

ALOE VERA IN DENTISTRY: CURRENT STATUS AND FUTURE PROSPECTS

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Abstract : This review declares the chemical composition, pharmacological actions, clinical applications, adverse reactions and future prospects of Aloe vera (AV) in the field of dentistry. Literature pertinent to Aloe vera in dental practice was explored in databases like PubMed, Scopus and Google Scholar. The relevant literature was reviewed and critically appraised in this review. Aloe vera is a miracle plant that has been applied as herbal therapy for thousands of years due to its multiple health benefits. In dental practice, AV has different applications and it attracts the attention of researchers due to its natural origin, low cytotoxicity, and various biological actions like anti-microbial, immunomodulatory, anti-inflammatory, antioxidant, wound healing, and antineoplastic actions. Therefore, it has been used for treatment of oral lesions, endodontic lesions, periodontal disease, oral wounds, and alveolar osteitis as well as in tissue engineering, reduction of plaque formation, decontamination of Gutta percha, around dental implants and others. AV has been used in treatment and prevention of several other oral and dental problems. Nevertheless, it has a lot to offer in the dental practice and future studies are recommended to maximize its beneficial role in the field of dentistry.

Keywords: Aloe vera, endodontic, medicinal plants, oral lesions, periodontal disease, tissue engineering.

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The authors declare no conflicts of interest.

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L'ALOE VERA EN DENTISTERIE: ÉTAT ACTUEL ET PERSPECTIVES FUTURES

Résumé : Cette revue de littérature déclare la composition chimique, les actions pharmacologiques, les applications cliniques, les effets indésirables et les perspectives d'avenir de l'Aloe vera (AV) dans le domaine de la dentisterie. La littérature impliquant l'Aloe vera dans la pratique dentaire a été explorée dans des bases de données comme PubMed, Scopus et Google Scholar. Cette littérature a été examinée et évaluée de manière critique dans cet article. L'Aloe vera est une plante miracle utilisée comme phytothérapie depuis des milliers d'années en raison de ses multiples bienfaits pour la santé. Dans la pratique dentaire, l'AV a différentes applications et attire l'attention des chercheurs en raison de son origine naturelle, de sa faible cytotoxicité et de diverses actions biologiques telles que les actions antimicrobiennes, immunomodulatrices, anti-inflammatoires, antioxydantes, cicatrisantes et antinéoplasiques. Par conséquent, l'AV a été utilisé pour le traitement des lésions buccales, des lésions endodontiques, des maladies parodontales, des plaies buccales et de l'ostéite alvéolaire ainsi que dans l'ingénierie tissulaire, la réduction de la formation de plaque, la décontamination de Gutta percha, autour des implants dentaires et autres. L'AV a été utilisé dans le traitement et la prévention de plusieurs autres problèmes bucco-dentaires. Néanmoins, il a beaucoup à offrir dans la pratique dentaire et des études futures sont recommandées pour maximiser son rôle bénéfique dans le domaine de la dentisterie.

Mots clés : Aloe vera, endodontie, plantes médicinales, lésions orales, maladies parodontales, création tissulaire.

Introduction

The use of medicinal plants has a long history in medical and dental practice worldwide. Various biological and bioactive characters of plants as well as their biocompatibility explain the people's growing interest in the use of herbal medications [1].

Aloe vera or *Aloe barbadensis*, as a medicinal plant, belongs to the family "*Asphodelaceae*" genus '*Aloe*'. It is one of the oldest medicinal plants due to its different biological characteristics and health benefits. The name AV derives from the Arabic word "alloeh" meaning "shining bitter substance", while "vera" in Latin means "true" [2].

Among more than 300 species of the aloe-plant, AV (*A. barbadensis*) species has excellent pharmacological actions and medicinal benefits. AV is grown in the Nile Basin countries, Near East, India United States, Mexico, Dutch Antilles as well as coastal regions of Venezuela [2, 3].

The AV plant (Fig. 1) has leaves made up of a hard rind as an outermost layer that synthesizes proteins and carbohydrates and has a protective action. The sap of AV presents below the hard rind, carries the materials up to the leaves and down to the roots and has high amount of anthraquinones [4]. Also the plant has a mucilage layer that is very rich in polysaccharides including the immunomodulator, acemannan and keeps the inner gel sterile. The gel or parenchyma of AV is the storage of all nutrients [1, 2, 5].

The AV plants are harvested from August until October and the medicinal part of it is the dried juice of leaves. The juice is dried by several techniques [1, 6].

Historically, ancient Chinese and Egyptians used AV for treatment of burns, wounds, and fever. Although AV has been considered a natural healer ever since it was discovered thousands of years, its use is mainly in the cosmetology and medication. Moreover, AV is especially attractive

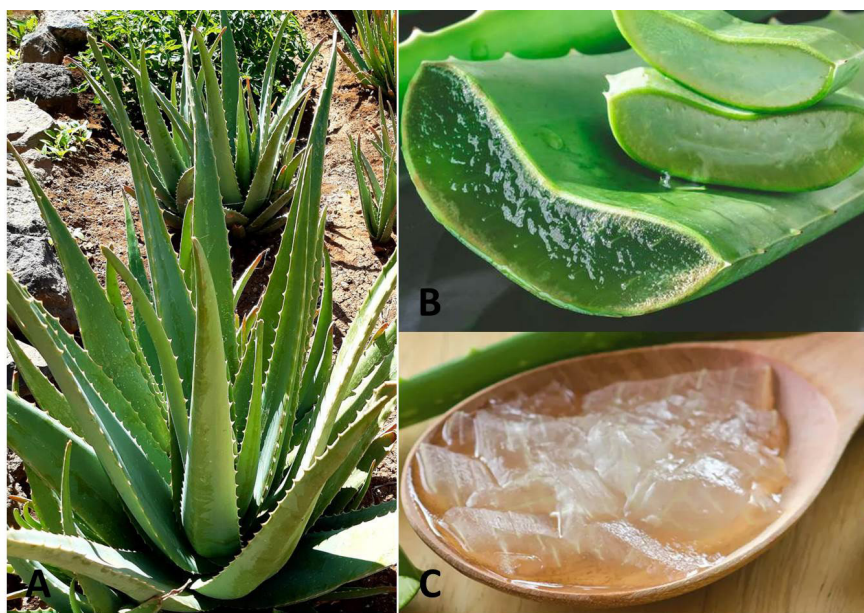


Fig. 1. Aloe vera plant (A), leaves (B) and gel (C).

as a tissue engineering agent due to its ability to enhance cell migration, proliferation, and growth [7].

This review describes the composition, pharmacological actions, clinical applications, adverse reactions, contraindications and future prospects of AV in the field of dentistry.

Composition of Aloe vera

The inner clear gel of AV consists of 99% of water, rich in glucomannans, amino acids, lipids, sterols, and vitamins. The middle layer contains anthraquinones and gly-

cosides. Active compounds almost 75 potentially active constituents have been reported in AV including; vitamins, essential amino acids, enzymes (like lipase and amylase), lignins, anthraquinone, minerals, sugars, salicylic acid, folic acid, sterols and saponins [2, 5]. On dry basis, AV gel has approximately 55% polysaccharides, 17% sugars, 16% minerals, 7% proteins, 4% lipids, and 1% phenolic compounds (Fig. 2) [8].

The main compounds present in AV are anthracene derivatives (particularly anthrone-10-C-glycosyls, including aloin A, aloin B, 7-hy-

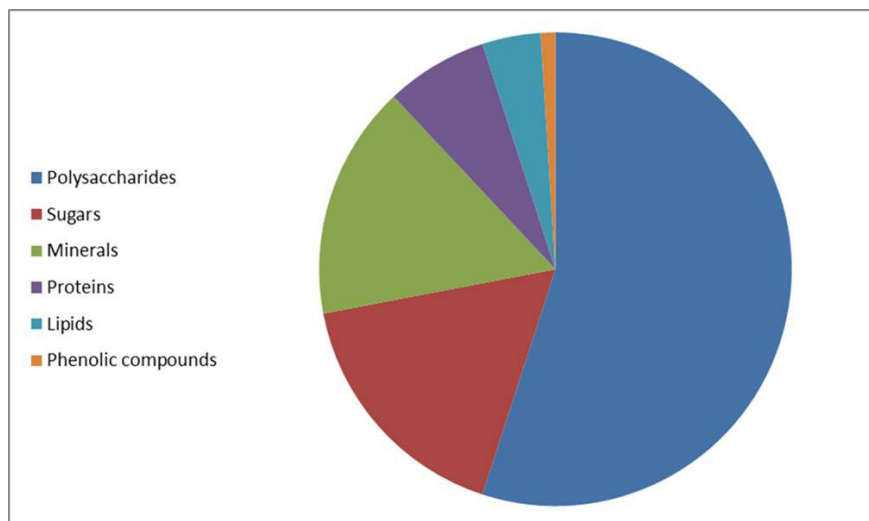


Fig. 2. Chemical composition of Aloe vera gel (On dry basis).

droxyaloin A and B, and 1,8-dihydroxy ions, including aloe-emodin, and 6'-cinnamic acid esters of these compounds), 2-alkylchromones (including aloe resins B, C and D) and flavonoids [9-12].

Aloe vera contains seven of the eight essential amino acids and 20 of the 22 human required amino acids. It is a good source of vitamins A (beta carotene), B1, B2, B3, B6, B12, C, E, folic acid and choline. Vitamins act as antioxidants which neutralize free radicals and have many known medicinal benefits [2, 9, 11]. Moreover, vitamins A, C and E have a positive effect on the immune system. Vitamin C enhances wound healing and synthesis of collagen which is essential for healthy skin, bone and joints [2].

The AV gel is also rich in minerals like calcium, magnesium, manganese, copper, sodium, potassium, zinc, chromium and iron which are essential for normal growth and health of bones and teeth as well as several health benefits [2, 10].

The mucilage layer of AV is rich in mucopolysaccharides sugars like glucomannans/ polymannose. Glucomannans enhances fibroblast growth factor and promotes the proliferation and activity of these cells that result in a greater number of collagen and elastic fibers. Moreover, Glucomannans is able to boosting the level of antibodies (immunomodulating properties), has antiviral action, reduces secondary infections, increases the activity of T-lymphocytes (up to 50%) and increases the activity of macrophages leading to enhancement of wound healing [2, 11, 13]. Also AV has monosaccharides, such as glucose and fructose which are essential for the body's health [9, 11].

The antiseptic agents like salicylic acid, lupeol, cinnamomic acid, sulfur and phenols have an inhibitory action on fungi, bacteria and viruses [11, 12, 14].

In addition, AV twelve anthraquinones, fatty acids, salicylic acid and hormones like auxins and gibberellins which have anti-inflamma-

tion action through stimulating immune system function and collagen growth, or by blocking the paths of irritants. Moreover, the AV sterols are important anti-inflammatory agents and lupeol has antiseptic and analgesic agent [2, 15].

Biological and pharmacological actions of Aloe vera

Aloe vera has various pharmacological effects like; laxative, antimicrobial, anti-inflammatory, antineoplastic, immunomodulatory and wound healer actions as shown in Figure (3) [13-17]. Therefore, it has been used as herbal therapy for constipation, stomach tumors, colic, skin diseases, amenorrhea, worm infestation, and infections techniques [1]. Due to its bioactive components, AV has become an attractive candidate in the field of biomaterials.

Different mechanisms have been proposed for the wound-healing effects of AV gel, which include keeping the wound moist, increasing epithelial cell migration, and rapid maturation of collagen, increasing angiogenesis and reduction in inflammation [17-20].

The anti-inflammatory action of AV gel is due to promotion of prostaglandin synthesis and increase of leukocytes infiltration. Both aqueous and chloroform extracts of AV were

found to inhibit the edema formation close to that of well-established anti-inflammatory agents [18, 21]. Novel anti-inflammatory compound called C-glucosyl chromone and brady kinase were isolated from AV gel extracts. The peptidase brady kinase can break down the bradykinin, an inflammatory substance that induces pain [22].

Regarding the antimicrobial effect of AV gel, Av has inhibitory action against both Gram-positive and Gram-negative bacteria; in particular *Streptococcus pyogenes* and *Streptococcus faecalis* [12]. Also, AV has a bactericidal effect against *Pseudomonas aeruginosa* and inhibits the growth of *Candida albicans* [23]. AV tooth gel is effective against *Streptococcus mutans*, *Candida albicans*, *Lactobacillus acidophilus*, *Streptococcus mitis*, *Enterococcus faecalis*, *Prevotella intermedia*, and *Peptostreptococcus anaerobius*. In addition, it has a superior antibacterial effect against *Streptococcus mitis* despite the absence of additional fluoride [24].

The antiviral effect of AV occurs due to indirect action via stimulation of the immune system, and direct action of the AV anthraquinones. AV has a virucidal activity against *Herpes simplex virus* type 1 and type 2, *Varicella zoster virus*, *Pseudorabies virus*, and *Influenza virus* [20].

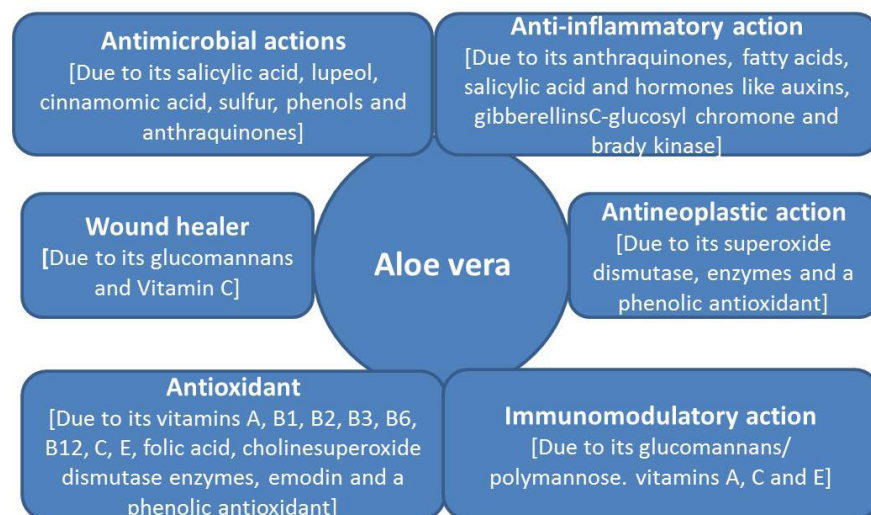


Fig. 3. Biological and pharmacological actions of Aloe vera in dentistry.

Aloe vera is considered a great immune stimulant contains 90% rhodium and iridium (trace minerals) in the Acemannan that dramatically increases the macrophages and T cells. Thus, immunomodulating effects occur via activation of macrophage cells to generate nitric oxide, secrete cytokines (e.g., tumor necrosis factor, interleukin-1, interleukin-6, and interferon- γ), and present cell surface markers [25]. Furthermore, AV gel has glutathione peroxidase activity, superoxide dismutase enzymes and a phenolic antioxidant, which may be responsible for its antioxidant effects [1, 18].

Aloe vera also contains vitamins A, C and E vitamins that get rid of the toxins and carcinogenic materials in the body from the pollution and poor-quality foods [26]. Plant extracts are gaining popularity as alternatives to the allopathic drugs in treatment of cancers. Quinones are plant-derived secondary metabolites that present some anti-proliferation and anti-metastasis effects in various cancer types both *in vitro* and *in vivo*. Aloe emodin, a plant-derived quinone, can inhibit cell proliferation and induce apoptosis in human liver cancer cell lines through p53- and p21-dependent pathway [12, 25].

In the market, AV is supplied in the forms of capsule (250 mg, 470 mg), cream, gel (99%, 72%) and soft gel (1000 mg) [1].

Clinical applications of Aloe vera in dentistry

In last decade, AV and AV-based biomaterials have attracted much attention as a herbal therapy for various oral diseases due to its attractive features, including different health benefits, availability, easily applicability, cost-effective, biodegradability, biocompatibility, hydrophilicity, and low toxicity effects [27, 28]. Aloe vera has been used in various oral indications such as lichen planus, aphthous stomatitis, oral submucous fibrosis, pulpotomy of primary teeth, prevention of

dry sockets, obturation of primary teeth, disinfection of irrigation units, bleeding and painful gums, disinfection of gutta percha cones, burning mouth syndrome, in radiated head and neck cancer patients, anti-plaque and for tissue engineering as shown in Figure (4) [29, 30].

Several derivative of AV have an effective treatment alternative in treating oral ulcers [37,38]. In addition, AV is a successful treatment for patients with burning mouth syndrome, chemical burns caused by accidents, and angular cheilitis due to its anti-inflammatory, antimicro-

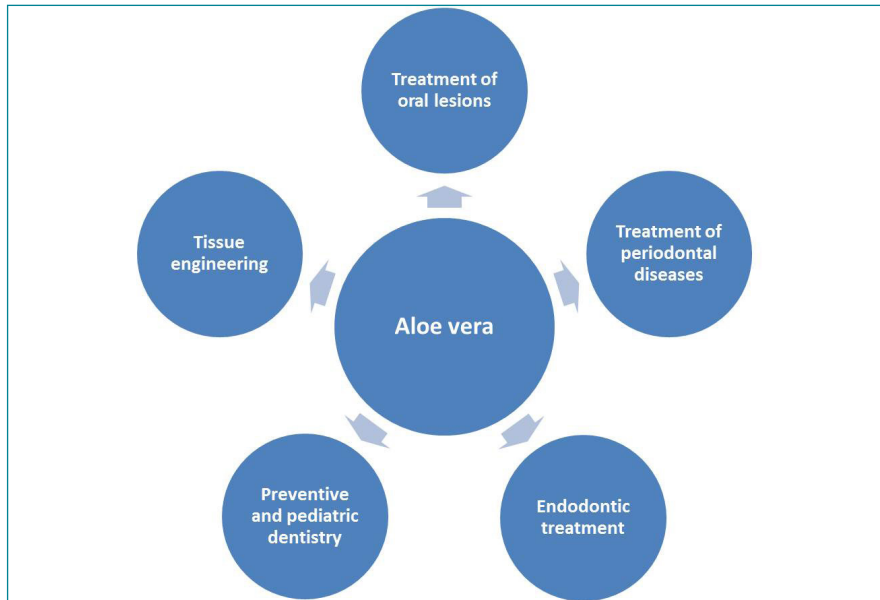


Fig. 4. Clinical applications of Aloe vera in dentistry

Treatment of oral lesions

Topical application of AV provides pain relief, improves the oral lesions and the quality of life of patients with oral lichen planus [31]. Steroids have remained the mainstay treatment in case of lichen planus, however, long term steroids therapy leads to multiple systemic complications which provides AV an added value due its low cytotoxicity and lesser side effects [12, 32].

In Aphthous Stomatitis, AV oral gel is not only effective in decreasing patient's pain score and wound size but also decreases the aphthous wound healing period. The new formulated Aloe and Myrrh-based gels proved to be effective in topical management of minor recurrent aphthous stomatitis [33, 34]. Moreover, Acemannan has been used for the treatment of oral aphthous ulceration in patients who wish to avoid the use of steroid medication [35, 36].

bial properties as well as enhancement of wound healing [39, 40].

Regarding oral submucous fibrosis (OSMF), AV gel is effective as an adjuvant in its treatment [41]. When compared with antioxidant (lycopene) better improvement in mouth opening and reduction of burning symptoms were recorded [42].

Acemannan hydrogel obtained from AV leaf plays a significant role in oral wound healing through induction of cell proliferation (gingival fibroblasts), and stimulation of keratinocyte growth factor 1 (KGF-1), vascular endothelial growth factor (VEGF) and type 1 collagen expressions [36].

Oral AV mouthwash prevents the radiation-induced oral mucositis via its wound healing and anti-inflammatory actions and reduces oral candidiasis of patients undergoing head and neck radiotherapy by its antimicrobial, antioxidant and immunomodulatory properties [43, 44].

Treatment of periodontal diseases

In periodontology, the clinical applications of AV can be attributed to its anti-inflammatory, antimicrobial and wound healing properties. The improvement in gingival index is attributed to the presence of sterols as anti-inflammatory agents and lupeol as an antiseptic analgesic [4]. Therefore, subgingival administration of AV gel improves the periodontal and gingival conditions [27]. Recently, topical application of AV within a periodontal pocket as an adjunct to nonsurgical scaling and root planning is effective therapy for periodontal disease [45, 46].

Several recent clinical studies recorded the beneficial role of AV gel as an alternative adjunctive therapy for periodontitis. Local subgingival delivery of AV decreased the plaque index, probing depths, and improved rate of attachment due to the antimicrobial, anti-inflammatory and antioxidant properties of AV [45-48].

Acemannan stimulates both soft and hard tissue healing and is a bioactive molecule and scaffold for periodontal tissue regeneration. Therefore, application of AV gel is done directly to the sites of periodontal surgeries along with periodontal dressing or to the gum tissues [18]. Moreover, Acemannan significantly increased alkaline phosphatase activity, bone marrow stromal cell proliferation, bone sialoprotein and expression and mineralization, and consequently induced higher bone mineral density and faster bone healing in both *in vitro* and *in vivo* studies [49].

Plaque-induced gingivitis was treated successfully with 10 ml of AV mouthwash twice daily for 3 months as an adjunct to mechanical therapy [50]. A study was conducted by Penmetsa et al. concluded that AV mouthwash is effective as antiplaque and anti-gingivitis agent and can serve as an affordable herbal substitute for chlorhexidine [51]. Moreover, AV gel can be used as a local drug delivery system in periodontal pockets [52]. In a recent

study, plaque-induced gingivitis was treated successfully with 10 ml AV mouthwash (99.6% [w/v]), without any recorded adverse effects [53].

Aloe vera mouthwash reduced significantly the plaque and gingivitis in comparison to chlorhexidine. Apart from its antiplaque quality AV also well accepted by patients because it has refinement taste and affordable shelf life [54]. Recently, toothpaste containing AV showed significant improvement in gingival and plaque index scores as well as microbiologic counts compared with toothpaste containing triclosan. Both AV tooth gel and toothpastes were equally effective against *Candida albicans*, *Streptococcus mutans*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, *Prevotella intermedia*, and *Pepto streptococcus anaerobius* [55].

Also, AV can be applied topically at the site of tooth extraction to prevent dry sockets and decrease the pain [18].

Endodontic treatment

A successful root canal therapy is based mainly upon elimination of microorganisms. *Enterococcus faecalis* is the most common isolated bacteria from persistent cases of root canal infection and in failed root canal treatments. AV extract is a good antibacterial agent against *E. faecalis* when used as intracanal medication due to its anthraquinones content [56]. AV with sterile water has superior antimicrobial activity against 18 strains of bacteria isolated from infected root canals of primary molar teeth [57-59]. Moreover, Khairwa et al. assessed clinical and radiographic success of zinc oxide combined with aloe vera when uses as an obturating material in pulpectomy and showed good success rate [58]. Therefore, they recorded that AV can substitute zinc oxide eugenol.

Many chemicals such as, chlorhexidine, ethyl alcohol, hydrogen peroxide, polyvinyl pyrrolidone iodine, and quaternary ammonium compounds as well as electron

beam sterilization have been tried for gutta percha (GP) decontamination. However, none of these methods have been proven as fully effective [60]. However, a concentrated extract of AV is effective as a GP decontaminant and can be used as a medium for storage of GP cones [61, 62].

Aloe vera extract can also be applied as canal lubricant in the closed dressings, by adding a drop of AV gel to the cotton pellet and then closed with temporary restorative material [63].

Also acemannan hydrogel significantly reduces the incidence of alveolar osteitis compared with Clindamycin-soaked gel foam [18, 64]. Acemannan is also effective in bone regeneration because it improves bone mineral density and promotes bone and periodontal ligament regeneration in animals [65]. Moreover, a randomized controlled trial with 12-month observation period evaluated bone regeneration after treatment with acemannan gel after apical surgery. Results of radiographic evaluations proved that acemannan gel administration significantly improves bone healing rate without any side effects [66].

Preventive and pediatric dentistry

Aloe vera tooth gel can control bacteria that cause cavities than other commercially available toothpastes due to its content of anthraquinones, which have anti-inflammatory effect [24]. Unlike most available toothpastes, AV gel has no abrasives, hence less harsh on teeth and it is a better alternative for people with sensitive teeth [2]. Moreover, it reduces dental plaque [54]. The AV gel demonstrated a remineralization capacity equal to that of the 1,450-ppm fluoride toothpaste. In contrast, fluoride-free AV toothpaste showed lower remineralization efficiency [67]. Further studies are required to understand its mechanism.

In a randomized clinical trial *in vivo*, AV extract had an efficient cavity-disinfection after minimally

invasive hand excavation of dental caries [68]. This suggests that application of AV as an alternative cavity-disinfecting agent may prevent secondary caries and contribute to the long-term success of restorative procedures. Although chlorhexidine is commonly applied as a cavity disinfectant or antimicrobial rinse after periodontal treatment, a more cost-effective antimicrobial agent, AV may represent a promising alternative preventive therapy [69].

Aloe vera can also be applied around dental implants to prevent inflammation caused by bacterial contamination [2, 18].

The sticky and viscous nature of acemannan was formulated into a denture adhesive and evaluated for adhesive strength in both wet and dry conditions. An optimal formula with a high and relatively stable adhesive bond strength and minimum cytotoxicity was observed [18, 70]. Therefore, acemannan denture adhesive formulation is an effective herbal substitute for traditional denture adhesives [40]. Also, AV can help patients with sore gums and teeth with dentures maladaptive [29].

The success of endodontic therapy in primary teeth depends mainly on the reduction or elimination of bacteria from the root canals by using appropriate obturating materials having good antibacterial properties. Therefore, there is a continuous search of an effective root filling material for primary teeth which can overcome all the anatomical complexities and instrumentation obstacles encountered, thereby leading to successful treatment outcomes. AV is a good material for obturation in primary teeth [71, 72].

Tissue engineering

The use of natural agents incorporated scaffolds shows a wide range of beneficial applications in tissue engineering. Polymer extracts of AV have potential to be used as biomaterials in tissue engineering due to numerous advantages such as biodegradability, oxygen permeability,

antioxidant action, and cell proliferation and regeneration [28].

Aloe vera has been used successfully in skin tissue engineering applications, improving the activity of amino acids, stimulating cell production, promoting skin regeneration, and preventing scar formation [73]. Moreover, AV gel-based 3D sponges were prepared by freeze-drying techniques, and can be used as an active biomaterial in regenerative medicine [73].

Aloe vera-based Poly (vinyl pyrrolidone) (PVP) fibers were prepared by the electrospinning method, which has shown excellent long acting antimicrobial activity against different microbial strains [74].

Contraindications and adverse reactions

Oral administration of AV is contraindicated in cases of intestinal obstruction, acutely inflamed intestinal diseases (e.g., Crohn's disease, ulcerative colitis), appendicitis, abdominal pain of unknown origin, pregnancy, breastfeeding, allergy to plants in the *Liliaceae* family and children under 12 years of age [2, 57].

Long term oral administration of AV may lead to cramping of the gastrointestinal tract, heart arrhythmias, nephropathies, hepatitis, edema, accelerated bone deterioration (in rare cases), pigmentation in the intestinal mucosa (pseudomelanosis coli), albuminuria, hematuria, hypersensitivity, loss of electrolytes, in particular potassium and damage of enteric nervous tissue [75, 76].

Systemic application of AV is not recommended in combination with antidiabetic, diuretic, or laxative drugs; sevoflurane; or digoxin [30].

Topical application of AV may produce redness, burning and stinging sensation. These reactions are mostly due to anthraquinones, like aloin and barbaloin. Therefore, allergic test should be performed in a small area first to avoid these possible reactions [2, 57].

Future prospects

Aloe vera has a lot to offer in the dental practice and future studies are recommended to maximize its beneficial role in the field of dentistry. More research on AV healing properties and antimicrobial, anti-inflammatory as well as immunomodulatory actions are needed in the future. Long-term studies are required with larger sample size are also essential to document the role of AV as a local drug delivery system in the field of dentistry. In addition, different methods of preparation, optimal concentrations and time of application of AV should be studied.

Future studies on the mixtures of AV and other herbal, natural, homeopathic or even chemical agents are also interesting prospects in the field of dentistry. Also, the effectiveness of AV under various conditions and the potential long term side effects need to be evaluated in the future. In addition, AV has promising future as a medium for storage of GP cones and further studies are recommended in this topic.

Moreover, the AV plant is a good source of natural polymers that remains to be explored extensively with other biomaterials for tissue engineering applications in the field of dentistry due to its unique and appealing physicochemical and biological characters. Therefore, more studies are required to declare the role of AV as tissue engineering scaffolds, gels, and films in the field of dentistry.

Conclusions

Although there are numerous *in vitro* and *in vivo* studies that have been documented the beneficial role of AV as a promising natural biomaterial in the field of dentistry, AV has a lot to offer in the dental practice and future studies are recommended to maximize its beneficial role in the oral health management.

Abbreviations

AV: Aloe vera

GP: Gutta percha

KGF-1: Keratinocyte growth factor 1

OSMF: Oral submucous fibrosis

PVP: Poly vinyl pyrrolidone

VEGF: Vascular endothelial growth factor

Declarations**Ethical Approval**

Not applicable

Competing interests

The authors declare no competing interests.

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