extract containing L-DOPA^{v}/*Mucuna gigantea*	Amino acid	Mesenchymal stem cells	Stimulation in mRNA expression of nestin,	50 μg/mL	Kongros (2012)

			MAP-2[w], and β-III tubulin messenger ribonucleic acid (as neural markers and neural protein)		
β-Mercaptoethanol/*Salvia miltiorrhiza*	Biological antioxidant	Human umbilical cord Wharton's jelly-derived mesenchymal stem cells	Induction of expression of neural protein markers; induction of nestin and pleiotrophin genes, β-tubulin III, NF[x], and GFAP[y]; stimulation of the differentiation into nerve-like cells (neuronal and glial cells); increase in proliferation of the neural cells	2–4 mmol/L	Leishi (2005)
Herb-derived small molecules such as resveratrol and stilbene (as WNT/β-catenin stimulators)/*Trifolium pratense* (leaves), *Salix aegyptiaca* (leaves and bark), and *Morus alba* (root)	Phytoestrogen and phenolic compounds, isoflavonoid derivate	Adipose tissue-derived mesenchymal stem cells	Stimulation of signaling pathways during stem cell differentiation of myocardial cells; improvement of stem cell differentiation into cardiomyocytes	1–3 μM	Azadian et al. (2019)
Quercetin and its metabolites (i.e., quercetin 3-glucuronide and 3′-*O*-methyl quercetin)/ fruit and vegetables	Flavonoid	Mitotic rat embryonic cardiomyoblast-derived H9c2 cells	The differentiation of cardiomyocyte-like phenotype; increase in the activation of PKB, JNK, ERK1/2, and p38 MAPK induced by H_2O_2; protective of	30–100 μM	Daubney et al. (2015)

(continued)

Table 13.2 (continued)

Bioactive compound name/ herb name	Classification	Source of cells/cell lines	Function	Effective dose	Reference
			cardioprotection against cell death and cardiotoxicity induced by oxidative stress		

[a] Estrogen response element
[b] Estrogen receptor alpha
[c] Runt-related transcription factor 2
[d] Peroxisome proliferator-activating receptor-γ
[e] Mitogen-activated protein kinase
[f] Extracellular signal-regulated protein
[g] Phosphatidylinositol 3-kinase
[h] Bone morphogenetic proteins
[i] Interleukin-6
[j] Reactive oxygen species
[k] Bone mineral density
[l] Fourth lumbar vertebrae
[m] Malondialdehyde
[n] Transcription factor activated by TGF-β
[o] Extracellular signal-regulated protein
[p] Extracellular signal-regulated kinase signaling
[q] p38 mitogen-activated protein kinase
[r] Protein kinase C
[s] Bone sialoprotein
[t] Transforming growth factor-beta1
[u] Vascular endothelial growth factor
[v] L-3,4-Dihydroxyphenylalanine
[w] Microtubule associated protein-2
[x] Neurofilament
[y] Glial fibrillary acidic protein

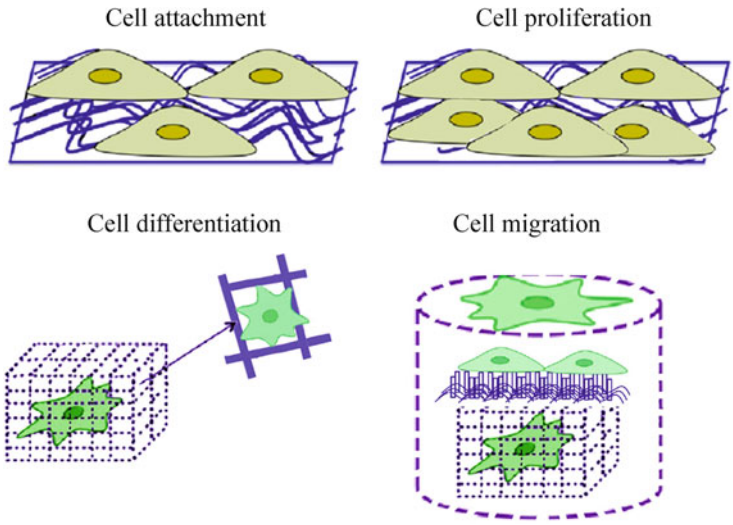

Fig. 13.3 The cellular interaction on the scaffold

engineered scaffolds as dynamic material (Barnes et al. 2007; Sell et al. 2010). Moreover, low antigenicity, low cytotoxic and inflammatory response, and biodegradability are other properties of this biomaterial (Farach-Carson et al. 2007; Sell et al. 2007, 2009). The study of Shih et al. indicates that electrospun collagen fibrous mat can promote growth, proliferation, adhesion, motility, and osteogenic differentiation of human MSCs[12] (Mano et al. 2007).

Many reports have shown that the blends of collagen with other biomaterials can increase the proliferation rate of cells and be used for regeneration templates in different tissues (Aghmiuni et al. 2020; Izadyari Aghmiuni et al. 2020). In this matter, Zhong et al. showed that collagen glycosaminoglycan (GAG)-based blended scaffolds can be led to an increase in the proliferation of dermal fibroblasts (FB) (Zhong et al. 2005). Moreover, the substrates based on chondroitin sulfate-collagen, collagen-nanohydroxyapatite, as well as aggrecan (chondroitin sulfate, dermatan sulfate, keratin sulfate)-collagen can be applied in the regenerating skin, bone, and cartilage, respectively (Choi et al. 2004; Thomas et al. 2007). Based on Chen's report, scaffolds of collagen/chitosan-PEO (as wound dressing) possessed good in vitro biocompatibility and led to the promotion of 3T3 FBs (Chen et al. 2008). In another study, collagen-chitosan scaffolds also illustrated an increase in the proliferation of smooth muscle cells (SMCs) and endothelial cells (ECs) (Chen et al. 2010). Indeed, mixing collagen with other biopolymers can lead to a decrease in the dimensions of the fibers or an increase in the porosity and tensile strength of the scaffold and consequently promotion of cellular attachment or adhesion on the scaffold surface (Barnes et al. 2007).

[12] Bone marrow-derived mesenchymal stem cells.

Gelatin also is known as an attractive biopolymer for tissue engineering applications due to its biological and biomechanical similarities to collagen (Zhang et al. 2005, 2009b; Heydarkhan-Hagvall et al. 2008). Although fibers of this biopolymer possess higher tensile moduli compared to collagen fibers, however, its gelation at room temperature and dissolution as colloidal-sol at 37 °C or > are major drawbacks of this biomaterial which is often solved via combining with other natural or synthetic polymers (Sell et al. 2010). Given the gelatin's similarity to collagen, electrospun gelatin-based blended scaffolds have been developed to apply in regenerative medicine (Zhang et al. 2005, 2009b; Heydarkhan-Hagvall et al. 2008; Li et al. 2005, 2006a; Gauthaman et al. 2009; Gupta et al. 2009a, b; Songchotikunpan et al. 2008; Song et al. 2008; Gui-Bo et al. 2010). The electrospun gelatin-polyurethane and poly (ε-caprolactone)-gelatin scaffolds are the samples of these substrates that can be used in wound healing and skin regeneration (Chong et al. 2007; Kim et al. 2009). Based on the reports, such scaffolds can lead to better migration of fibroblasts and decrease therapeutic costs. Poly(ε-caprolactone)-gelatin scaffolds can also act as a positive factor for supporting neurite outgrowth and nerve differentiation, proliferation, and nerve regeneration (Ghasemi-Mobarakeh et al. 2008). Likewise, conductive nanofibrous scaffold of polyaniline-poly(ε--caprolactone)/gelatin can lead to nerve stem cell attachment and proliferation, as well as neurite outgrowth via electrical stimulation of scaffold (Ghasemi-Mobarakeh et al. 2009). Moreover, an electrospun composite based on the synthetic polypeptide-gelatin can lead to the induction of calcium phosphate mineralization and be used as dental biomaterials or a biocompatible substitute for the regeneration of the hard tissue ECM (Ohkawa et al. 2009). Nanohydroxyapatite-gelatin nanofibrous scaffolds are one of the other substrates that are capable of imitation of natural ECM of bone tissue along with effective mineralization, the proliferation of osteoblasts, and successful bone regeneration (Francis et al. 2010).

Indeed, electrospun gelatin or gelatin-based scaffolds can be also used in the regeneration of cardiac tissue. According to the study of Li et al., the combination of gelatin with conductive polymers such as polyaniline leads to the improvement of cardiac myoblast attachment or adhesion, spreading, and migration, as well as an increase in cellular proliferation on the scaffold, modulus, and tensile strength (Li et al. 2006b). Studies have shown that blended gelatin with natural and synthetic polymers can significantly improve mechanical properties and facilitate the excellent proliferation of cardiac myoblasts. In this field, Li et al. indicated that gelatin composites composed of poly(lactic-co-glycolic acid) and α-elastin can be effective in soft tissue engineering applications, such as heart, blood vessels, and lung (Li et al. 2006c). Such composites possess low average diameters; however, upon hydration of the scaffold, the average diameter increases due to the swelling of fibers, without disintegrating the scaffold.

Elastin is one of the main biomaterials in this regard that naturally is found in the wall of many tissues such as vessel walls; hence, the use of fibrous structures of this biopolymer in tissue engineering applications can be favorable (Daamen et al. 2007; Bailey et al. 2003; Deborde et al. 2016). Based on the studies, elastin or elastin-like polypeptides can be effective in the regeneration of cartilage, heart valves, and skin

tissues (Neuenschwander and Hoerstrup 2004; Nettles et al. 2010; McHale et al. 2005; Betre et al. 2002). Wang et al. showed that collagen and elastin as the main components of ECM in tissues can improve the proliferation of valve interstitial cells, when used as the engineered 2D or 3D substrates (Wang et al. 2018b). Moreover, such substrates constitute effective tools to engineer 3D tissues and increase endothelial-mesenchymal transition. Chen et al. also illustrated that bilayer collagen-elastin scaffolds play an important role in mimicking the mechanical and biological activities of heart valves (Chen et al. 2013b). Chitosan/γ-poly(glutamic acid) scaffolds modified by albumin, elastin, and poly-L-lysine are another sample of elastin-based scaffold application in cartilage tissue engineering (Kuo et al. 2017). The study of Kuo et al. shows that such a scaffold can provide an effective approach to inhibition of chondrocyte apoptosis and lead to promotion in the growth of chondrocytes, secretion of ECM, and improvement of cartilaginous tissue regeneration. Moreover, the existence of single bond $–NH_3^+$ and single bond $–COO^-$ in the structure of this scaffold plays an important role in its porous morphology and interconnected network, as well as the mechanical properties of the scaffold.

Chitosan is one of the important polysaccharides in the design of tissue-engineered scaffolds due to the structural similarity to the glycosaminoglycans (GAGs) of ECM of tissues (Huang et al. 2015c). The functional groups of hydroxyl (–OH) and amine (–NH) in this biopolymer can link to other materials to make a new scaffold (He et al. 2011; Du et al. 2016). In this regard, Izadyari Aghmiuni et al. stated that polyethylene glycol-chitosan-poly(ε-caprolactone) copolymers containing collagen can be considered as base bio-composites for the design of dermal substrates. Such substrates can imitate dermis properties and lead to the induction of keratinocyte differentiation from stem cells (Izadyari Aghmiuni et al. 2021; Aghmiuni et al. 2020). The design of injectable chitosan-based hydrogels is another example in this field that can be used in cartilage tissue regeneration (Jin et al. 2009). Jin et al. showed that the hydrogels of chitosan-glycolic acid/phloretic acid that are designed via enzymatic crosslinking can increase chondrocyte proliferation and then be degraded by a hydrolytic enzyme such as lysozyme. Likewise, chitosan hydrogels modified by cartilaginous ECM are another type of hydrogel that can be used in cartilage tissue engineering applications (Choi et al. 2014). Mori et al. also stated that spongelike dressings containing chitosan and sericin can treat chronic skin ulcers. Such a substrate possesses suitable mechanical resistance and high hydration, along with cellular proliferation and antioxidant activities on human fibroblast cells (Mori et al. 2016).

Hyaluronic acid (HA) also is a linear polysaccharide and is classified in the group of glycosaminoglycans of native ECMs and can maintain the structural integrity of tissue ECMs when used in the structure of engineered scaffolds (Izadyari Aghmiuni et al. 2021; Kogan et al. 2006; Volpi et al. 2009; Petrey and de la Motte 2014). This biomaterial possesses various biological activities (like modulation of immune cell function, synthesis of proteoglycan, reduction of pro-inflammatory cytokine activities, etc.) and can act as the signaling factor for improvement of cell-to-cell and cell-to-scaffold interactions and acceleration of tissue regeneration (Izadyari Aghmiuni et al. 2021; Lam et al. 2014; Li et al. 2018). Based on the study of Shirzaei

Sani et al., HA/elastin-like polypeptide-based hydrogels can act as antimicrobial substrates for tissue engineering applications (Shirzaei Sani et al. 2018). This study illustrated that these hydrogels possess high adhesive strength to attach to the tissue and can support cellular spreading, growth, and proliferation. Izadyari et al. also demonstrated that control of HA content can provide a microporous environment along with higher tensile strength and modulus (Izadyari Aghmiuni et al. 2021). According to the reports, given that hyaluronic acid plays an important role in osmotic balance and regulation of tissue hydration, HA-based substrates can significantly mimic the physical and mechanical properties of ECM (Chan and Tayama 2002).

Silk fibroin (SF) is another biopolymer that can play an important role in cell attachment and spreading when mixed with collagen (Yeo et al. 2008). This biomaterial also possesses high elasticity, resistance to failure (under compression), minimal inflammatory response, slow degradation rate, as well as high biocompatibility, toughness, and strength (Pérez-Rigueiro et al. 2001; Liu et al. 2007; Zhang et al. 2009c). Notably, the existence of hydrophobic domains in the protein's random coil network of this biomaterial has led to the formation of a β-sheet structure, which is responsible for the elastic properties and tensile strength of SF (Aghmiuni et al. 2020; Zhang et al. 2009c). This property plays a crucial role in the scaffold structure and improves the module and stress strain of scaffolds (Zhang et al. 2010). Moreover, the β-sheet structures of SF can affect the biodegradation rate of the scaffold, so that the biodegradation rate of the scaffold matches with the rate of tissue repair (Izadyari Aghmiuni et al. 2021; Sell et al. 2010; Alessandrino et al. 2008; Bayraktar et al. 2005; Liu et al. 2008; Silva et al. 2008). Hence, silk-based scaffolds can be designed for the ligament, bone, and vascular skin applications (Izadyari Aghmiuni et al. 2020, 2021).

Generally, in our opinion, the features of these biomaterials and other bio- or active materials can provide an exciting opportunity to design engineered hybrid/composite substrates with a high ability to differentiate stem cells and regenerate tissue.

13.5 Future Prospective and Conclusion

Nowadays, the advancement in the field of phyto-sciences, technologies, and the development of studies on herbal extracts have revealed their excellent repairing properties and role in regenerative medicine. Based on the studies, herbal bioactive compounds or active ingredients can play a crucial role in the process of tissue regeneration. Such that, the cellular and molecular researches on herbal extracts indicate that herbs possess positive effects on the promotion, proliferation, and differentiation of types of stem cells. It can be due to the existence of flavonoids; coumarins; glycosides; terpenoids such as mono-terpenoids, sesquiterpenoids, and diterpenoids; as well as anthraquinones, phenolic acids, diarylheptanoids, phenols, and tetrameric stilbene. Hence, if protocols or methods can be created via the use of herbal extracts to proliferate and differentiate stem cells into targeted cells in

damaged tissues, it will offer hope to cure many incurable diseases. In this field, knowledge of herbs and the effects of their extracts and therapeutic doses can play a crucial role in the determination of suitable therapeutic methods, such as the design of substrates, encapsulation, gel, etc. Moreover, the studies of tissue engineering demonstrate that a combination of modern and traditional medicine (i.e., use of biomaterials along with herbal bioactive compounds) can provide new developments in the fields of regenerative tissue techniques and stem cell differentiation into targeted tissue cells. This not only can decrease the therapeutic economic burden and healthcare problems but also develop new drugs or methods with easier availability and least/no side effect.

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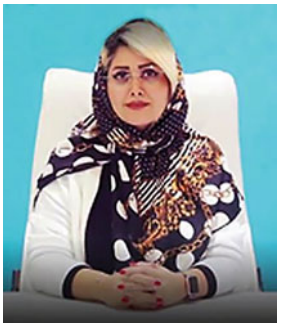

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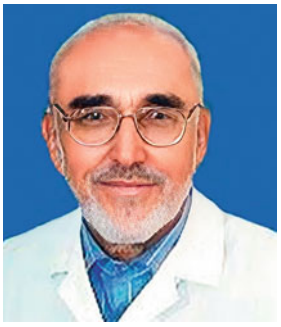

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