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An Overview of the Use of Medicinal Plants in Regenerative Dentistry

Sara Dhoum[1], Samir Ibenmoussa[2], Mustapha Sidqui[1]

[1]Faculty of Dental Medicine, Hassan II University, Casablanca, Morocco
[2]Faculty of Medicine and Pharmacology, Hassan II University, Casablanca, Morocco
Email: saradhoum@hotmail.com, m.sidqui@yahoo.fr

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Abstract

Aim: The oral cavity has the particularity to host multiple hard and soft tissues, in this paper, we will discuss the current therapies that lead to cell differentiation by regenerative therapies and the future alternatives proposed by medicinal plants and all the regenerative potential of these different tissues. **Material and Methods:** A detailed review of the literature through the various search engines: Scopus, PubMed, google scholar, Cochrane, etc., uses the selected keywords to explore the effect of the regenerative potential of several medicinal plants. **Results:** Through our research, we have proceeded to sort different medicinal plants, according to their repairing and regenerative potential on the different tissues of the oral cavity. **Conclusion:** Future studies are conceivable to explore the opportunities and potential provided by medicinal plants in the field of regenerative dentistry.

Keywords

Medicinal Plants, Medicinal Herbs, Tissue Regeneration, Enamel Remineralization, Dental Pulp, Periodontal Regeneration, Bone Regeneration, Wound Healing, Stem Cells Differentiation, Odontoblastic Differentiation, Oral Cavity, Herbal Extract, Oral Tissues

1. Introduction

As defined by Mason and Dunnill, the subject of regenerative medicine aims to replace and regenerate human cells, tissues or organs [1].

Herbs and plants have been used to cure many diseases since ancient times, and their medicinal and therapeutic importance has been proven in the prevention and treatment of many pathologies.

Inexpensive and without major side effects, several studies have shown that natural compounds, especially secondary metabolites isolated from plants, have many biological and medicinal activities such as antibacterial, antiviral, antifungal, anticancer, analgesic, anti-inflammatory, regenerative and antitumoral.

The role of medicinal plants in disease treatment has been the subject of many studies in odontology, especially for their antibacterial and anti-inflammatory potential, their regenerative potential needs to be explored.

2. Particularities of Oral Cavity

The human teeth are composed of organized, mineralized tissue layers of dentin, cementum and enamel. In native tooth architecture, an enamel-encased crown surrounds the internal pulp chamber and roots [2].

Enamel is derived from oral epithelium tissue, while dentin, pulp and periodontium derive from the neural crest.

In healthy tooth anatomy, the dentin-pulp complex lies below a continuous layer of ordered enamel, protecting the vessel and nerve rich pulp [2].

In the dentin layer, odontoblasts create and regulate tissue matrix components. Epithelial-mesenchymal interactions are essential for the transition of mesenchymal embryonic pulp cells to the pre-odontoblastic stage. Signaling molecules from the inner enamel epithelium encourage differentiation of peripheral dental papilla cells, odontoblast precursors, which eventually become secondary odontoblasts [3] [4] [5].

Human dental pulp stem cells (DPSCs) originate from migrating neural crest cells, are derived from the embryonic ectoderm layer and possess mesenchymal stem cell properties. This feature confers them vast differentiation potential, in addition to their ability to secrete trophic factors and their immunoregulatory properties. DPSCs can differentiate into odontoblasts, osteocytes/osteoblasts, adipocytes, chondrocytes, or neural cells [6] [7].

DPSCs can also regenerate dental tissue composed of vascular, connective, and neural tissues. During tooth development, primitive ectomesenchyme becomes enclosed within the prospective teeth to form the dental pulp, a rich source of stem cells. Odontogenesis (the process of tooth development) involves the cell matrix of types and specific cellular processes which result in the differentiation, growth, maturation and eruption of developing teeth in the mouth [5] [6].

2.1. Soft Tissues

Gingiva and oral mucosa: The gingiva is the oral mucosa that covers the alveolar bone and cervical part of the tooth. It forms a physical barrier against oral bacteria and provides mechanical protection to the underlying tissues. Given its protective nature, the gingiva is a key for wound healing since is constantly exposed to trauma or bacterial products that lead to inflammatory and infectious events.

The gingiva is composed of a layer of epithelial tissue (divided into three functional compartments; gingival, sulcular, and junctional epithelium) and connective tissue: superficial and deep compartments [8].

The cellular processes of oral soft tissue are similar to the healing of skin wounds. Nevertheless, it is commonly stated that oral wounds heal better and with less scar formation than dermal wounds.

The normal response to injury involves three overlapping stages: Inflammation, new tissue formation and remodeling.

After tissue injury, distinct biological pathways immediately become activated and are synchronized to prevent infection and restore the damaged tissues.

The cells recruited during wound healing include components of the immune system, endothelial cells, keratinocytes, and fibroblasts [8] [9].

Pulp tissue: The dental pulp is a soft ecto-mesenchymal tissue surrounded by dentin and it is highly vascularized and highly innerved.

The pulp is composed of 75% water, 25% organic material, heterogeneous population of cells: fibroblastic cells, stem cells, capillary blood vessels, peripheral nerves, lymphatic elements, as well as cells from the immune system and an extracellular matrix: fibers, and fundamental substance, concentration of Collagen fibers to support blood vessels and nerves [10].

The pulp tissue is unique given its volume and its confinement within the dentin. It has low blood supply, except in the apical foramen, and lacks collateral blood supply.

Dental pulp is an important component of teeth and plays important roles: Formation of the dentin (odontoblasts), Nutrition: the pulp is responsible for nourishing the dentine through the odontoblastic extensions and metabolites coming from the pulp vascular system, the essential function of the pulp and it is maintained as long as the pulp is vital, Sensitivity: in the face of stimuli, aggression or pain and Defense/repair: ability to form dentin face to an aggression.

There is a strong belief that the dental pulp offers a potentially viable source of MSCs for regenerative medicine-based applications. Such principles are based on their availability and ease of isolation [4] [10].

2.2. Hard Tissues

Enamel: The main challenge in the regeneration of enamel is its acellular nature.

Dental enamel is a calcified tissue that forms the outer protective shield of the anatomical crown of a tooth, it's produced by ameloblasts. These enamel forming cells go through apoptosis when amelogenesis is finalized and they are lost when the tooth erupts. The *in vitro* culture of ameloblasts is yet unestablished in a scale needed for appropriate tissue regeneration [3] [11].

Mature enamel is mainly composed of Inorganic material 96% hydroxyapatite crystals (HA), 3% of water and 1% proteins: amelogenin, tuftelin … [3].

Actual research follows a biomimetic approach by using amelogenin, peptide fragments of amelogenin, or various synthetic peptides as a template matrix to mimic the environment for the deposition of enamel [3].

Dentin: It constitutes the most mineralized part of the tooth, it is covered and protected by the enamel in the dental crown and by the cement in the radicular part.

The responsible cells in the dentin formation are the odontoblasts, these cells are long-living post-mitotic cells and they are not replaced throughout the whole life of the tooth.

Its inorganic matrix is composed of HA crystals while its organic matrix is mainly composed of a collagenous structural component, formed of collagen type I (about 90%), collagen type III and V, and a small quantity of organic matrix molecules (proteoglycans of chondroitin sulfate (biglycan and decorin), heparan sulfate (perlecan and entactin), keratan and dermatan sulfate. It has also non-collagen proteins that participate in the mineralization process [12].

These proteins are members of the SIBLING family (small integrin-binding ligand N-linked glycoprotein) and include the sialophosphoprotein (DSPP), Dentin Matrix Protein 1 (DMP-1), osteopontin (OPN), Matrix Extracellular Phosphoglycoprotein (MEPE), and Integrin-Binding Sialoprotein (IBSP). DSPP and DMP-1 are considered specific markers for these cells [13].

Dental Cementum: It is a hard and avascular connective tissue located on the dental root; the main function of cementum is to connect the fibers of the PDL that emerge from the alveolar bone to the root. It is involved in the development, repair, and regeneration of periodontal support structures [14] [15].

We can distinguish two types of cementum: Cellular and acellular.

Their composition is distributed:

- 50% of mineral: Hydroxyapatite $Ca_{10}(PO_4)_6(HO)_2$;
- 50% of organic matrix: type I collagen 90%, cement-related collagen protein includes type III collagen, Cementum Attachment Protein (HACD1/CAP), Cementum protein 1 (CEMP-1);
- Cells: predominance of fibroblasts, the epithelial cell rests of Malassez, monocytes, macrophages, cementoblasts, osteoblasts, myofibroblasts, nerve cells, epithelial cells, endothelial cells and a low level of stem cells [14] [15].

Alveolar Bone: It's the portion of the bone that surrounds the teeth and represents the primary support structure for the teeth.

Two of the main causes of alveolar bone loss are periodontitis and trauma.

The procedures for the regeneration of the alveolar bone are mainly based on the use of natural or synthetic scaffolds and bioactive agents (**Figure 1**).

However, there are some inherent limitations associated with biomaterials and traditional techniques [16] [17].

Composition:

- Inorganic matrix 67%.: calcium, phosphate and calcium hydroxyapatite crystals.
- Organic matrix 33%: collagen and non-collagenous materials.
- Cells: osteoblasts, osteocytes and osteoclasts.

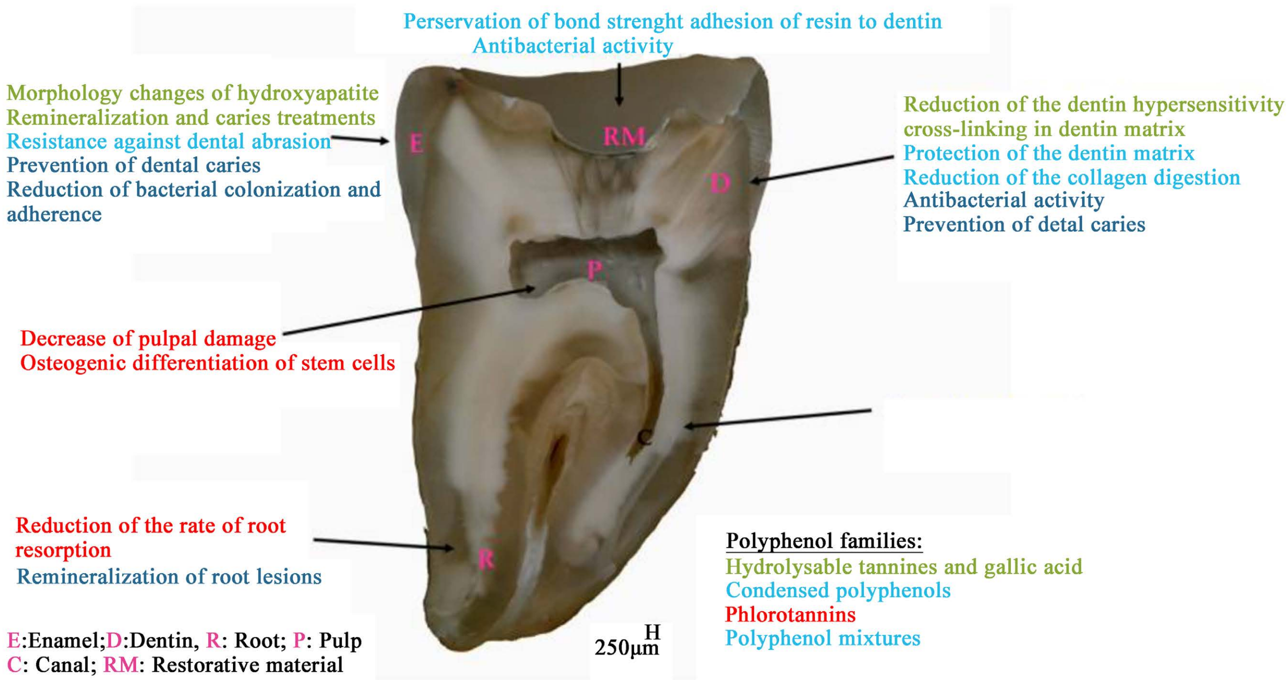

Figure 1. Overview of the applications of polyphenols in dental field [19].

3. Use of Medicinal Plants in the Oral Cavity

Regenerative, antibacterial, antiviral, anti-inflammatory and analgesic effects of medicinal plants on oral tissues have been proved by several studies, numerous active principals have been studied and have shown interesting results in terms of accelerating the healing process [18] [19].

3.1. Action on Enamel

Enamel remineralization includes the incorporation of minerals such as carbonate, magnesium, sodium, fluoride, calcium and phosphate, among others. Generally, a direct association is observed between these ions in saliva and reduced tooth enamel demineralization (dental caries) [20] [21].

The effect of natural compounds on enamel remineralization has already been proved and clinically used with the Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) complex [22].

The anticariogenic effect of several medicinal plants has been subject of many studies (**Table 1**): Galla chinesis that contains metabolites such as tannins and flavonoids, promoting the mineral apposition in cavity lesions [23] [24] [25] [26], Carboxymethyl chitosan, Ilex guayusa have being studied for their anticariogenic effect and enhancing enamel remineralization [27] [28] [29] [30], Piper marginatum have been studied for its antifungal properties but has shown cytotoxicity in an invivo study on rats [27] [29] [31] [32] [33], Prilla frutescens seed shown an antibacterial effect and preventing dental caries [26] [34], and Coconut fruit extracts: virgin coconut oil (VCO), coconut milk (CM), and coconut water (CW) hold properties which enable them to prevent dental caries. Previous

Table 1. Summary based on the literature review of the medicinal plants studied with a potential of enamel reparation, remineralization and protection.

Medicinal plant	Effect	Author	Year	Ref
Galla chinensis	**Anticariogenic**	Zhang J	2022	[24]
	contains metabolites, such as tannins and flavonoids	Kumar	2022	[25]
	Promotes mineral apposition in cavity lesions	Zhang J	2015	[26]
		Cheng,	2010	[23]
Carboxymethyl chitosan	**Anticariogenic** Some natural toothpastes use present in the exoskeleton of crustaceans	Cicciù, M	2019	[28]
Ilex guayusa	**Anticariogenic, enamel remineralization**	Gutiérrez,	2022	[29]
	Used by indigenous and rural communities for the treatment of oral cavity diseases	Bernal	2011	[30]
	Mouthwash, herbal tea and energizing drink, among others	Sequeda-Castañeda,	2016	[27]
	Phytochemically it contains caffeine, triterpenes, chlorogenic acids, tannins, and flavonoids			
Piper marginatum	**Antifungal**	Gutiérrez,	2022	[29]
	Commonly known as "tooth healer," its leaves topically applied against tooth cavities	Gonçalves	2019	[32]
	Phytochemical studies demonstrate the presence of steroids, alkaloids, flavonoids, phenolic compounds, phenylpropanoids and terpenoids, among others.	Sequeda-Castañeda	2016	[27]
	Cytotoxic *in vivo* study on rats	Brú & Guzman,	2016	[33]
		Reigada	2007	[31]
Perilla frutescens seed	**Prevents dental caries, antibacterial**	Zhang J,	2015	[26]
	↑ Remineralization of enamel caries lesions, volume & mineral density values,	Yamamoto H	2002	[34]
	↓ Severity of molar enamel caries			
	Contains various polyphenols such as luteolin, quercetin, gallic acid, and epigallocatechin gallate			
Coconut extracts	Coconut milk and coconut water are potentially capable for enamel remineralization.	Rahamat F	2019	[35] [36]

studies found that VCO exhibited anti-microbial properties while CM contained high content of calcium [35] [36].

3.2. Action on Dentin-Pulp Complex

Regenerative endodontic treatment is defined as the biological-based processes that enable replacement of damaged structures of the dentin-pulp complex (Murray *et al.* 2007) [37]. The main purpose behind the regenerative endodontic treatment is to regain normal physiological features such as innate immunity, tertiary dentinogenesis, sense of occlusal pressure and pain that the necrotic pulp does not aloud.

Three elements are necessary to achieve pulpal regeneration: dental stem cells, biomaterials, and growth factors [38] [39].

Over the past decade, interest in drugs derived from medicinal plants has markedly increased, the commun known treatments are based on synthetic bioactive materials such: Biodentin®, Mineral Trioxyd Aggregate (MTA), Calcium hydroxide based materials [38] [39].

Some of medicinal plants have been studied for their regenerative potential since 1982 by llewicz *et al* (39), several studies (**Table 2**) have been conducted to explore the action of Propolis (apis mellifera) and Aloe vera (acemannan) that proved their clinical efficiency to induce odontogenic differentiation equal to synthetic products currently used for the same purpose [40]-[60]. Pinus massoniana have been studied [40] for inducing odontogenic differentiation, also Astragalus membnaceus [41], curcuma longa [42] [43] [44], Camellia sinensis [45] and Cinnamomum verum [43] [45], Allium sativum have shown an acceleration on the healing process and antibacterial effects [46].

Cafeic acid combined to MTA have shown angiogenic properties and formation of hydroxyapatite, immunosuppressive and odontogenic properties [47] [48] [49], Proanthocyanidins induces odontogenic differentiation and increases the expression of biomineralization and odontogenic differentiation regulators: RUNX2, BMP2, OCN and DSPP [36] [46] [47] [48] [40] [50] [51] [52].

Schisandra chinensis is effective in anti-oxidative mechanisms in dental pulp cells [53] [54] [55] [56].

3.3. Action on Cementum and Periodontal Ligament

The process of periodontal tissue regeneration is initiated at the moment that the damage takes place by the production of growth factors and cytokines by the damaged and inflammatory cells.

New therapeutic approaches to periodontal regeneration using molecular approaches have emerged over the last twenty years:

- Growth factors,
- Platelet-derived growth factor,
- Insulin-like growth factors,
- Transforming growth factor-beta1,
- Basic fibroblast growth factor,
- Dexamethasone Bone morphogenetic proteins.

Medicinal plants offer a new field of exploration of their regenerative potential, but still more studies are needed to evaluate their efficiency in cementum regeneration.

Icariin [82] [83] [84] proved their action in regulation of osteoclast differentiation and enhancement of cementum repair, Acemannan induces an acceleration of the healing process in periodontal disease [85] [86] [87] [88] [89], Baicalin induce periodontal tissue regeneration [90], Salvadora persica (siwak/miswak) [91] and Rutin (buckwheat, japanese pagoda tree) [92] showed their interest in maintaining periodontal health.

3.4. Action on Alveolar Bone

Periodontitis is commonly characterized by the formation of intrabony defects.

Table 2. Summary based on the literature review of the medicinal plants studied with an action on dentin-pulp complex.

Medicinal plant	Effect	Author	Year	Ref
Aloe vera	Induce Odontogenic differentiation	Soudi A,	2021	[43]
Acemannan	Root formation in Vital Pulp Therapy	Vu TT	2020	[57]
	Dentin bridge formation in pulp capping	Songsiripradubboon S	2017	[58]
		Songsiripradubboon S	2016	[59]
		Sholehvar F,	2016	[60]
		Jittapiromsak N,	2010	[61]
Astragalus membranaceus Astragaloside IV	Differentiation effect in odontoblast-like MDPC-23 cells	Ding Q,	2019	[41]
	Odontogenic differentiation	Soudi A,	2021	[43]
Propolis	Anti-inflammatory	Mohanty S,	2020	[62]
	Antibacterial	Shi B	2020	[63]
	Dentinal de-sensibilization	Abdel Raheem IA,	2020	[64]
	Potentializes Bonding and sealing ability	Kim JH	2019	[65]
		El-Tayeb MM	2019	[66]
		Ahangari Z,	2018	[67]
		Abbasi AJ	2018	[68]
		Sabir A	2017	[69]
		Moradi S,	2015	[70]
		Ahangari	2012	[71]
		Sabir A	2005	[72]
		Al-shaher A	2004	[73]
		Bretz WA	1998	[74]
		Llewicz L	1986	[75]
		Llewicz L	1982	[76]
Curcuma longa	Anti-inflammatory	Soudi A	2021	[43]
C. longa gel	Antibacterial	Sinjari B	2019	[44]
Curcumin	Antitumor	Prabhakar AR	2019	[42]
	Enhancement of cells proliferation			
Adipose tissue	Enhancement in odontogenic differentiation	Martin Gonzalez *et al.*	2022	[77]
Leptin	Angiogenetic	Choi SH	2019	[78]
	Reparative dentin formation as a pulp capping agent			
Allium sativum	Antibacterial	Mohammad SG,	2015	[46]
GARLIC: Water extract/oil extract	Healing potential			
Caffeic acid	Angiogenic properties	Tu MG,	2020	[48]
caffeic acid/mineral trioxide aggregate CAMTA°	Hydro-apatite formation	Kuramoto	2019	[49]
	Odontogenic properties	Grga *et al*	2008	[47]
	Immunosuppressive properties			

Continued

Proanthocyanidins	Inhibiting demineralization of root dentin	Zhou	2020	[51]
	Induce odontogenic differentiation	Aydin B	2019	[52]
	Increase the expression of biomineralization and odontogenic differentiation regulators: RUNX2, BMP2, OCN and DSPP	Kulakowski D.	2017	[40]
		Chengfang	2016	[50]
Hinokitiol Chamaecyparis taiwanensis	Antimicrobial	Lin CP	2019	[79]
	Enhancement in cell viability of dpscs and odontogenic differentiation	Shieh TM	2017	[80]
		Huang MH,	2016	[81]
Camellia sinensis EGCG	Odontoblastic differentiation	Kwon YS,	2017	[45]
Cinnamomum verum Cinnamaldehyde	*In vitro*/Evaluating odontogenic gene expression in hdpcs after treatment with cinnamaldehyde: Promotion in differentiation and proliferation of stem cells/No effect on ALP activity	Soudi A,	2021	[43]
		Kwon YS,	2017	[45]
Schisandra chinensis	Anti-inflammatory, anti-oxidant and anti-cancer properties	Park	2013	[55]
		Kim	2010	[56]
		Park	2009	[53]

Multiple surgical approaches for treating these defects have shown effectiveness in improving clinical and radiographic parameters. Moreover, histologic evidence demonstrates the potential to achieve regeneration of the periodontal attachment: new bone, cementum, and periodontal ligament (PDL) using different therapeutic approaches [93] [94].

The implication of medicinal plants in bone regeneration has been the subject of many studies and experiment (**Table 3**).

Berberine and Icariin promote odontoblastic and odontogenic differentiation, they are both responsible of the inhibition of alveolar bone osteoporosis and promote periodontal bone regeneration [43] [82] [95]-[102], Drynaria iisos increases bone cell viability [103] [104], Rhizoma drynariae enhances the proliferation of hmscs [2] [103] [104], Foeniculum vulgare promotes differentiation of hMSCs into osteoblasts [104], Ferula gummosa has antibacterial effects and induces proliferation of hMSCs into osteocytes [105], Resveratrol induces proliferation and differentiation of articular cartilage, enhances bone healing by its anti-inflammatory properties, responsible for the inhibition of boneloss and increases the blood supply [104] [106]-[111]. Fructus ligustri lucidi increases osteogenesis stimulating genes [112] [113].

Osthole (cnidium monnieri/angelica pubescens) has osteoprotective activity, osteogenic activity, and induces bone formation [114] [115] [116] [117] [118], China herba epimedii improves osteogenesis and inhibition of osteoclasts in hMSCs [119], Naringin (rhizoma drynariae) has been the subject of several studies that proved its effect on the proliferation and osteogenic differentiation of

Table 3. Summary based on the literature review of the medicinal plants studied with an action on cementum, periodontal ligament and alveolar bone.

Medicinal plant	Effect	Author	Year	Ref
Epimedium Icariin	Regulation of osteoclast differentiation and enhancement of cementum repair, Enhancement in osteogenic differentiation/No effect on cell proliferation, Osteogenic activity in BMSCs and increase in bone volume and density in the defect area, Improvement in bone healing process, Enhancement in angiogenesis and mechanical properties of regenerative bone, Inhibition of alveolar bone osteoporosis, Promotion of periodontal bone regeneration: periodontal structure regeneration Enhancement in cellular attachment, proliferation and osteogenic activity in pre-osteoblastic cells	Soudi. A Xu H Xie Y Zhang X Gong M Lai Y Li M Yin L Wu Y, Wang.F	2021 2020 2019 2018 2018 2018 2017 2017 2015 2012	[43] [160] [161] [100] [162] [163] [164] [165] [166] [167]
Aloe vera Acemannan	Enhancement in rapid early healing process in bone defects Enhancement of bone volume, surface and mineral density Enhancement in osteogenic markers genes expression and periodontal regeneration Enhancement in cellular proliferation, differentiation and matrix formation	Le Van C Godoy DJD Jansisyanont P Escobedo-Lozano AY Chantarawaratit P Boonyagul S	2020 2018 2016 2014 2014 2014	[86] [87] [88] [89] [85] [168]
Salvadora persica (siwak/miswak)	Anticariogenic effects, Treatment or prevention of periodontal diseases Anti-inflammatory and anti-oxidant activity Antibacterial effect: equal to or better than antibiotics widely used during periodontal therapy Activation of stem cell proliferation and cell viability support	Aljarbou F Mekhemar M Farag M Malik A, Al Bayaty FH Akhtar J	2022 2021 2021 2021 2018 2011	[169] [91] [170] [171] [172] [173]
Rutin (buckwheat, japanese pagoda tree)	Osteogenic differentiation of periodontal ligament stem cells	Zhao B	2020 2020 2020 2019	[92] [174] [175] [176]
Berberine/ Berberis aristata	Odontoblastic differentiation and mineralization activity; antibacterial activity Enhances Runx2, osteocalcin (OCN), and osteopontin (OPN) expression and activation of the canonical Wnt/β-catenin pathway	Xin BC, Wu A, K. Tao, Xie Q,	2020 2019 2016 2012	[96] [177] [95] [97]
Drynaria fortunei	Increased bone cell viability, intracellular total protein as well as alkaline and acid phosphates.	Alaribe F N, Udalamaththa DL, Zhang P	2019 2016 2009	[104] [103] [120]

Continued

Rhizoma drynariae	Enhanced the proliferation of BM-derived hMSCs by regulating β-catenin and AMP-activated protein kinase (AMPK)	Alaribe F N,	2019	[104]
		Udalamaththa DL,	2016	[103]
		Zhang P,	2009	[120]
Foeniculum vulgare	Promotes the proliferation and differentiation of BM-derived hMSC into osteoblasts	Alaribe F N,	2019	[104]
Ferula gummosa	Antibacterial effect	Abbaszadegan A	2015	[105]
	Enhance proliferation and differentiation of BM-derived hMSCs into osteocytes.			
Resveratrol	Proliferation and differentiation roles of articular cartilage	Alaribe F N,	2019	[104]
	High regulation of collagen type II has been observed chondrocytes treated with resveratrol	Wang CC,	2018	[178]
		Ozcan-Kucuk A	2018	[106]
	bone regenerative and anti-osteoporotic efficacy: Enhancement of entochondrostosis and osteogenic markers expression	Ikeda E,	2018	[111]
		Mmadira MG,	2016	[108]
	Improvement in bone regeneration	Zhai JL,	2016	[179]
	bone-healing properties in periodontitis: Significant anti-inflammatory property and inhibition of bone loss	Rutledge KE,	2016	[180]
		Ornstrup MJ,	2016	[181]
	Significant increase in blood supply in necrotic area: Increase in expression of angiogenic factor	Wang W,	2014	[182]
		Kamath MS,	2014	[183]
	Stimulation of osteoblastic differentiation in presence of inflammation	Casarin RC,	2014	[107]
	Induces higher expression of BMPs and improves bone regeneration	Lee AM,	2014	[184]
RUTTIN/ MORINDA citrifolia extract	Induction of osteogenic differentiation in human periodontal ligament cells	Zhao B,	2020	[92]
		Min SK,	2020	[174]
	Regulation of bone formation, improvement of chondrocytes cellularity	Wan Osman WN,	2020	[175]
	Induction of cellular proliferation and matrix formation	Zhao B,	2020	[185]
	Enhancement of matrix mineralization	Gu H,	2019	[186]
	Improvement in bone mechanical and physical properties/ Enhancement in osteogenic biomarkers expression	Shalan NA,	2019	[176]
		Hussain S	2018	[187]
	Increases bone density		2017	[188]
			2016	[189]
Fructus Ligustri Lucidi	Increases ALP activity,	Ko. C	2010	[113]
	Increases the expression of osteogenesis-stimulating genes, osteoprotegerin	Li. G	2009	[112]
Cnidium monnieri/ Angelica pubescens Osthole	Induction of osteoclastogenesis: Enhancement in osteogenic activity	Zhao D,	2018	[190]
	Enhancement of bone healing and formation	Zhang ZR,	2017	[115]
	Enhancement of bone strength and fracture healing by through BMP2 signaling pathway	Sun J,	2017	[116]
		Wang P,	2017	[117]
	Enhancement in bone formation rate, ALP activity, OCN and BMP2 expression	Zhang Z,	2016	[118]
		Gao LN,	2013	[114]
China Herba epimedii	Increases ALP activity and enhances mRNA expression of BMP-2, Runx2 (runt-related transcription factor 2), and OPN (osteopontin)	Zhang JF	2009	[119]

Continued

Rhizoma drynariae	Increases expression of ALP, collagen I, osteopontin, and osteocalcin genes	Sharma	2021	[121]
	Increases alkaline phosphatase activity	Zhang KP	2009	[120]
Ginkgo biloba	Increases transcriptional levels of bone morphogenetic protein 4 (BMP4), runt-related transcription factor 2 (Runx2), β-catenin, and cyclin D1	Gu. Q,	2015	[122]
	Enhances Runx2, osteocalcin (OCN), and osteopontin (OPN) expression and activation of the canonical Wnt/β-catenin pathway	K. Tao,	2016	[95]
Salvia miltiorrhiza	Increases expression of alkaline phosphatase activity, osteopontin, Runx2, and osterix and promotes osteogenesis	Bian Y,	2020	[124]
Salvia miltiorrhiza extract	Enhancement of osteogenic differentiation markers expression	Wu Y,	2019	[125]
TANSHINOL/ Salvionic acid B	Angiogenic and osteogenic property *in vitro* & *in vivo*	Ji C	2019	[126]
	Improvement in bone healing process	Yang YJ,	2018	[127]
	Bone-protective ability	Lee DH,	2018	[128]
	Prevention of glucocorticoid-related loss of bone mineral density and enhancement of bone quality	Han J,	2017	[129]
	Anti-osteoporotic capability by minimizing the decrease of bone formation	Chen G,	2017	[130]
	Promotion of osteogenesis by hMSCs without reported cytotoxicity	Yang Y,	2016	[131]
	Enhancement in osteogenic markers expression	Xu D,	2014	[132]
		Cui L,	2012	[133]
		Chin A,	2011	[123]
Epimedium pubescens (TCM)	Increases activity of ALP and Osteogenic BMP-2	Wang Q,	2013	[134]
Ocimum basilicum	increase the level of Osteonectin and osteocalcin	Mendi AH.	2017	[135]
licorice root	Osteocalcin, Runx2, BMP2, and ALP gene expression upregulate	Azizsoltani A.	2018	[136]
Foeniculum vulgare	17β-Estradiol and ALP activity increase	Mahmoudi Z.	2013	[137]
Thymbra spicata var. intricata	Osteocalcin (OCN) (late osteogenic marker) level increases	Mendi A.	2017	[138]
Cissus quadrangularis (Linn.)	Increases ALP activity	Potu BK	2009	[139]
Propolis	Induction of bone formation	Meimandi-Parizi,	2018	[141]
	Activation and differentiation of osteoclasts	Somsanith N,	2018	[142]
	Enhancement in osteoblastic activity	Zohery AA,	2018	[143]
	Increase cellular proliferation and differentiation	Altan BA,	2013	[144]
	Increased bone mineral density	Yanagita M	2011	[145]
	Enhancement in bone production and hyaline cartilage in the defect area	Al-Hariri M.	2011	[140]
	Osteoblastic activity after systemic administration of propolis			
	Enhancement in calcium and magnesium bone deposition after systematic administration			
	Significant anti-inflammatory properties			

Continued

Camellia sinensis	Significant reduction in premature senescence after Local EGCG and systemic senolytic administration in bone defects	Chu C,	2019	[147]
	Enhancement in osteogenesis by periodontal ligament cells	Xie Y,	2019	[161]
	Enhancement in anti-inflammatory and bone healing activity	Soares IMV,	2019	[146]
	Enhancement in healing process, cell proliferation and attachment	Honda Y,	2018	[191]
	Inhibition of osteoblast migration	Kawabata T,	2018	[192]
	Diminution of osteoclastic activity through its anti-oxidant property	Katsumata Y,	2018	[193]
	Improvement in healing process	Kuroyanagi G,	2017	[194]
	Increases osteogenic markers, proliferation and mineralization	Hong JY,	2015	[195]
	Increases cell proliferation	Kaida K,	2015	[196]
	Anti-oxidant properties thus increase periosteal cell viability for a short-term period	Mah YJ,	2014	[197]
	Maximum bone regeneration in combination of tricalcium phosphate particles	Kamiya M,	2012	[198]
Curcuma longa/ Curcumin	Enhancement in osteoblastic cell viability and proliferation	Sarkar N,	2019	[149]
	Mineralized bone formation increased	Bose S,	2018	[150]
	Enhancement of osteoblastic cell viability	Li Y,	2018	[151]
	Improvement in cell migration and differentiation	Jain S,	2016	[148]
	Improvement in bone formation			
	Enhancement in ALP expression and mineral deposition			
Coffea arabica	Significant anti-bacterial property against K. pneumonia and S. aureus	Palaniraj S,	2019	[153]
Chlorogenic acid	Enhancement of chondrogenesis, cartilage matrix synthesis and angiogenesis	Cheng X,	2018	[154]
		Fujita K,	2017	[155]
	Enhancement in levels of bone turnover markers and cellular osteogenic differentiation	Zhou RP,	2016	[152]
Coconut oil	periodontal tissue regeneration via expressions of tnf-α and tgf-β1	Thahir	2022	[159]

hMSCc [120] [121], Ginkgo biloba promotes osteogenesis [122], Tanshinol and salvionic acid b (salvia miltiorrhiza) promote osteogenesis of hMSCs and periodontal ligament cells, angiogenesis, inhibition of adipogenesis [123]-[133].

Epimedium pubescens has osteogenic activity [134], Ocimum basilicum increases osteonectin and osteocalcin levels [135], Glycyrrhiza glabra (licorice root) enhances proliferation and osteogenic differentiation [136].

Foeniculum vulgare extract has effect on osteogenesis in hMSCs [137], Thymbra spicata varintricata and Cissus quadrangularis (linn) both induce mesenchymal stem cell proliferation and osteogenic differentiation [138] [139]. Propolis proved its effect in improving the bone healing [140]-[145], Camellia sinensis and acemannan (aloe vera) induce osteogenic activity and cellular proliferation and differentiation, and periodontal regeneration [85] [86] [87] [88] [89] [94] [146] [147].

Curcuma longa (curcumin) enhances cell's proliferation, viability and bone formation [148] [149] [150] [151], Coffea arabica through chlorogenic acid induces osteogenic differentiation [152] [153] [154] [155], Kanroin ganluyin reduces osteoclast differentiation *in vitro* and prevents alveolar bone resorption [156], Nicotiana benthamiana induces osteogenic differentiation [157] [158] and Coconut oil induces periodontal tissue regeneration via expressions of tnf-α and tgf-β1 [159].

3.5. Action on Oral Mucosa (Wound Healing)

The wound healing process is distinguished by four phases, which are respectively, hemostasis, inflammation, proliferation, and remodeling. The physiology of wound healing is a complex biological and molecular process of recovering the normal structure and functions of injured tissues. This process includes several phases, such as inflammation which consists of hemostasis and inflammation of the tissue, then the proliferation, where the angiogenesis and the construction of an extracellular matrix are the main steps with the intervention of several cellular mediators. Finally, the wound closed, and the healthy tissue recovered during the remodeling phase [199] [200] [201].

Findings in literature proved that medicinal plants are widely used in the treatment of wounds (**Table 4**).

Rosmarinus officinalis has antimicrobial action, effective against gingivitis and periodontitis, accelerate the healing process. [202] [203] [204], Moringa extract, is antitumoral, stimulation of hMSCs proliferation [204]-[212], Nigella sativa (black seed or black cumin) based on the systematic review conducted by Nordin 2019 [213] balance between wound healing and tissue fibrosis depending on the state of inflammation, several studies had proven its effects in accelerating the healing process [214]-[219]. Curcumin, hamamelis virginiana, seaweed extract, thyme oil (thymus vulgaris), thymol oil (ac: 2-isopropyl-5-methyl phenol), macrotyloma uniflorum, triphala (catechin), tecomella undulate, clover honey, centella asiatica, myrica rubra all these medicinal plants are responsible for providing bioactive components that would induce tissue regeneration in a review conducted by Das *et al.* (2016) [220], Camellia sinensis was evaluated for its anti-inflammatory effects [221] [222] [223] [224] [225], Ziziphus mauritiana (bidara leaf) induce gingival wound healing [226] [227]. Achillea millefolium has effects on arachidonic acid metabolism and has anti-inflammatory and healing properties [228]-[234]. Malva sylvestris promotes granulation tissue formation, increases collagen synthesis and reduces fibrosis, reducing healing time and has anti-inflammatory effects in burn wounds [229] [232] [234] [235], a clinical trial was conducted to establish its pharmacological potential in the reduction of the plaque control record and gingival index [236].

Salvia officinalis and Casearia sylvestris, they both have angiogenesis properties accelerate healing process [229] [237] [238] [239], Propolis increases migration and proliferation of fibroblasts, anti-inflammatory & anti-microbial actions [63] [68] [70] [240]-[249], Aloe vera, increases type III collagen synthesis, induces the synthesis of hyaluronic acid. Induces granulation tissue formation in the remodeling phase increases wound contraction and increases macrophage

Table 4. Summary based on the literature review of the medicinal plants studied with an action on wound healing.

Medicinal plant	Effect	Author	Year	Ref
Rosmarinus officinalis	Antibacterial properties	Toma AI	2021	[204]
		De Macedo ML	2020	[203]
		Valones MA,	2016	[202]
Moringa	Stimulates cells proliferation	Al Ghanayem A	2022	[206]
	Effect on cancer cell lines: antitumor and hepatoptotective effects.	Shafie Nm	2022	[207]
		Shang A	2021	[208]
		Toma Ai	2021	[204]
		Ali A	2020	[209]
		Fayemi Oe,	2018	[210]
		Fernandes Ee,	2016	[211]
		Eyarefe Od	2015	[271]
		Amali Am	2013	[212]
		Rathi Bs	2006	[205]
Nigella sativa/	Promotion of wound healing,	Sallehuddin N	2020	[215]
Black seed/	attenuate tissue inflammation,	Nordin A,	2019	[213]
Black cumin	Fibrosis prevention.	Nourbar E	2019	[216]
		Sari Y	2018	[217]
		Javadi Smr	2018	[218]
		Han Mc	2017	[219]
		Ab Rahman R	2014	[214]
Seaweed extract Hamamelis virginiana Thymus vulgaris Thymol oil Macrotyloma uniflorum Curcumin Triphala (AC: catechin) Tecomella undulate Clover honey Centella asiatica Indigofera aspalathoides, Azadirachta indica, Memecylon edule Myristica andamanica	Wounds, burns, The bioactive components of medicinal plants and supporting biopolymeric materials have been widely exploited for wound healing applications, owing to the multifaceted challenges associated with providing support for bioactive components that would actually induce tissue regeneration.	Das U,	2016	[220]
P. ginseng G. glabra Z. jujuba/ P. ternata/ Z. officinale/ Scutellaria/ Coptis	Induction of *in vitro* and *in vivo* wound healing	Miyano K,	2020	[272]
Schisandtrin chinensis	Evaluation of reactive oxidative stress and nitric oxide production in dental pulp cells	Kim JS,	2018	[273]

Continued

Camellia sinensis	Anti-inflammatory properties in oral epithelium	Tafazoli A	2020	[222]
		Hashemipour AM	2017	[223]
		Zaheer N,	2017	[224]
		Hajiaghaalipour	2013	[225]
		Goenka P	2013	[221]
Ziziphus Mauritiana	Enhancement of wound healing	Noor A	2022	[227]
Bidara Leaf	Anti-bacterial activity	Maruf MT,	2021	[226]
Achillea millefolium	Anti-inflammatory and healing properties: effects on the arachidonic acid metabolism.	Medell´ın-Luna M F,	2019	[229]
		Hajhashemi M,	2018	[230]
		Dorjsembe B,	2017	[231]
		Nasiri E,	2015	[232]
		Akkol EK,	2011	[233]
		Pirbalouti AG,	2010	[234]
		Benedek B,	2007	[228]
Malva sylvestris	Promotes granulation tissue formation,	Aravena P	2018	[236]
	increases collagen synthesis.	Medell´ın-Luna M F	2015	[229]
	Reduces fibrosis.	Nasiri E,	2015	[232]
	Reduces time to complete wound closure.	AFSHAR M	2015	[235]
	Anti-inflammatory effects in burn wounds	GHASEMI PIRBALOUTI A	2011	[234]
Salvia officinalis	Improves capillary permeability and angiogenesis	Medell´ın-Luna M F	2018	[229]
		Qnais EY,	2010	[238]
		de Mattos ES,	2007	[239]
Casearia sylvestris	Improves capillary permeability and angiogenesis	Medell´ın-Luna M F	2018	[229]
		Oberlies NH,	2002	[237]
Propolis	Increases migration and proliferation of fibroblasts	Marizela S	2022	[241]
	Anti-inflammatory activity reduces migration and synthesis of pro-inflammatory molecules.	Zulhendri F	2021	[242]
		Saeed Ma	2021	[243]
	Induces wound contraction and closure.	Shi B,	2019	[63]
	Improves granulation tissue formation	Afkhamizadeh M	2018	[244]
	Inhibits activity of metalloprotease 9.	Abbasi Aj	2018	[68]
	Potent antimicrobial activity.	Oryan A	2018	[245]
	Increases wound healing.	Pobiega K	2017	[246]
	Reduces wound area	Takzaree N,	2016	[247]
	The anti-inflammatory action of propolis mediated by mast cells was more effective than dexamethasone in the inflammatory phase of healing.	Jacob A,	2015	[248]
		Moradi S,	2015	[70]
		Jain S	2014	[249]
		Barroso, P.R	2012	[240]

Continued

Aloe vera	Increases type III collagen synthesis. Induces the synthesis of hyaluronic acid. Induces granulation tissue formation in the remodeling phase Increases wound contraction. Increases macrophage activation markers. Stimulates fibroblasts and collagen synthesis. Regulates the expression of MMP-3 and TIMP-2 in the granulation tissue.	Ali F Sánchez M Sari Y Jamil M Tanaka M, Hashemi SA Tabandeh MR, Budai Babaee N Davis RH	2021 [251] 2020 [252] 2018 [217] 2018 [253] 2015 [254] 2015 [255] 2014 [256] 2013 [257] 2012 [258] 1989 [250]
Scrophularia striata	Decreases the wound area and lymphocytes number, Enhanced the number of fibroblasts at the earlier stages Increased the number of fibrocytes at the later stages of wound healing. Alignment of the healing tissue, re-epithelilization and epithelial formation, Enhancement of the maturity of the collagen fibers and fibroblasts and large capillary-sized blood vessels	Chatzopoulos GS Kerdar T Haddadi R Ghashghaii A Tanideh N	2022 [260] 2019 [261] 2019 [262] 2017 [263] 2015 [259]
Alternanthera sessilis	Enhancement of cell migration	Muniandy K, Enechi OC Jalalpure SS	2018 [265] 2013 [266] 2008 [264]
Euphorbiaceae species	Acceleration of the wound healing process and wound contraction.	Ahmed S,	2016 [267]
Abelmoschus esculentus Okra	Increases angiogenesis during the wound healing process in oral cavity	Luthfi M,	2020 [269]
Amla/ Emblic myrobalan Bilberry fruit/Vaccinium myrtillus Hawthorn berry/Crateagus oxycanthus Liquorice root/Glycyrrhiza glabral Neem extract Mango leaf The miswak/Miswaak, siwak, sewak Sesame oil Yellow dock root, Alfalfa leaf, Cinnamon bark, Turmeric root.	Benefic effects on gingivitis Antibacterial effect Collagen stabilization	Singh A,	2011 [268]
Roots of Albizzia lebbeck	Antibacterial properties Enhancement of collagen synthesis Antioxidant activity. Acute oral toxicity	Joshi A,	2013 [270]

activation markers [217] [250]-[258], Scrophularia striata decreases the number of lymphocytes and enhanced the number of fibroblasts also the maturaty of collagen fibers and showed an additional angiogenic action [259] [260] [261] [262] [263]. Alternanthera sessilis has showed an effect on cell migration of human dermal fibroblasts and keratinocytes [264] [265] [266].

Euphorbiaceae species accelerates the rate of wound healing process and showed 100% wound contraction [267], Abelmoschus esculentus okra & Amla (emblic myrobalan) showed benefic effects on gingivitis, antibacterial effect and stabilizing collagen [268] [269].

Bilberry fruit (vaccinium myrtillus), Hawthorn berry (crateagus oxycanthus) and Liquorice root (glycyrrhiza glabral), Neem extract, Mango leaf, the Miswak (miswaak, siwak, sewak), Sesame oil, Yellow dock root, Alfalfa leaf, Cinnamon bark and Turmeric root increase the angiogenesis during the wound healing in post extraction sockets [268].

Roots of albizzia lebbeck have anti-bacterial properties which may be attributed to the enhanced collagen synthesis and a potential antioxidant activity but an evaluation for their toxicity is necessary [270].

4. Conclusion

The present review offers an in-depth analysis of the high potential of medicinal plants in promoting oral tissues regeneration and reparation although new pharmaceutical technology and pharmacological research should be performed in order to explore the potential for their active compounds, the appropriate doses and the delivery mode for the administration of the plants or their compounds.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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