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ROLE OF PHYTOMEDICINE AGAINST DENTAL PLAQUE IN FIXED ORTHODONTIC APPLIANCES (FOA) TREATMENT- A LITERATURE REVIEW

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ABSTRACT

Oral diseases such as Dental caries /plaque and Periodontal diseases are caused by micro organisms belonging to the resident micro flora rather than by classic microbial pathogens. They are caused by the ecological imbalance in oral bio films. In clinical studies, an increasing incidence of incipient carious lesions and generalized gingival inflammation have been found in patients undergoing fixed orthodontic appliance. Oral microbial flora is dominated by gram positive micro organisms and hence dental plaque which is formed on the tooth surface contains gram positive cocci and bacilli. Oral health also influences the general quality of life and poor oral health is linked to chronic conditions and systemic diseases. The association between oral diseases and the oral microbiota is well established. Acidogenic bacteria like Streptococcus mutans, Streptococcus sobrinus, Streptococcus oralis, Streptococcus intermedius, Streptococcus anginosus, Lactobacillus acidophilus, streptococcus salivarius, Streptococcus mitis, Streptococcus sanguis is an potent initiator that causes dental caries/plaques in the Patients receiving fixed appliances in the orthodontic treatment . These dental plaques are more difficult to be removed in the fixed appliances patients. Hence, in our present article, natural products like Acacia catechu willd, Glycyrrhiza glabra, Achillea millifolium, Aesculus hippocastanum, Anacardium occidentale and Eremophila Longifolia that inhibit the growth of oral pathogens, reduce the development of biofilms and dental plaque in orthodontic patients with fixed appliances is reviewed extensively.

Keywords: Dental plaque, fixed appliances, orthodontic patients, phytomedicine, remedy.

INTRODUCTION

Dental plaque, the biofilm that forms on the surface of teeth, can induce some of the most common diseases affecting mankind, which includes caries, gingivitis, and periodontitis.[1] A healthy mouth is a premise of overall health. The oral cavity can be a mirror image of other areas of the body and many systemic illnesses are manifested in the soft tissues of oral mucosa of the mouth. When oral health is compromised, over all health can be affected [2].The oral cavity provides a habitat for a diverse range of bacteria, viruses, protozoa and fungi. These micro-organisms colonize various surface in the mouth, including the cheeks, tongue, palate and teeth.

Under certain circumstances, the acidogenic bacteria may cause diseases of the oral cavity, although this usually only occurs when there is a break in, or loss of, maintenance of oral hygiene[3]. Loss of oral hygiene may lead quickly to the development of oral diseases or conditions such as gingivitis, halitosis , dental plaque, dental calculus, dental caries and periodontitis. More severe outcomes of poor oral hygiene include the loss of teeth and/or bone.[4]

Oral cavity is a complex ecosystem with higly divergent acid tolerant and acid-producing microbiota.acidogenic oral microbes is the key factor of Dental plaques.the primary acid tolerant bacteria associated with Dental plaque includes *streptococcus mutans, Streptococcus oralis streptococcus sobrinus,Lactobacillus acidophilus, streptococcus salivarius, Streptococcus mitis, Streptococcus sanguis ,Streptococcus intermedius, Streptococcus anginosus* that surround orthodontic appliances are a common orthodontic problem in many patients undergoing Orthodontic treatment. [5-9]

Such bacteria can lead to tooth enamel breakdown and potential discoloration of the tooth surface, and these aesthetic changes can persist for many years after orthodontic treatment. While the newer bonded orthodontic brackets have many advantages over the old metal bands that were fitted around each tooth, they do impede good oral hygiene, resulting in plaque accumulation and increased tooth enamel breakdown.

It also has been reported thet presence of fixed orthodontic appliance greatly inhibitis oral hygiene and creates new retentive areas for plaque and debris [10] ,which in turn predisposes to increased carriage of microbes and subsequent infection .Therefore, prevention of bacterial attachment to orthodontic wires is a critical concern for orthodontists[11-12].

Several literature review proves that plants as intact crude organs and their products (e.g., powdered plants, extracts, etc) have been widely used by different cultures to promote oral hygiene since antiquity[13].

Hence, our present review is an attempt to generate interest among the people regarding the potential of the natural herbs like *Acacia catechu willd, Glycyrrhiza glabra, Achillea millifolium, Aesculus hippocastanum, Anacardium occidentale and Eremophila Longifolia* against acidogenic oral microbes in preventing and treating the Dental plaques in orthodontic patients with fixed Applainces.

PHYTOMEDICINE EFFECTIVE AGAINST DENTAL PLAQUE

Acacia catechu willd

Family –*Fabacea***, Sub family-** *Mimosoideae***.**

Parts used: Leaf, Bark, Heartwood**.**

Pharmacological activity

Acacia Catechu willd also known as Black cutch has a diverse pharmacological actions and has been widely used in traditional medicinal system to treat various diseases. The main chemical constituents of *Acacia Catechu* are catechin, epicatechin, epigallocatechin, epicatechin gallate, phloroglucin, protocatechuic acid, quercetin, poriferasterol glucosides, lupenone, procyanidin, kaemferol, L-arabinose, D- galactose.D-rhamnose andaldobiuronic acid, afzelchin gum, mineral and taxifolin. [14, 15-19]

Acacia catechu is highly valuable for its powerful astringent and antioxidant activities. It is commonly known as Katha which is an indispensable ingredient of Pan that is betal leaf preparation chewed in India. It is useful in dental, oral, throat infections and also as an astringent for reducing oozing from chronic ulcers and wounds.

The concentrated aqueous extract known as Khair gum or cutch is an astringent, cooling and digestive, beneficial in cough and diarrhea. The extracts of ***Acacia catechu*** exhibits various pharmacological effects like antipyretic, anti-inflammatory, anti diarrhoeal, hypoglycaemic, hepatoprotective, antioxidant and antimicrobial activities. [14, 20-31, 33, 34] ***Acacia catechu*** is useful as a topical agent for sore gums and mouth ulcers.[32]

Role of *Acacia catechu willd* against Dental plaque

Pawar *et -al* explained a dentifrice / herbal tooth powder comprised of *Acacia catechu*, Menthol and camphor in the proportion 91%, 2.7% and 6.3% respectively. In his study it was proved that the powder of *Acacia catechu* was used to remove tarter, plaque, and stain and in cleansing and polishing tooth surface without producing any abrasion whereas menthol and camphor were used as flavouring agents. A clinical study

on this herbal dentifrice , reported 87-95%, 70-72% and 80-95% reductions in plaque, gingivitis and dental calculus respectively, in about 15 days of treatment. [35]

Acacia catechu heartwood extract is found to be an effective antibacterial agent. A study conducted by Lakshmi.T and co workers in ethanolic and aqueous heartwood extract of *Acacia catechu*, proved its efficacy as a potent anti bacterial agent. Taxifolin present in heartwood of *Acacia catechu* is found to be responsible for its Anti bacterial effect.[19]

Similar study was conducted by Geetha and co workers evaluated the potency of *Acacia catechu* heartwood extract against dental caries causing microbes and organism associated with endodontic infections like streptococcus mutans, streptococcus salivarius, Lactobacillus acidophilus and Enterococcus faecalis using disc diffusion method.[20] Streptococcus mutans and Lactobacillus acidophilus are potent initiator for dental plaques that results in destruction of mineralised tissues in the teeth .

Hence the study suggests *Acacia catechu* heartwood extract is higly active on oro dental pathogens and can be applied in Dental practice for periodontal patients and Orthodontic fixed appliances patients to eradicate dental plaques, gingivitis, mouth sores and it is also applied in Endodontal treatment as *Enterococcus faecalis* is found to be the root cause of failure in Root Canal Treatment(RCT).

***Glycyrrhiza glabra*(Liquorice Root)**

Family : *Fabaceae/Papilionaceae*

Parts Used: Root, rhizomes (powder, teas, tonics, extracts, tinctures and decoctions)

Pharmacological activity

Glycyrrhiza glabra, also known as Liquoirice and sweet wood, is native to the Mediterranean and certain areas of Asia. Liquorice(*Glycyrrhiza glabra*), is a perennial herb which possesses sweet taste [36] Liquorice has extensive pharmacological effects for human being. liquorice is used for treating upper respiratory ailments including cough, hoarseness, sore throat and bronchitis.[37,38]

Liquorice extracts have been used to treat chronic hepatitis, and also have therapeutic benefit against other viruses, including human immunodeficiency virus , cytomegalovirus , and Herpes simplex. Deglycyrrhizinated liquoirice preparations are useful in treating various types of ulcers, while topical liquoirice preparations have been used to sooth and heal skin eruptions, such as psoriasis and herpetic lesions.It is used in Respiratory and digestive disorders [39].

It is also considered as anti stress and anabolic agent. *Glycyrrhiza Glabra* constituents possess significant antioxidant and hepatoprotective properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation. [40, 41]

Studies also show liquoirice constituents to be effective in the treatment of eczema, [42] melasma, [43]eosinophilic peritonitis, [44] postural hypotension, [45] erosive gastritis, [46]and as anti-malarial [47] and anti-Leishmanial agents.

Role of *Glycyrrhiza glabra* against Dental plaque

Manoj *et al* determined the antibacterial activities of *Glycyrrhiza Glabra* root extract in ether, chloroform, acetone on bacteria using the agar well diffusion method. The extracts showed significant antibacterial activities against two gram positive(*Bacillus subtilis and Staphylococcus aureus*) and two gram-negative (*Escherichia coli and Pseudomonas aeruginosa*) bacteria.The study concluded that It can be used in the folk medicine at different parts of the world to treat many diseases including bacterial infections.[49]

Jian HE *et al* found that liquorice exhibits potent antimicrobial activity against *streptococcus mutans* and are now being used in lollipops to reduce caries/plaques.[50]

Dhanya kumar N.M and Preena sidhu proved the antimicrobial activity of Neem, Liquorice, Cinnamon,Clove and babool against *Streptococcus mutans* and *Enterococcus faecalis* .In their study it was concluded that babool and Liquorice ethanolic extract exhibited significant antimicrobial activity against *streptococcus mutans* an cariogenic pathogen. They suggest

thatLiquorice and babool extract is beneficial against Dental caries/plaques caused by *Streptococcus mutans*.[51]

Hence the available data suggest that *Glycyrrizha glabra* extract is effective against oral microbes and it can also be applied in Dental practice to treat Dental caries/plaques in periodontal patients and orthodontic fixed appliance patients where the dental plaques are difficult to be removed.it can be applied in Endodontic patients where root canal failure is major problem caused by *Enterococcus faecalis*.

Achillea Millifolium

Family :*Asteraceae* **Subfamily** : *Asteroideae*.

Parts used : Flower, Leaf and Stem

Pharmacological activity

Yarrow, ,is closely related to chrysanthemums and chamomile. yarrow (*Achillea millefolium*) was named after Achilles, the Greek mythical figure who used it to stop the bleeding wounds of his soldiers. Decoctions have been used to treat inflammations, such as hemorrhoids, and headaches. The medicinally active part of the plant is the flowering tops.[52]

The flowers are used to treat various allergic mucus problems, including hay fever

the dark blue essential oil, extracted by steam distillation of the flowers, is generally used as an antiinflammatory [53]or in chest rubs for colds and influenza. The leaves encourage clotting, so it can be used fresh for nosebleeds.[54]

The aerial parts of the plant are used for phlegm conditions, as a bitter digestive tonic to encourage bile flow, and as a diuretic.[55] aerial parts act as a tonic for the blood, stimulate the circulation, and can be used for high blood pressure.

It has analgesic [56,57] amenorrhea, antiphlogistic,[58,59] anti-inflammatory agent, used to control bleeding, blood clots, blood pressure , blood purifier, blood vessels , colds, chicken pox, circulation, cystitis, diabetes treatment, gastro-intestinal disorders [60], choleretic [61] dyspepsia, eczema, fevers, flu's, gastritis, glandular system, gum ailments, heartbeat , influenza, insect repellant,inflammation[62], emmenagogue[63], internal bleeding, liver , lungs, measles, menses , menorrhagia, menstruation , nipples , nosebleeds, piles (bleeding), smallpox,stomach sickness, toothache, thrombosis, ulcers, urinary antiseptic, uterus (tighten and contract), gastroprotective agent[64] varicose veins, vision, it may also reduce autoimmune responses.

Role of *Achillea Millifolium* against Dental Plaque

G. A. Van der Weijden *et al* evaluated *in vitro* inhibiting effect of a herbal extract mixture on a selected number of micro-organisms and did *in vivo* study related to effect of a mouthwash containing 6.3 mg/ml herbal extract mixture on plaque and gingivitis as compared to a negative control mouthrinse. The herbal extract was a mixture of: *Juniperus communis* (juniper), *Urtica dioca* (nettle), *Achillaea millefolium* (yarrow); 1:1:1. The *in vitro* analysis reveals that *streptococcus mitis* found susceptible with MIC value of 1mg/ml when compared to other bacterial strains.

Based on *in-vivo* study, 45 volunteers were selected on the basis of having moderate gingival inflammation. As efficacy parameters the plaque index, modified gingival index and angulated bleeding index were assessed.

In conclusion, his data suggest that the mixture of the 3 herbal extracts, *Juniperus communis, Urtica dioca* and *Achillaea millefolium* when used in a mouthrinse has no effect on plaque growth and gingival health. *invitro* data also provides weak Antibacterial activity but *Streptococcus mitis* which is an initiator for dental plaques showed significant Antibacterial activity against *Juniperus communis, Urtica dioca and Achillaea millefolium.*[65]

Beukes an orthodontist conducted an *invitro* study on eight medicinal plants including *Achillea millifolium* (Acetone,ethanolic,hexane form of extract).The control treatments were chlorhexidine and fluoride.in his study he concluded that *Achilla millifolium* Acetone extract exhibited low MIC value comparitively to other herbal extracts tested against acidogenic oral bacteria.[66]

Allium sativum

Family : *Alliaceae* **Subfamily** ; *Allioideae*

Parts used : Plant's Bulb, Garlic Cloves

Pharmacological activity

Allium sativum, commonly known as **garlic**, is a species in the onion genus, *Allium.* It has been used throughout its history for both culinary and medicinal purposes. The garlic plant's bulb is the most commonly used part .Garlic cloves are used for consumption or for medicinal purposes. *Allium sativum* has been found to reduce platelet aggregation [67]and hyperlipidemia.[68]It is also an anti-diabetic agent [69]

When crushed, *Allium sativum* yields allicin, an antibiotic[70]and antifungal compound It also contains the sulfur-containing compounds alliin, ajoene, diallylsulfide, dithiin, S-allylcysteine, and enzymes, B vitamins, proteins, minerals, saponins, flavonoids, and Maillard reaction products, which are not sulfur-containing compounds. Furthermore, a phytoalexin (allixin) was found, a nonsulfur compound with a γ-pyrone skeleton structure with antioxidant effects, antimicrobial effects,[71] antitumor promoting effects,[72] and neurotrophic effects.

Garlic possess diaphoretic, expectorant, antispasmodic, antiseptic,bacteriostatic, antiviral, antihelminthic and hypotensive effects; it is commonly used to treat chronic bronchitis, recurrent upper respiratory tract infections and influenza [73] In Europe and India, garlic remedies are used to treat coughs, colds, hay fever and asthma. Many modern herbalists and folk healers still rely on garlic oil ear drops to heal the pain of a child's ear infection.

The German Commission E recommends garlic as a supportive dietary measure to

lower elevated blood lipids and as a preventive measure for age-dependent vascular changes; it does not note any contraindications[74]

Role of *Allium sativum* against Dental plaque

The active component of garlic is allicin. It is antibacterial and has immune regulatory functions. Allicin destroys cell wall and cell membrane of root canal bacteria[75]This is used as irrigant alternative to NaOCl.

Garlic extract inhibits the growth of oral pathogens like *streptococcus mutans* and *porphyromonas gingivalis* hence used for management of dental infections in periodontal and **Orthodontic Fixed Appliances** patients developing dental plaques.[76]

Despite of its antibacterial action, *Allium sativum* extract also increases biofilm formation by *S.mutans* to orthodontic wire, likely through up regulation of glucosyl transferase expression. Garlic extract thus play an important role in increased bacterial attachment to orthodontic wires.[77]

MM Fani conducted an study based on *in vitro* inhibitory activity of garlic extract on multidrug-resistant (MDR) strains of *Streptococcus mutans* isolated from human carious teeth. The data obtained in this study indicates that mouthwashes or toothpaste containing optimum concentration of garlic extract could be used for prevention of dental caries/plaques.[78]

Aesculus Hippocastanum

Family : *Hippocastanaceae* **Sub Family :** *Hippocastanoideae*

Parts used :Seed

Pharmacological activity:

Horse chestnut, is believed to be derived from the brown conkers that look similar to chestnuts and because a horseshoe shaped mark (spots resembling horseshoe nails) is left on the twig when the leaves drop off in autumn.[79,80] Anciently, the seed extract was used as a treatment for many ailments, including rheumatism, rectal complaints,[81] bladder and gastrointestinal disorders, fever , hemorrhoids ,[82] and leg cramps.[83] Currently, horse chestnut seed extract (HCSE) is widely used in Europe for chronic venous insufficiency, post-operative edema, and topically for clearing skin conditions.

HCSE is as an effective therapy for venous disorders and edema, The primary active constituent found in horse chestnut seed extract is aescin. Aescin is primarily an mixture of triterpene saponins present in two forms, which are distinguished by their water solubility and

melting points. Other constituents include bioflavonoids (quercetin and kaempferol),proanthocyanidin A_2 (an antioxidant), and the coumarins fraxin and aesculin.[84]Aescin from HCSE has been shown to possess anti-edematous[85,86,87], anti-inflammatory[88,89] and venotonic properties that may be attributable to decreased vascular permeability.[90] Horse chestnut has been used as an analgesic, anticoagulant, antipyretic, astringent, expectorant, and tonic. It has also been used to treat skin ulcers, phlebitis, leg cramps, cough, and diarrhea[91].

Role of *Aesculus Hippocastanum* against Dental plaque

Extract of horse chestnut bark (*Aesculus hippocastanum*) is one of the ingredients that gives Fortifying Mint Toothpaste, Sensitive Orange Tooth Gel for Children und Sage Mouthwash their fortifying effects. It contains aesculin, which firms the gums and has a harmonising influence on the formation and hardening processes within the body. These two opposing tendencies play an important role in the development of the teeth as the tooth grows and requires both forming and hardening [92].

Anitha and coworkers evaluated the Antibacterial efficacy of Aqueous and Ethanolic extract of *Aesculus Hippocastanum* against oral microbes Causing dental caries/plaque.the bacterial strains used in our study are *Streptococcus mutans, streptococcus salivarius,streptococcus mitis ,streptococcus sanguis, Lactobacillus acidophilus* .the antibacterial efficacy was significant against *streptococcus mutans* and *streptococcus sanguis* when compared to the other bacterial organism tested. Hence the authors suggest that *Aesculus hippocastanum* is highly efficient against dental plaques caused primarily by *streptococcus mutans*.[93]

Anacardium Occidantale

Family : *Anacardiaceae* **Sub Family :** *Anacardioideae*

Parts used : Leaf and Seed coat

Pharmacological activity

Cashew is the common name for a tropical and subtropical evergreen tree, *Anacardium occidentale* Linn., in the flowering plant family Anacardiaceae. It is also the name for the commercially important kidney-shaped, nut like seed of this plant, which is edible when roasted or cooked [94].The Anacardiaceae family consisting of several plants with immense pharmacological activity[95]. Various research work carried out has proved it to be used in various diseases like dermatitis, hyperglycemia, antiviral, anti inflammatory activity.

It is traditionally used in Ayurveda because of its anthelmentic activity. *Anacardium occidentale* is used medicinally wherever it is found growing. All parts of the plant like leaves, false fruit and bark have been traditionally used to relieve variety of ailments. The bark is said to have alternative properties .The root is considered purgative and the fruit is mainly used as antidiarrheal.agent. The tar from the bark is used as a counter irritant .As an external application it has been recommended in leprosy, ring worm, and ostinate ulcers, it is powerfully rubifacient and vesicant and requires to be used with caution[96].Tannins are isolated from *Anacardium occidantale*[97].It also possess good Antioxidant and Antimicrobial activity.[98]

Role of *Anacardium Occidantale* against Dental plaque

Jozinete Vieira Pereira *et al* Conducted a antimicrobial analysis of an extract from stems of the cashew tree, *Anacardium occidentale* Linn., was evaluated on three cultures of bacteria, *Streptococcus mitis, Streptococcus mutans, Streptococcus sanguis,* found in dental plaque.

The results showed effective inhibitory action of the extract when compared with Chlorexidine gluconate. Their study had proved that the extract from *Anacardium occidentale* were found to be effective for CIMA (adherence) at concentrations of 0.31mg/L for L for *S. mutans* and *S. mitis* and 0.15 mg/L for *S. sanguis*.

The extract from the cashew tree stems showed a potential inhibitory action on the synthesis of glucan measured as the adherence to glass in sub inhibitory conditions. The data suggest that the cashew trees may have some therapeutic use in dental practice and could be used as an oral antibacterial agent to treat dental plaques.[99]

Eremophilia longifolia

Family :*Myoporaceae* **Subfamily** : *Scrophularioideae*

Parts used :Flowers,Fruit,Leaves

Pharmacological activity

Eremophila longifolia (*Myoporaceae*), commonly known as "emu bush" is a large shrub that is found in the dry inland areas of all Australian mainland states [100]. Ethnobotanic literature frequently cites the *Eremophila* genus as an integral part of the traditional medicine of indigenous Australian populations, and *E. longifolia* is often considered to be the most sacred and mystical plants used within these cultures . Therapeutic uses of *E. longifolia* include treatments for colds, headaches, sores [101], skin ailments, eye conditions [100], boils and muscle ache [102].

Recent studies investigating the medicinal properties of the genus have demonstrated the presence of bioactivity in a number of species. In particular, extracts of a number of *Eremophila* species have shown inhibitory effects against Gram positive bacteria [103-107], including antibiotic-resistant strains [108-110]. Previous studies have also revealed anti mycobacterial activity , antiviral activity ,cardioactive effects [111] and *in vitro* inhibition of serotonin release and platelet aggregation.

Role of *Eremophilia longifolia* against Dental plaque

E.A Palambo investigated the Antibacterial activity of solvent and aqueous extracts of *Eremophilia longifolia* stem and leaves against *Streptococcus mutans* and *Streptococcus sobrinus*. Stem ethanol extract (SEE) demonstrated growth inhibition of the two cariogenic bacteria with a minimum inhibitory concentration (MIC) of 0.5% (w/v).

His study also assessed the anticariogenic activity of SEE in terms of its effect on glycolytic pH drop, viability of cells within an artificial biofilm and cell attachment to a membrane. Preliminary phytochemical investigations suggested that the active components within SEE were phenolic compounds but unlikely to be flavonoids. His study advocates SEE as a worthy candidate for further research into alternative chemotherapeutic approaches to dental caries/plaques[112].

CONCLUSION

Dental caries/plaque is an extremely prevalent infectious disease that has been shown to be associated with serious health problems. It is an important task for the dental practioner to teach individuals to take correct actions to minimize the risk for the disease .Although there has been a slight decline in the prevalence of dental caries in many developed countries, there is an increase in occurrence amongst people of lower socioeconomic status and those within indigenous populations.The disease is associated with the colonisation and biofilm development of the Acidogenic bacteria like *S. mutans* , *S. sobrinus S.mitis,S.sangis and Lactobacillus acidophillus* .

The occurrence of *mutans streptocooci* and *streptococcus sobrinus* together makes the oral environment more conductive to caries/plaque. These cariogenic pathogens utilise dietary sucrose and produce adhesive exopolysaccharides and acids which lead to plaque formation and carious lesions on susceptible tooth surfaces.

Acid production by both *S. mutans* and *S. sobrinus* plays an important role in the pathology of dental caries/plaques.patients undergoing Orthodontic treatment ie.,Fixed orthodontic appliances patients frequently exposed to dental plaues.such plaques are difficult to be removed.the herbal extracts like Acacia catechu willd, Glyczyriza glabra, Achillea millifolium, Aesculus hippocastanum, Anacardium occidentale and Eremophila

Longifolia were found to be effective in eradicating dental plaques caused by acid producing bacteria like streptococcus mutans,streptococcus mitis, streptococcus oralis ,streptococcus sobrinus,streptococcus sanguis and Lactobacillus acidophilus.

Further studies should be carried out to explore the active component present in the plant extract which is found to be responsible for the anti cariogenic and anti bacterial activity. hence our article helps the orthodontist to know about the traditionally active medicinal plants that is highly effective in treating the dental plaques seen in fixed appliance patients. we also suggest that these extracts after undergoing toxicological studies it can be applied in human subjects to treat the dental infections.

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CONFLICT OF INTEREST Nil.

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