Review Article

Natural products in endodontics

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ABSTRACT

يستخدم العلاج/ التداوي بالأعشاب في كافة أنحاء العالم سواء في السابق أو في الوقت الحالي. ازدادت الدراسات في نظام العلاج بالطب البديل في العقود الأخيرة، وفي هذا البحث المراجع من موقع البحث " ميدلاين"، دراسة في استخدام المنتجات الطبيعية في علاج قناة جذر السن. استخدام النباتات الطبية في علاج أقنية جذور الأسنان يتضمن التنظيف وتعقيم قناة الجذر وعلاج داخل/ ما بداخل قناة الجذر بين المواعيد وكذلك في إزالة مواد الحشو. كما أن دراسات أخرى تبين تأثير المواد الطبيعية على لب السن وإصلاح العاج. استخدام هذه المواد الطبيعية ليس مبنياً على دراسات علمية دقيقة، فقد أظهرت اختلافاً في تأثيرها ودائما ما يقارن تأثيرها بتأثير المواد الكيميائية التي تستخدم حالياً كمعايير. النباتات لها قدرة غير محدودة في تصنيع المركبات ذات الروائح العطرية والتي قيّمت احتماليتها العلاجية/ إمكانيتها في العلاج. كما يتعين إجراء مزيد من الدراسات/ البحوث عن فوائد المنتجات الطبيعية، وهذه تتضمن المركبات شبه القلوية و الكومارين والصابُونين وفلافونويد.

Herbal remedies are used throughout the world, either in earlier or in recent times. The number of studies on this alternative therapeutic system increased in the last decades. In this paper, the relevant literature on the use of natural products in root canal therapy is revised from a MEDLINE database search. The uses of medicinal plants in endodontics include cleaning and disinfection of root canals, intracanal medicaments between appointments, sealer cements, and for removal of obturation material. Other studies showed the effect of natural products in pulpal and dentin repair. Their use is anecdotal, and their effectiveness showed to be variable and is always compared to the chemical standards currently being used. Alkaloids, coumarins, saponins, and flavonoids are aromatic substances that are produced by plants and evaluated for their therapeutic potential. Further investigation into benefits of natural products is warranted.

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Endodontic infection is characterized by multiple types of microbial species. It consists mainly of anaerobic bacteria and some facultative bacteria. Teeth with untreated inflamed and infected pulps will lead to periradicular inflammation, which will end up by developing abscess and cellulitis.[1] The goal of endodontic treatment is disinfecting the contaminated root canal system by both mechanical and chemical means, that creates a favorable condition for periradicular healing.[2]

In dentistry in general and endodontic therapy specifically, the number of papers on anecdotal utilization of medicinal plants as antimicrobial therapy has increased over the past few years. There is increasing worldwide interest in the production of high-value chemicals, and pharmaceuticals by green, sustainable processes as an alternative and complement to oil-based processes and in strategic terms engineered biosynthesis of natural products could eventually form a valuable part of an industrial bio-refining operation.[3] The purpose of this review is to evaluate the literature on the use of natural products in root canal therapy.

The literature search used the MEDLINE database without time limit. Reference lists in English language of potentially relevant articles and review articles were also screened. For the search strategy, the following keywords were used: "Plants endodontic", "Natural products endodontic", "Plants dentistry", "Natural products endodontic", "Plants antimicrobial effect", "Natural products antimicrobial effect", "Plants bioactive compounds", "Natural products bioactive compounds".

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Only studies that addressed the use of natural products in Endodontics were included, those used in other dental specialty were excluded. Some articles were categorized as review articles. The papers were screened by one reviewer. The search resulted in a total of 87 articles of which 41 were excluded because they did not correspond with the inclusion criteria.

Forty-six articles were included where they correspond with the inclusion criteria. The use of natural products in endodontics include cleaning and disinfection, sealer cements to lubricate and assist in bonding of Gutta-percha obturation material, removal of obturation material through softening and dissolving it, removal of smear layer, storage media for avulsed teeth, and pulp and dentin repair. **Table 1** summarizes the utilization and effectiveness of herbs in endodontic therapy included in this review.

Cleaning and disinfection. Natural products have been used in cleaning and disinfecting root canals either as intracanal medicaments or as irrigants. Potent antibacterial properties against *Enterococcus faecalis (E.faecalis)*, *Streptococcus mutans, Actinomyces viscosus,* and *Streptococcus sanguis* were observed when liquorice ethanolic extract (*Glycyrrhiza glabra*) was used.[4] Furthermore, Miswak extract from *Salvadora persica*, showed antimicrobial effect against several oral microorganisms.[5] Also it demonstrated effective antibacterial action on *Streptococcus salivarius, Streptococcus sanguis, Lactobacillus vulgaris,* and *Candida albicans*, and *E.faecalis*.[6,7] Moreover, derivatives of *Salvadora persica* miswak demonstrated strong antimicrobial effects on the growth of Streptococcus species and Staphylococcus aureus.[8] Essential oil of *L.sidoides* (The second largest genus of the family Verbenaceae that are found in South America (approximately 70–75% of the known species are in Brazil), Central America, and tropical Africa) reduced colony-forming units in biofilms of *E. faecalis* in vitro with an exposure time of 30 and 60 minutes at concentrations of 2.5 and 10%.[9] The antimicrobial activity of methanolic extract of Azadirachta indica (*Neem*), Ocimum sanctum (*Tulsi*), Mimusops elelngi (Bakul), and Tinospora cardifolia (*Giloy*) was evaluated against *Streptococcus mutans*, *Enterococcus faecalis* and *Staphylococcus aureus*. All the plants' extracts showed considerable antimicrobial activity.[10] Moreover, *Morinda citrifolia juice* 'Triphala' (it consists of dried and powdered fruits of 3 medicinal plants: *Terminalia bellerica*, *Terminalia chebula,* and *Emblica officinalis*, and considered an Indian ayurvedic herbal formulation), green tea polyphenols, and propolis were studied and showed antibacterial effect against *E.faecalis* biofilm when used as irrigants.[11] Propolis, which is a resinous hive product collected by honey bees from plants, exhibited antimicrobial action against *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis*, and *Enterococcal* species of human and animal origin.[12] Another study evaluated, in vivo, the antimicrobial and inflammatory ability of 4% Dimethyl Sulfoxide (DMSO) extract of propolis against endodontic aerobic and anaerobic bacteria, and compared to 2% chlorhexidine, 4% calcium hydroxide. Chlorhexidine proved to have the highest antimicrobial effect, followed by propolis, then Calcium hydroxide.[13] Furthermore, propolis, morinda citrifolia juice (MCJ), and Azadirachta indica (Neem) were investigated for their potential to disinfect candida albicans-infected root canals. Results showed that propolis and Azadirachta indica (Neem) have effective antifungal activity, however, MCJ had limited antifungal activity.[14]

The antimicrobial activity of ethyl acetate extract of Arctium lappa plants (Flowering plant of the Arctium family) was compared to calcium hydroxide against mixed bacterial suspension of P*seudomonas aeruginosa*, *Escherichia coli*, *Lactobacillus acidophilus*, *Streptococcus mutans* and *Candida albicans* that were inoculated in vitro. No growth of bacteria was found at 14 and 30 day.[15] *Uncaria tomentosa* (Willd.) (Medicinal Amazonian herb), at 2% concentration gel, showed effective antimicrobial action against *E.faecalis*, *Staphylococcus aureus*, and *Candida albicans* and that effect increased when it was combined with chlorohexidine.[2] The antimicrobial activity of the aroeira-da-praia (*Schinus terebintifolius Raddi*) and the *quixabeira (Syderoxylum obtusifolium Roem & Schult)* (Both are flowering plants native to tropical south America) hydroalcoholic extracts, when used as irrigation solutions, were evaluated against *E.faecalis* bacteria in vitro. The antimicrobial activity was evaluated by using agar well diffusion method, and the cleaning ability was evaluated by using scanning electron microscope. Both agents were able to eradicate *E.faecalis* bacteria, but none of them was able to remove the smear layer in the different thirds of the root canal.[16] The antibacterial activity of the hydroalcoholic extract of *Rosmarinus officinalis plant* (Rosemary) against *E.faecalis*, and its ability for disinfecting gutta-percha cones contaminated with the same bacteria was evaluated. In the antibacterial experiment, the disc diffusion method was used. In the disinfection experiment, the plant extract was compared to the disinfection ability of 2% CHX and 2.5% NaOCl for 5-minutes treatment. The results showed that the hydroalcoholic extract of *Rosmarinus officinalis* showed a bactericidal effect against *E.faecalis*, and the ability to disinfect the gutta-percha cones with no significant difference between the other 2 disinfectant solutions.[17]

Table 1 - Utilization and effectiveness of herbs in endodontic therapy.

Context of use of herb in endodontics	Effective in/against	Reference
Cleaning & disinfection (root canal medicament)		
Liquorice extract	-*E.faecalis* -*Streptococcus mutans*	Sedighinia et al 2012[4]
Propolis	-*Candida albicans*	Tyagi et al 2013[14]
Morinda citrifolia	-*Candida albicans*	Tyagi et al 2013[14]
Ethyl acetate extract of Arctium lappa plants	-*Pseudomonas aeruginosa* -*Escherichia coli* -*Lactobacillus acidophilus* -*Streptococcus mutans* -*Candida albicans*	Karygianni et al 2014[15]
Cleaning & disinfection (irrigant)		
Miswak extract from *Salvadora persica*	-*Streptococcus salivarius* -*Streptococcus sanguis* -*Lactobacillus vulgaris* -*Candida albicans* -*E.faecalis*	Moeintaghavi et al 2012[6] Al-Azzawi et al 2015[7] Halawany 2012[8]
Essential oil of *L.sidoides* (the family Verbenaceae)	-*E.faecalis*	Veras et al 2014[9]
Methanolic extract of *Azadirachta indica (Neem)*, *Ocimum sanctum (Tulsi)*, *Mimusops elelngi (Bakul)*, and *Tinospora cardifolia (Giloy)*	-*Streptococcus mutans* -*Staphylococcus aureus* -*E.faecalis*	Mistry et al 2014[10]
Morinda citrifolia juice from *Terminalia bellerica, Terminalia chebula*, and *Emblica officinalis* plants	-*E.faecalis biofilm*	
Green tea polyphenols	-*E.faecalis biofilm*	Garg et al 2014[11]
Propolis	-*Streptococcus pneumonia* -*Haemophilus influenza* -*Moraxella catarrhalis* -*Enterococcal species* -Mixed aerobic and anaerobic bacteria	Garg et al 2014[11] Moncla et al 2012[12] Jolly et al 2014[13]
Hydroalcoholic extract of *Aroeira-da-praia (Schinus terebintifolius Raddi)* and the *quixabeira (Syderoxylum obtusifolium Roem & Schult*	-*E.faecalis*	
Hydroalcoholic extract of *Rosmarinus officinalis* plant (Rosemary)	-*E.faecalis*	Costa et al 2012[16]
Berberine	-Multispecies biofilm: *F.nucleatum, E.faecalis,* and *Prevotella intermedia*	
Aqueous ethanolic extracts of *Ocimum sanctum, Cinnamomum zeylanicum,* and *Syzygium aromaticum*	-Planktonic and biofilm forms of *E.faecalis*	Brito-Júnior et al 2012[17] Xie et al 2012[18]
Extracts of *Ipomoea alba, Symphonia globulifera, Moronobea coccinea, Connarus ruber var. ruber, Psidium densicomum,* and *Stryphnodendron pulcherrimum*	-*E.faecalis* biofilm	Gupta et al 2013[19]
Methanolic extracts of *Azadirachta indica (Neem)* and *Mimusops elengi (Bakul)*	-Multispecies biofilm of *streptococcus mutans, E.faecalis, staphylococcus aureus* and *candida albicans*	de Castilho et al. 2013[20]
Azadirachta indica *(Neem)*	-*E.faecalis* -*Candida albicans*	
Aqueous and alcohol extracts) of passion fruit juice (PFJ)	-*E.faecalis*	Mistry et al 2015[21] Dutta et al 2013[22] Jayahari et al 2014[23]
Pulp and dentin repair		
Baicalein	Stimulated and promoted: *The odontoblastic differentiation of HDPCs *The angiogenesis of HDPCs *Mineralization and alkaline phosphatase (ALP) activity *Angiogenic factors *Morphogenetic protein (BMP).	Lee et al 2016[24]
Genipin	Increased: *Alkaline phosphatase activity *The expression of odontogenic markers *The mineralized nodule formation	Kwon et al 2015[25]

Table 1 - Utilization and effectiveness of herbs in endodontic therapy (continued).

Context of use of herb in endodontics	Effective in/against	Reference
Pulp and dentin repair		
Nigella Sativa (NS) oil	-Possesses anti-inflammatory effect -The pulp maintains its vitality after its application.	Omar et al 2012[26]
Smear layer removal		
Chitosan (natural polysaccharide)	-Removed the smear layer from the middle and apical thirds of the root canal using SEM	Silva et al 2012[27]
Apple vinegar	-Effective in removing smear layer when used as irrigant using SEM	Candeiro et al 2011[49]
Sealer cements		
Hinokitiol-modified calcium silicate	-Suitable setting time -Suitable solubility -Antimicrobial synergistic effect -Active ability of odontoblastic differentiation of hDPCs	Huang et al 2016[29]
Storage media for avulsed teeth		
Aloe Vera	-Maintained the viability of human periodontal ligament cells	Badakhshh et al 2014[30]
Coconut water	-Maintained viable periodontal ligament (PDL) cells after exposure of PDL cells to up to 45 minutes dry storage	Al-Haj Ali et al 2013[31]
Thai propolis extract	-Thai propolis (2.5 mg ml^{-1}) was the most effective dose for preserving the viability of PDL cells	Prueksakorn et al 2016[32]
Solvents		
Grapefruit, tangerine, lime, and lemon oils	-Effective in dissolving gutta-percha -Grapefruit oil and tangerine oil > lime oil and lemon oil	Jantarat et al 2013[33]
Orange oil	-Effective in removing 3 different root canal sealers (AH Plus, Apexit Plus and Endoflas FS)	Mushtaq et al 2012[34]
Eucalyptus oil, orange oil, and clove oil	-Effective in dissolving resin-coated Gutta-percha (RCGP) -Orange oil was the most effective	Kulkarni et al 2017[35]

NS - Nigella Sativa, RCGP - Resin-coated Gutta-percha, SEM - Scanning Electron Microscope, HDPCs - Human Dental Pulp Cells, BMP - Bone Morphogenetic Proteins, ALP - Alkaline Phosphotase Proteins, HDPCs - Human Dental Pulp Cells, PFJ - Passion Fruit Juice, FS - Endoflas FS (It is a brand name)), PDL - Periodontal Ligament

The antimicrobial ability of berberine (A plant alkaloid isolated from many medicinal plants) solution was evaluated against multispecies biofilm that consisted of *F.nucleatum, E.faecalis*, and Prevotella intermedia using tooth models and bacterial sampling method. The results revealed that all tested solutions reduced bacteria significantly when compared with the saline control. When berberine (2 mg/mL) was combined with 1% CHX, it had a comparable bactericidal activity to 5.25% NaOCl, 2% CHX, and 1% CHX. However, when it was used alone, it was less effective than the other test irrigants.[18] Different concentrations of aqueous ethanolic extracts of *Ocimum sanctum*, *Cinnamomum zeylanicum*, and *Syzygium aromaticum* against *E.faecalis* were assessed for their antibacterial efficacy at various time intervals. The agar well diffusion test, microdilution test, and biofilm susceptibility assay (BSA) on cellulose nitrate membrane as well as in a tooth model were used. The results showed that these natural plants demonstrated antimicrobial activity against planktonic and biofilm forms of *E.faecalis*.[19] Group from Brazil obtained extracts from *Ipomoea alba*, *Symphonia globulifera*, *Moronobea coccinea*, *Connarus ruber var. ruber*, *Psidium densicomum*, and *Stryphnodendron pulcherrimum*. These plant's extracts showed significant bactericidal activity against *E.faecalis* biofilm.[20] Mistry et al[21] checked the antimicrobial activity of methanolic extracts of *Azadirachta indica (Neem)* and *Mimusops elengi (Bakul)* on multispecies biofilm of *streptococcus mutans, enterococcus faecalis, staphylococcus aureus* and *candida albicans*, by using *in vitro* dentin disinfection model.[21] Saline was used as a negative control, and 2% chlorohexidine was used as positive control. Both plant extracts were effective as antimicrobial agents when compared to negative control.[21] Another study evaluated the efficacy of 5 irrigants formulated from different parts of the tree *Azadirachta indica (Neem)* against candida albicans and enterococcus faecalis, and compared with 2.5% sodium hypochlorite and 0.2% chlorhexidine gluconate through an agar diffusion test. The results showed that the leaf extract of the tree and the seed-bark powder dissolved in dimethyl sulfoxide

were effective against both organisms. Moreover, the leaf extract had larger inhibition zones than chlorhexidine.[22] Jayahari et al investigated the antimicrobial ability of several concentrations of 2 forms (aqueous and alcohol extracts) of passion fruit juice (PFJ) against enterococcus faecalis and compare it to that of sodium hypochlorite (NaOCl) when used as intracanal irrigant.[23] Broth dilution test was used for nine different time periods after determining the concentrations of both extracts through the minimum inhibitory concentration (MIC) test. The MIC test showed that *E.faealis* was sensitive to PFJ extracts at various concentrations. The results of the broth dilution test showed a negative growth of *E.faecalis* by 20% PFJ alcohol extracts at 30 minutes, 20% PFJ aqueous extracts at 1 hour, 2.5% NaOCl at 10 minutes, and 5.25% NaOCl at 1 minute. They concluded that PFJ aqueous and alcohol extract showed promising results as antimicrobial agents.

Pulpal and dentin repair. A group of investigators studied the osteoblastic and angiogenic potential of baicalein, which is considered a flavonoid that is extracted from the root of *Scutellaria baicalensis* plant, when used on human dental pulp cells (HDPCs). Results showed that baicalein (1-10 µM) stimulated the odontoblastic differentiation and angiogenesis of HDPCs by promoting mineralization and alkaline phosphatase (ALP) activity, angiogenic factors, and morphogenetic protein (BMP). It was concluded that baicalein might play a useful role in dental pulp repair.[24] Genipin, is a chemical compound found in gardenia fruit extract, was investigated regarding its odontogenic differentiation ability on human dental pulp cells (hDPCs). Results showed that genipin increased alkaline phosphatase activity, the expression of odontogenic markers, and mineralized nodule formation which suggested the ability of genipin to induce the odontogenic differentiation of hDPCs.[25] Omar et al investigated histo-pathologically the pulp response to Nigella Sativa (NS) oil, which is an annual flowering plant in the family of Ranunculaceae, native to south and southwest Asia, and compared it to that of formocresol.[26] Both materials are used as pulpotomy medicaments in forty premolar teeth of 4 male dogs. The animals were sacrificed 4 weeks after treatment. Specimens in the NS group exhibited mild to moderate vasodilatation. Few specimens showed inflammatory cell infiltration and continuous odontoblastic layer. They concluded that NS possesses anti-inflammatory effect and its ability to maintain pulp vitality.

Smear layer removal. The ability of 0.2% chitosan, which is a natural polysaccharide, to remove the smear layer was evaluated using the scanning electron microscope (SEM), *in vitro*. The results showed that it was efficient in removing the smear layer from the middle and apical thirds of the root canal.[27] Oregano extract solution (OES) was evaluated for its ability in removing the smear layer on 180 human maxillary central incisors. Results showed that different concentrations of OES (5% and 2%) was not able to completely remove the smear layer alone, but when it is combined with 17% ethylenediaminetetraacetic acid (EDTA) the smear layer was removed without dentin erosion.[28]

Sealer cements. Calcium silicate (CS) cement was modified by the addition of the hinokitiol material (which is a natural material found in the wood of trees in the family of Cupressaceae). Hinokitiol-modified calcium silicate (CS) cement was examined for its physical characteristics by investigating its setting time and diametral tensile strength. Also its antimicrobial effect, the expression levels of cyclooxygenase 2 (COX-2) and interleukin-1 were examined. Then its odontogenesis potential was studied by investigating the markers of odontoblastic differentiation, mineralized nodule formation, and calcium deposition of human dental pulp cells. Results showed that Hinokitiol-modified calcium silicate (CS) cement can be clinically effective by having suitable setting time and solubility, also hinokitiol had antimicrobial synergistic effect. Moreover, it had active ability of odontoblastic differentiation of hDPCs.[29]

Storage medium. The ability of Aloe Vera (10%, 30%, and 50% concentration) to maintain the viability of human periodontal ligament cells, when used as a storage medium for avulsed teeth for 1, 3, 6, 12, and 9 hours, was evaluated and compared to that of cell culture media. The results indicated that the ability of aloe vera to maintain human periodontal cells viability is similar to that of cell culture media.[30] The potential of coconut water to maintain viable periodontal ligament (PDL) cells after being exposed to dry storage up to 120 minutes was studied. The results showed that avulsed teeth, which have been left dry for more than 45 minutes, soaked in mature coconut water for 45 minutes in mature coconut water could be beneficial.[31] Prueksakorn et al[32] examined the preservative and proliferative effects of Thai propolis extract. Their results exhibited that 2.5 mg ml-1 of Thai propolis was the appropriate dose for preserving the viability of PDL cells, and it was comparable to Hanks Balanced Salt Solution (HBSS).

Solvents. The ability of grapefruit, tangerine, lime, and lemon oils as solvents for softening gutta-percha

in root canal retreatment procedures was investigated, and compared to chloroform. Eighty-four cylinder-shaped glass tubes were filled with gutta-percha, and the surface-dissolving depth and the maximum force used to penetrate the spreader to 5mm were measured. The results showed that chloroform was significantly the best solvent in softening gutta-percha, followed by grapefruit oil and tangerine oil, then lime oil and lemon oil.[33] Moreover, the efficacy of orange oil in removing 3 different root canal sealers (AH Plus, Apexit Plus, and Endoflas FS) was examined and compared to xylene and tetrachloroethylene. Xylene showed the greatest dissolving efficacy for AH Plus, followed by orange oil and tetrachloroethylene. The same results were found with Apexit Plus sealer, except that orange oil and tetrachloroethylene were equally effective in dissolving Apexit Plus. In contrast, tetrachloroethylene showed the maximum dissolving ability for Endoflas FS, followed by orange oil and xylene.[34] The capability of eucalyptus oil, orange oil, and clove oil in dissolving resin-coated Gutta-percha (RCGP) cones were compared. Orange oil was the most effective solvent of EndoREZ RCGP and conventional GP among all tested solvents.[35]

There has been an expanded universal concern in traditional medicine, and there are attempts to control and regulate herbal drugs. However, the literature on the use of medicinal drugs in root canal therapy is limited. Plants have the capability to synthesize aromatic substances that have been evaluated for their therapeutic ability. The secondary plant metabolites defined as bioactive compounds in plants that exhibit pharmacological or toxicological effects in humans and animals.[36] Such secondary compounds are phenols, flavonoids, coumarins, alkaloids, terpenoids, resins, and steroids. Several studies investigated the antimicrobial effect of these bioactive compounds against several microorganisms, and they showed effective actions.[37,38] The natural products have been investigated in other dental specialties rather than endodontics. In oral medicine, the effect of 1% curcumin gel and aloe vera was investigated in the treatment of oral *Lichen planus*.[39,40] In periodontics, Miswak extract from Salvadora persica was evaluated in its ability to improve the gingival health.[41] Black currant extract was suggested to treat smoking-related periodontal diseases.[42] Neem extract showed improvement in the treatment of chronic periodontitis.[43,44] In caries control researches, the antibacterial effect of herbal lollipop containing licorice root (From the root of Glycyrrhiza glabra plant) was investigated against *Streptococcus mutans*.[45] Propolis had an effective antimicrobial action against investigated bacteria, and it was also effective in decreasing dental caries in the rat model system.[46] In operative dentistry, theobromine, which is the principle xanthine species in *Theobroma cacao* (Cacao tree), protected the enamel surface in a dose-related manner.[47] Powdered grape seed extract, rich in proanthocyanidins (PA) (Which are natural collagen crosslinker) improved the bond strength of water/ethanol-based adhesive.[48]

In conclusion, the use of plants has a long heritage in dentistry and studies have been ongoing to find further natural solutions to existing problems.

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