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Aloe Vera in Pediatric Dentistry: Back to the Origin?

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ABSTRACT

Aloe vera (Aloe barbadensis) is a plant that belongs to Liliaceae family. It has been used in phytotherapeutic fields for many years, being empirically indicated for constipation, skin burns, rheumatic pains, and wounds. Furthermore, there is a shift nowadays in the paradigm consisting of the use of natural substances, among others, aloe vera. Given its numerous benefits, its applications have been investigated and extended to the field of dentistry. The aim of this manuscript is to overview its application in pediatric dentistry, its mechanism of action and efficacy.

Key words: Aloe vera, Phytotherapeutic, Pediatric dentistry

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INTRODUCTION

The use of natural substance has become an area of interest in dentistry, particularly in young children. Aloe vera is a tropical plant that's belongs to family Liliaceae. It is widely used in dermatology for skin burns and wounds for its moisturizing and pain-relieving properties. It also exhibits excellent antioxidative activity, anti-inflammatory, anti-bacterial, antifungal, and antiviral properties [1].

It is important to determine the efficacy but also the safety of this product since it is gaining popularity in the field of dentistry. The purpose of this review is to give an overview of aloe vera : its potential applications in pediatric dentistry, its biological action and safety will be discussed.

Aloe vera: Description, composition, and properties

There are more than 300 species, but the Aloe vera barbadensis species exhibits the best medicinalproperties. The plant has triangular leaves with serrated edges, yellow tubular flowers and fruits that contain numerous seeds. Each leaf is composed of three layers [2]:

- An inner layer: made of clear gel that mainly contains water. The remaining constituents is active ingredients including polysaccharide, essential amino-acids, enzymes, vitamins. To date, 75 actives nutrients have been identified in stabilized Aloe vera gel (Table 1).
- A middle layer: composed of yellow sap of latex. It is very rich in anthraquinones, which are powerful laxatives. It's a circulation system that basically moves materials up to the leaves and down to the roots.
- An outermost layer: hard rind of 15 to 20 cells which has protective function and synthesizes all the nutrients [3].

Table 1: Summary of the chemical composition and properties of aloe vera.

Constituents		Properties
Vitamins	A, C ,E, B1, B2, B3, B6, B12	- antioxidants, essential in the fight against damaging free radicals.
		- positively influence the immune system and Vitamin C in particular assists in wound healing.
		- it also makes collagen, keeping bones skin and joints firm and strong

Saponins	Glycosides	- Cleansing and antiseptic
Enzymes	Brady kinase	- anti-inflammatory
	amylase lipase	- aid digestion
minerals	calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc.	- Co-enzyme : They are essential for the proper functioning of various enzyme systems in different metabolic pathways
		few are antioxidants
Sugars	Polysaccharides:	
	- Glucomannan	- Anti-viral
	- Acemannan	immune modulating activity
Anthraquinones	- Aloin	Analgesics
	- Emodin	Anti-bacterial
		Anti-viral
Fatty acids	cholesterol	All these have anti-inflammatory action
	campesterol	lupeol also possesses antiseptic and analgesic properties.
	β-sisosterol	
	lupeol	
Hormones	- Auxins	wound healing
	- gibberellins	anti-inflammatory action

Applications of Aloe vera in pediatric dentistry: A multipurpose medicament

There is increased interest among researchers in the use of aloe vera in dentistry. Various studies have investigated its effectiveness in numerous applications in:

- Maintaining oral health: prevention of periodontal and dental diseases.
- Traumatology as a storage media for avulsed teeth.
- Conservative and endodontic therapy.
- Dermatological disease affecting the oral cavity.

Maintaining oral health

Oral hygiene plays a key role in the prevention of periodontal disease and dental caries. Mechanical debridement of plaque by brushing is the basis of oral care. However, given that the ability to mechanically remove dental plaque using toothbrushes is low in the pediatric age group [4]; adjunct chemotherapeutic agents like mouthwash is needed to ensure a heathy oral environment for children over six years old [5].

The efficacy of chlorhexidine against plaque formation is known [6]. However, it is associated with many side effects if used long-term such as staining of teeth and tongue, a temporary altered taste, an increasing rate of supragingival calculus formation and burning sensation [7-9]. The assumed absence of such detrimental effects with Aloe vera and its antimicrobial along with its anti-inflammatory properties has led to an increasing interest for this product for oral care [10].

Mechanism of action

In vivo and in vitro studies demonstrated that aloe vera can inhibit the growth of diverse oral microorganisms including *streptococcus strains*, actinomyces viscosus and candida, which explains the anti-plaque efficacy of aloe vera [11,12]. It is particularly effective against S. mutans [13]. This has been attributed to the negatively charged polysaccharides it contains [14]. To mention, each concentration of aloe vera extract has a different inhibitory effect on *streptococcus mutans*, and the resulting inhibitory effect is greater when higher concentrations are used [15].

Its efficacy can also be attributed to its strong anti-inflammatory properties. Indeed, Aloe vera contains numerous anti-inflammatory components that act against pro inflammatory precursors such as bradykinin and histidine, and hence, contributes to alleviating the signs of gingivitis [16,17]. Moreover, aloe vera contains many substances (mannose-6-phosphate, hyaluronic acid, dermatan sulphate, vitamin C) all of which are suggested to stimulate collagen synthesis fibroblast activity and wound healing, further contributing to a decrease in gingival inflammation [18,19].

To sum up, the anti-gingivitis effect of aloe vera is largely dependent on the association of its anti-inflammatory properties with its antimicrobial effect, whereas the action of chlorhexidine in reducing gingival inflammation is mainly dependent on its antimicrobial effects.

Efficacy

A systematic review conducted in 2019 to evaluate the effectiveness of aloe vera in improving oral heath in adult patients concluded that aloe vera shows promising results in reducing plaque and gingivitis scores, without any adverse effects reported. However, considering the quality and heterogeneity among the included studies this conclusion must be weighed cautiously [20].

When considering school-aged children, a randomized controlled clinical trial was conducted to evaluate the effectiveness of Aloe vera mouthwash [21]. For that purpose, a crossover design was applied with three type of mouthwashes: Aloe vera 100%, chlorhexidine 0,12% and a placebo mouthwash. The subjects were asked to rinse with 10ml of the mouthwash for 1 min, once daily. The efficacy was assessed by calculating the difference between plaque index, gingival index and gingival bleeding index at the third day of plaque accumulation [T1] and then after five days of rinsing among the three mouthwashes [T2]. The results showed the efficacy of Aloe vera mouthwash in improving plaque, gingival and gingival bleeding indexes which was similar to chlorhexidine mouthwash effectiveness when both compared to the placebo mouthwash.

In addition, another study with a different design was done to evaluate the effect of two herbal mouthwashes: one of them containing aloe vera [7%] and the other tea tree oil on the oral health of school-age children [22]. The children were divided in four groups: Group 1 [aloe vera], Group 2 [Chlorhexidine], Group 3 (tea tree oil), Group 4 (placebo). The recordings of plaque index, gingival index, and salivary *streptococcus mutans* was performed at baseline, after 4 weeks of supervised rinsing with 10 ml of their respective mouthwashes for 30 s twice a day and then after 2 weeks of stopping the rinse. All the indexes investigated were found to be significantly lowered in a comparable way to that of chlorhexidine mouthwash. However, at the end of the 2-week washout phase a significant increase in *S. mutans* counts was reported with aloe vera mouthwash compared to chlorhexidine group, suggestive of a greater substantivity of chlorhexidine against *S. mutans*.

Side effects

One important concern with traditional mouthwashes is related to the various side effects associated with the use of these products, particularly in children who can swallow them, even after the age of 6. The findings of these studies demonstrate that aloe vera mouthwash is safe and well tolerated with no or very minimal side effects reported. However, it does not address the possible outcomes after long-term use of these herbal preparations. According to the American Dental Association a 6-month period is the optimum period to evaluate the efficacy and safety of a mouthwash [23]. Hence, further studies exploring the potential adverse effects of their usage are needed before presuming their safety in pediatric use.

In traumatology as a storage media for avulsed teeth

Avulsion is one of the most severe forms of dental trauma. It refers to a complete displacement of the tooth from its alveolar socket. Hence, it is mainly characterized by compromised neurovascular supply and a loss of periodontal ligament (PDL) cells [24].

Immediate replantation is the ideal treatment for avulsed permanent tooth [25]. However, this is not always possible at the place of the accident. In those situations, the tooth should be maintained in a suitable medium capable of preserving the viability of the PDL cells until reimplantation. It's essential for the roots surface be repopulated by fibroblasts, thus avoiding the adherence of osteoclasts in this area to prevent external root resorption [26]. For that purpose, various storage media has been proposed. The American Association of Endodontists recommend the Hank's Balanced Salt Solution [HBSS] as a storage medium of choice for treatment of avulsed teeth. Its essential function is to maintain pH and osmotic balance as well as provide the cells with water and essential inorganic ions for cell metabolism [27]. As it is not commonly available, alternative natural medium which includes aloe vera have been investigated. Especially since natural products may be suggested to be more effective in maintaining the PDL cell viability when compared to synthetics medium [28].

Mechanism of action

The most important factors for survival and optimal cell growth are osmolarity (around 230-400 mosmol/kg; with the optimal value for most cell lines being approximately 300mosmol/kg) and pH (around 6.6-7.8) along with temperature [29-31]. Hence, the improved viability of cells subjected to aloe vera may be due to its optimal osmolarity (280-300300mosm/kg) and pH [9-11] [32,33]. In addition, to that the cytoprotective effects of its nutrient such as acemannan, sugars, amino acids, fats, ions (calcium, magnesium, potassium), and vitamins [A, B, C, F, and E) may help nourish the cells [34]. Also. Buttke et al also suggested that reimplantation success may be increased by storing avulsed teeth in medium containing one or more antioxidants. As it's containing a catalase enzyme, an antioxidant that may inhibiting the generation of free radicals thereby minimizing cell damage, aloe vera is an excellent antioxidant [35]. In addition, it has also the capacity to protect the cell viability by its antibacterial and antifungal properties preventing further infection.

Efficacy

When considering the effectiveness of aloe vera based on different concentration, Badakhsh et al. conducted an in vitro study with multiple concentrations (10%, 30%, 50% and 100%) to evaluate the survival of the PDL cells [36]. Results revealed that for up to 9 hours aloe vera at 10%, 30% and 50% concentration performed similarly and had the greatest capability in maintaining the cell viability. However, at 100% concentration, it had the

poorest ability. This may be explained by the fact that even if the 100% concentration has the most nutrients, it is highly viscous, hence it may have possibly prevented the accessibility of oxygen to cells. As a result, the more deficiency in oxygenation, the more cell death occurrence. Furthermore, the mean pH level of the 100% concentration of Aloe Vera was found to be a bit more acidic [pH =5.21] compared with others concentration. This may be considered as another causative factor for reducing the effectiveness of aloe 100%.

These same results were obtained later in 2016 with dental pulp stem cell (DPSC) which indicated that 50% Aloe vera gel was effective in maintaining the viability of DPSCs and promoting the growth kinetics of DPSCs when compared with HBSS [37].

A systematic review based on in vitro studies conducted in 2019 concluded that even if aloe vera shows promising effects on the viability of PDL cells, the evaluation of the pharmacological potential of plants as a storage media on dental tissues still requires more research [38].

CONSERVATIVE AND ENDODONTIC THERAPY

As a pulp dressing material

The rationale of using pulp dressing material is based on the healing ability of the pulp [39]. Hence, providing a favorable environment for the pulp to heal by using biocompatible materials is a major interest. It is also important for the material to promote dentin bridge formation. The research of Gala-Garcia.et al [2008] demonstrated that aloe vera is biocompatible and have the potential to form tertiary dentinal bridge formation [40]. This result paved the way for the investigation on the effect of the acemannan, a polysaccharide extracted from A. vera gel which may be the responsible constituent of this effect.

Mechanism of action

Although, the regenerative mechanism of acemannan has not been explicitly identified it was suggested that it upregulate growth factor secretion (eg BMP-2) and dentin matrix protein expression [e.g., osteopontin, dentine sialophosphoprotein, alkaline phosphatase] which may accelerate new dentin bridge formation [41].

Efficacy

A split mouth design study was directed to compare the clinical and radiographic effects of acemannan as pulpotomy dressing agents with formocresol. Within the context of observed results at one year follow-up, the acemannan group showed high clinical (96,5%) and radiographic success (93.1%) rate with no significant difference with the formocresol group. The authors considered it as an acceptable biomaterial for vital pulp therapy in deep caries in primary teeth [42]. However, these clinical and radiographic examinations criteria alone are not sufficient to draw robust conclusion. Histopathological examination has long been suggested to be the best method to evaluate the effectiveness of a biomaterial at the cellular and pulp tissue levels [43]. For that purpose, a clinical study was conducted to investigate clinically, radiographically and histologically the action of acemannan as a direct pulp capping material in primary teeth and compared it with calcium hydroxide (Ca(OH)2) at 6 months follow-up [44]. No significant difference between the clinical and radiographic success rates between the two group were found: both groups demonstrated 100 % success rate based on clinical and radiographic evaluation revealed 72.73 % success rate in the acemannan-treated group versus 70.0% in the Ca (OH)2-treated group. In contrast, the acemannan group had a significantly better histopathological response Histopathological findings in successful cases for the acemannan group were as follow: no or mild pulp inflammation under the exposure site was found. Also, a layer of odontoblast-like cells appeared under complete homogenous dentin bridge formation, with a normal soft tissue organization. In comparison, the Ca(OH)2–treated group shows moderate inflammation, partial dentin bridge formation, and partial loss of soft tissue organization. One main limitations of this study are the choice of the control material. Indeed, DPC performed with Ca(OH)2 in primary teeth had a poor prognosis as Ca[OH]2 is highly alkaline. In addition, this was a short-term evaluation.

To the best to our knowledge, no in vivo on human teeth study investigated the use of this material for a longer period and compare it with the gold standard MTA. However, when considering animal studies showed that the effectiveness of acemannan on dentin regeneration is comparable to that of MTA and that Acemannan can be an alternative natural material for vital pulp therapy of primary teeth and avoids the cost barriers associated with the use of more expensive materials [45]. Further in vivo studies with a long term are needed to ascertain this result.

As an intracanal medicament

The use of intracanal medicaments is an adjunct way to eliminate or reduce the microbial population that may persist in roots canal even after a rigorous procedure. This is particularly true in primary teeth because of the high complexity of the root canal system. Calcium hydroxide (Ca(OH))2 is the most commonly intracanal medicament used [46]. Its high pH [12.5] has a destructive effect on bacterial cell membranes and can cause denaturation of proteins and DNA which leads to bacterial death [47]. Despite its appropriate antibacterial spectrum, [Ca[OH]]2 has little effect on *E. faecalis* [48–51]; It's a Gram-positive facultative anaerobic bacterium who is particularly virulent for its high resistance to high pH and for its high ability for biofilm formation [52]. It is associated with different forms of periradicular infections, both primary and secondary endodontic infections. Hence to overcome this limit the use of herbal medicines like Aloe vera who as antibacterial properties has recently been considered as an intra canal medicament.

Mechanism of action

This herbal compound has an inhibitory effect on many oral pathogens, including *E. faecalis*, due to the anthraquinone phenolic compounds. They can inhibit protein synthesis from bacterial cells, thus explaining their antimicrobial activity [53].

Efficacy

An in vitro study was conducted in 2020 to investigate the antibacterial effect of 100 % Aloe vera gel on 4thand 6th weeks of *E. faecalis* biofilm and to compare it with calcium hydroxide. The results of the study showed a significant positive effect of Aloe vera on the elimination of biofilms at both biofilm development stages; in contrast, calcium hydroxide represented a very weak antibacterial effect [54]. However, further long-term studies regarding its effect on the successional teeth, physical properties of the dentin, interference with the obturating material, discoloration need to be evaluated.

As a root canal irrigant

An ideal irrigating solution should possess maximal antimicrobial and tissue solving properties and minimal toxic effects [55]. Sodium hypochlorite has long been advocated as a root canal irrigator of choice [56,57]. However, sodium hypochlorite has some negative features such as unpleasant taste and odour, allergic reactions in some patients, risk of sodium hypochlorite accident [58]. In the recent years, the use of herbal products as root canal disinfectants has been widely investigated in endodontics because of their efficiency, safety and accessibility [59].

Efficacy

In vitro studies with the aim of comparing the inhibitory effect of aloe vera solution [80%] and sodium hypochlorite [2,5%] on *E. faecalis* as a root canal irrigant shows that Aloe vera and normal saline [control group] have a similar inhibitory effect on *E. faecalis* which is far less than the antimicrobial effect of sodium hypochlorite. Several factors could be considered for this outcome: first, a period of 15- 0 minutes might not be sufficient for Aloe vera to apply its inhibitory effect against *E. faecalis* [60]. However, no studies were available to suggest a specific duration or concentration for Aloe vera to act as an antimicrobial agent. Also, the gel-like consistency of Aloe Vera could cause limited flow of the substance through the irregularities of the root canal system. Hence, the authors concluded that Aloe vera solution is not recommended as a canal irrigator.

To sup up, when used as an intracanal medicament aloe vera shows promising result against *E. faecalis* but poor effect when used as a root canal irrigant, hence further clinical trials are required to consider the formulation delivery and to state the specific merits or demerits of this substance.

Oral lesions

The following chapter discuss the aloe vera's application in alleviating the symptoms of oral lesions. The reported uses in the literature concerns:

- Dermatological diseases: oral lichen planus.
- oral mucositis induced by radiation/chemotherapy.

Oral lichen planus [OLP]

OLP is a chronic inflammatory disease in which cytotoxic T cells trigger apoptosis of oral epithelial cells. Symptomatic treatment can be achieved with topical [or systemic medications for recalcitrant lesion] treatment such as corticosteroids, ciclosporin and retinoic acid [60-62] but there is a lack of strong evidence supporting their efficacy [63,64].

Mechanism of action

It it's admitted that Aloe vera can inhibit the inflammatory process by interfering in the arachidonic acid pathway via cyclooxygenase [19]. In addition, animal studies research suggests that Aloe vera could also inhibit the inflammatory process by the reduction of leucocyte adhesion as well as pro-inflammatory cytokines including TNF-alpha level [65-66]. As it was suggested that the upregulation of intercellular adhesion molecules and cytokines secreted by activated lymphocytes and keratinocytes can play a role in the pathogenesis of OLP; aloe vera has been considered in different studies as a therapeutic modality for OLP in adults [19,67].

Efficacy

A systematic review conducted in 2017 to assess the effect of aloe vera on pain alleviation and clinical improvement in adults' patients with symptomatic OLP confirmed its effectiveness. It was comparable to corticosteroids. The authors concluded that although corticosteroids remain the gold standard, Aloe vera shows promising results especially with no adverse effects compared with various adverse effects and contraindications of corticosteroids [66].

To the best to our knowledge, as OLP is a seldom condition in pediatric dentistry [68], only one case reported the treatment of symptomatic OLP in a pediatric population that was successfully managed with a sequential modality of topical retinoids followed by aloe vera gel application [67].

Radiation/chemotherapy induced oral mucositis

Oral mucositis is an inflammatory mucosal destruction characterized by erythema and/or ulceration of oral mucosa because of chemotherapy and/or radiation therapy. The most common features include oedema, erythema, ulcerations, bleeding pain, problems in swallowing, eating, drinking, talking and taste changes appearing in different levels of severity [69]. Currently no generally approved treatment or prophylaxis protocol exists [70].

Efficacy

A meta-analysis published in 2021 support the positive effect of Aloe vera in reducing mucositis in patients receiving cancer therapy [71].

When considering children, a randomized clinical trial was conducted to assess its effects and to compare it to sodium bicarbonate in children who are undergoing chemotherapy. The auhtors found out that topical application of aloe vera is effective in the prevention of OM in all children [72]. However, this evidence was very low quality and insufficient for concluding with certainty that aloe vera has any benefits in preventing OM compared with sodium bicarbonate in children [73].

Application of aloe vera: is it safe for children?

No adverse effect has been reported by the studies included in this review. However, topical application could lead to allergic reactions [due to anthraquinones], episodes of contact dermatitis, burning and erythema. Ingestion of aloe vera is sometimes associated with diarrhea, electrolyte imbalance [laxative action sometimes may lead to low potassium levels], worsening of constipation and conventional drug interactions [74,75]. However, these side effects are not seen in all patients.

CONCLUSION

Aloe Vera is a promising agent in pediatric dentistry for its excellent anti-oxidative activity, anti-inflammatory, anti-bacterial, antifungal, and antiviral properties.

In the future, it can become a cost-effective approach in maintaining oral health, in low-income countries. However, further research should investigate its long-term effects on tissues and should aimed to standardize its method of use (preparation, optimal concentration, time of application). Also, the potential long-term side effects need to be studied and evaluated, particularly in children.

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