



## Review article

# Exploring the therapeutic potential of medicinal plants and their active principles in dental care: A comprehensive review

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## ARTICLE INFO

**Keywords:**

Oral diseases  
Herbal therapy  
Dental caries  
Antimicrobial  
Halitosis

## ABSTRACT

Since the human population realized how important it was to maintain overall health and the weight of disease, they have been looking for therapeutic qualities in natural environments. The use of plants having medicinal qualities for the treatment and prevention of illnesses that may have an impact on general health is known as herbal medicine. There has been a noticeable increase in interest lately in the combination of synthetic contemporary medications and traditional herbal remedies. About 80 % of people rely on it for healthcare, particularly in developing nations. One important aspect of overall health is said to be oral healthcare. The World Health Organization views oral health as a crucial component of overall health and well-being. Because they are more readily available, less expensive, and have fewer adverse effects than pharmaceutical treatments, using natural medicines to treat pathologic oro-dental disorders can make sense. The current evaluation of the literature sought to investigate the range and scope of the use of herbal products and their secondary metabolites in maintaining oral health, encompassing several oral healthcare domains such as halitosis, gingivitis, periodontitis, and other oral disorders. Therefore, there are many herbs discussed in this work and their mechanism in the treatment and improvement of many oral ailments. Besides, compounds that are useful in oral treatment with their natural sources and the cases where they can be used. To prevent any possible side effects or drug interactions, a doctor's consultation is necessary before using dental medicine. Although herbal therapy is safe and with minimum side effects, it is also strongly advised to do a more thorough preclinical and clinical evaluation before using herbal medicines officially.

## 1. Introduction

Dental health is crucial for general health and well-being, facilitating essential daily functions. Expanding upon preexisting definitions, oral health can be described as multifaceted, including physical, psychological, emotional, and social aspects that are crucial to an individual's entire health and wellness [1,2]. Oral disorders are among the most common pathologies in the world and have spread rapidly, becoming a true worldwide epidemic in recent years [3].

In 2022, the World Health Organization estimated that oral diseases affect nearly 3.5 billion people worldwide. Dental caries, periodontal disease, tooth loss, and malignancies of the lips and oral cavity are the most common and serious oral disorders worldwide

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[4].

A variety of diseases and disorders summarized in Figure (1), including craniofacial disorders, congenital defects, traumas, and infections, affect the soft and hard tissues of the mouth [3]. These disorders include dental caries, abscesses, erosion, attrition, and periodontal illnesses. Tooth caries is a complicated, dynamic, biofilm-mediated disease that causes phasic demineralization and remineralization of tooth hard tissues. Caries can affect the tooth crown and exposed root surfaces in later life, and it can happen at any age in both primary and permanent dentitions [5]. The patient's systemic health, economic level, lifestyle choices, age, gender, ethnic background, genetics, environmental elements, and immune response all influence the disease's progression in addition to local factors like calculus and plaque [6]. If periodontal disease is not treated, the patient may become more susceptible to other systemic illnesses. These conditions include respiratory tract infections, pneumonia, oral and colon cancer, Alzheimer's disease, cardiovascular disease, digestive disorders, insulin resistance, diabetes, and poor pregnancy outcomes [7].

As a result, the various chemical and synthetic agents employed to maintain oral hygiene have quite different approaches to the prevention and treatment of these oral disorders. Sadly, they have several drawbacks, such as changing the oral microbiota, discoloring teeth, not being very cost-effective, and increasing pathogenic bacteria resistance to them. As a result, it is necessary to find alternative therapeutic and preventive measures to maintain oral hygiene [8].

Herbal extracts and their derivatives provide an affordable, safe, and biocompatible substitute for synthetic drugs in the treatment of oral problems [9]. This is matched with the international trend as stated by the World Health Organization, over 75 % of people worldwide rely on herbal plants for their main healthcare requirements due to their exciting physicochemical and medicinal properties. In the treatment of oral disorders, herbal therapy can be utilized as an antibacterial, anti-inflammatory, astringent, anesthetic, and anti-cariogenic medicine [10].

In dentistry, herbal therapy is used in different departments such as oral medicine, periodontology, oral surgery, and prosthodontics where various herbal products in different formulations are used to treat various dental problems [11]. A wide range of medicinal plants and herbs, including myrrh, bloodroot, caraway, chamomile, rosemary, thyme, aloe vera, propolis, neem, and peppermint, are used as mouthwashes, dentifrices, intracanal medications, and irrigants. These herbs have anti-inflammatory, anti-bacterial, and anti-fungal properties [12].

Recently, herbs and their extracts have been used successfully as mouth rinses to prevent biofilm formation, dentifrices, demineralizing agents, periodontitis treatment, intracanal irritants, medications for critical pulp therapy procedures, and precancerous lesion treatment [13]. It has been demonstrated that the green synthesis of metal nanoparticles, such as silver, gold, and copper nanoparticles, manufacturing organic toothpaste that are more compatible with the oral cavity using extracts from medicinal plants is beneficial in treating a range of oral and dental conditions, even surpassing the usage of traditional materials [14,15]. Additionally,

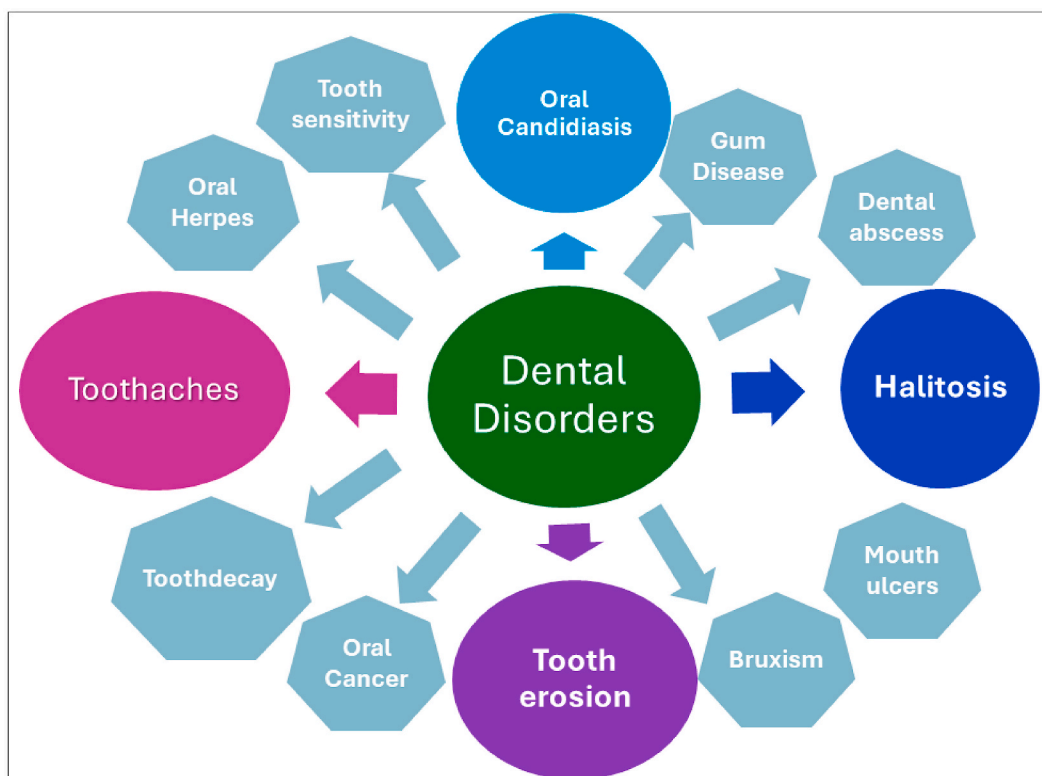


Fig. (1). Common Dental Diseases treated by herbal formulations.

natural products, which make up dental polymers, are known to possess favorable qualities such as being readily available, changing chemically, being biodegradable, and being biocompatible. These attributes make them highly appealing in the fields of periodontology, prosthodontics, caries management, and the regeneration and reconstruction of oral tissues [16,17].

Reliability, affordability, and lack of side effects make natural medications a more sensible choice when treating pathologic oral problems than pharmaceutical ones. The goal of the current literature assessment was to find out how herbal products are used in various oral healthcare domains, including gingivitis, halitosis, periodontitis, and other oral disorders.

In this review, we will discuss the different dental disorders and focus on the value of medicinal herbs that may be used on teeth to perform various restorative and curative effects. On the other hand, the delivery mode for the administration of the herbs or their active principles with their mechanism in treating different oral diseases. Potential uses of natural ingredients in dental care have been identified thanks to pre-clinical research. As a result, they are crucial to the growth of the fields of study for herbal dentistry. This review mentions a few of these lab workups to compile a database of pertinent literature for every subject. Concerning clinical ramifications, these therapeutic alternatives are typically employed in dentistry as substitute therapies. Nonetheless, several clinical research assessed their effectiveness and produced encouraging outcomes. Many practitioners have been inspired by this finding to incorporate herbal medications into their regular clinical practice.

## 2. Common dental diseases

### 2.1. Oral candidiasis

The most prevalent fungal infection among people is oral candidiasis, particularly in early and later life [18]. Fungal overgrowth and superficial tissue invasion are the hallmarks of oral candidiasis, sometimes known as "thrush," which includes tongue infections, and other oral mucosal locations. The main cause, *Candida albicans*, is a common opportunistic fungal pathogen that commonly causes superficial infections of the oral mucosal surfaces of vulnerable people. *Candida albicans* is a normal commensal of the mouth and usually causes no problems in healthy people. The primary factor that determines the kind of interaction the Candidate has with its host is the way it engages with the epithelial surface it invades. There's no denying that the host's immunological response and the potentially harmful consequences of *Candida* virulence factors are delicately balanced. *Candida* frequently appears to switch from a commensal to a pathogenic life due to changes in host characteristics [19]. It affects many elderly people, especially those who wear dentures and is frequently preventable with proper oral hygiene practices. Furthermore, it is a common problem among those with impaired immune systems and may indicate systemic conditions such as *diabetes mellitus* [20].

On the other hand, an overgrowth of *Candida* can cause dysphagia due to esophageal overgrowth, which can result in inadequate nutrition, a delayed recovery, and an extended hospital stay. It can also cause local discomfort and change taste perception. Infections can spread through the upper gastrointestinal tract or bloodstream in immunocompromised patients, resulting in severe infections that have a high morbidity and death rate [20].

### 2.2. Oral cancers

The mucosa that lines the cheeks, lips, teeth, floor of the mouth, gums, anterior two-thirds of the tongue, hard palate, and retromolar trigone posterior to the wisdom teeth are the primary sites of origin for oral mucosa cancer [21].

The most prevalent kind of cancer in the mouth is squamous cell carcinoma. Tobacco use, chewing areca nuts, and alcohol usage are the main risk factors for oral malignancies [22]. Human papillomavirus infection is the primary cause of the sharp increase in young people's oropharyngeal cancer incidence in several high-income communities [23].

Oral cancer is more common in men, the elderly, and people from low-income families, with socioeconomic disparities reported both between and within different countries [24]. South Asia, the Pacific regions, Latin America, and sections of central and eastern Europe are among the places with the highest incidence [25]. Prevention of this terrible disease can be achieved through fundamental socioeconomic reforms as well as demand-reduction measures [26].

### 2.3. Mouth ulcers

Oral ulcers typically cause extreme pain and necessitate medical attention. Among its causes are lesions from trauma, immunological diseases, gastrointestinal problems, rheumatic diseases, blood disorders, infectious processes, and other conditions [27]. Although uncommon in developed nations, oral ulcers caused by *Mycobacterium tuberculosis* and *Treponema pallidum* infections are becoming more common in individuals with HIV/AIDS or those who are particularly at risk for the disease. HIV/AIDS patients may also develop fungal, viral (mostly *Herpes* viruses), lymphoma, or Kaposi's sarcoma ulcers [28].

The primary lesion is not a blister or vesicle; rather, it is direct ulceration caused by epithelial necrosis that extends into the basement membrane, exposing nerve terminals and producing pain or discomfort [27]. When they heal, they may leave a scar if they are large. Clinically, they appear as painful ulcerations with clean edges that can be round or oval. The necrotic fundus is surrounded by a border or red halo of hyperemic origin and tends to relapse. It is covered in a yellowish-white fibrinous exudate [29].

Aphthoid ulcers are secondary lesions, infectious ulcers that start with vesicles or vesicular pustules. They differ from canker sores in both clinical and histological aspects. Other aphthoid ulcers are trauma-related, developing acutely or chronically in response to frequent mucosal damage. Some are chronic and recurrent (for example, herpetic stomatitis) [30].

## 2.4. Periodontal diseases

Periodontal diseases, sometimes referred to as chronic inflammatory illnesses, affect the tissues that support and surround teeth. The first sign of periodontal disease is gingivitis, a reversible inflammation of the periodontal soft tissues that results in gingival bleeding and swelling. Gingivitis may progress to periodontitis in vulnerable people with weakened immune systems, which gradually destroys the bone that surrounds the teeth and the periodontal tissue support. Periodontitis is characterized by a loss of periodontal tissue support, which manifests periodontal pocketing, gingival bleeding, and radiographically shown alveolar bone loss [31].

Although it may happen in children and teenagers as well, periodontitis is more frequent in adults. Tissue loss is often correlated with host defenses, dental plaque levels, and other risk factors. In 10–15 % of the world's population, advanced periodontitis results in considerable tooth loss and severe loss of supporting tissues [32]. This estimated prevalence range covers both severe aggressive periodontitis and severe chronic periodontitis [33].

Poor oral hygiene that results in the buildup of pathogenic microbial biofilm (plaque) at and below the gingival edge is the primary cause of periodontal disease [34]. Bleeding during brushing is the first sign of gingivitis; pain is rarely mentioned. The destruction of the tooth's supporting structures (alveolar bones and ligaments), recession of the marginal gingiva (which exposes the root), increased tooth mobility and drifting, bleeding of the gingival pocket area on probing, and increased depth of the periodontal pocket (detected by a narrow-diameter probe) are among the clinical features of chronic periodontitis. Acute exacerbations resulting from abscesses or tooth dislodgment due to deteriorating dental support can cause pain. However, most cases of periodontal disease are painless, and before treatment is initiated, the disease frequently reaches severe stages of severity [35].

## 2.5. Dental caries

The progressive deterioration of the crown and root tissues as a result of microbial activity is the hallmark of dental caries, a multifactorial infectious and transmissible disease. *Streptococcus mutans* is the principal pathogen. Cariogenic oral flora, or biofilm, interacts intricately with fermenting dietary carbohydrates over time to cause caries. Nonetheless, a person's likelihood of developing caries will depend on a number of factors, including their immune system, genetic predisposition, diet, tooth structure, biofilm (or dental plaque), pH, oral hygiene, and social standing. Lactic acid is a byproduct of the bacteria in biofilm breaking down carbohydrates into sugars for energy. This eventually causes the pH of plaque to drop to dangerously low levels (below 5.5), which starts the demineralization process, which removes calcium and phosphate from dental structures and results in cavities [36].

## 2.6. Toothache

The most frequent cause of mouth pain is toothache. Most dental pain is localized, acute, and unilateral in the mouth. It can manifest as swelling and be made worse by osmotic or thermal stimuli, as well as biting [37]. A toothache is defined as a pain inside or near a tooth. On the other hand, pain is an unpleasant feeling that can range from minor discomfort to severe distress created by actual or possible tissue damage.

Antibiotics are only administered in addition to final treatment when there are systemic signs of infection, the illness spreads quickly, or the patient is immunocompromised. Antibiotics used to treat odontogenic infections include phenoxymethylpenicillin or amoxicillin, amoxicillin with metronidazole, and amoxicillin with clavulanate or Clindamycin [38]. Prophylactic antibiotics are now only recommended before dental treatments linked with a high risk of bacteraemia [39].

## 2.7. Bruxism (tooth grinding)

A parafunctional behaviour that occurs during the day or night and involves teeth clenching, gnashing, bracing, and grinding is called bruxism. Bruxism is defined as the consciousness of the jaw clenching in waking persons.

Chronic bruxism has several consequences, including a sore jaw, face pain, annoying one's sleeping partner, exposing the inner layers of teeth owing to enamel erosion, tooth loss, hearing loss, and temporomandibular joint illness. While this widespread sleep problem is believed to have a complicated etiology, many persons have reported psychological explanations. Bruxism appears to be more acute at periods of intense tension and concern [40].

## 2.8. Sensitivity of teeth

Dental hypersensitivity is a chronic dental ailment that can last from a few days to a few months. It can develop gradually and manifest for a variety of reasons. It is most common in adults between the ages of 20 and 50, but it can affect anyone younger or older. External triggers or stimuli, such as hot or cold, extremely sweet, or sour food and beverages, or a sudden rush of air spray, stimulate the nerves inside the tooth once a layer of dentin is exposed to the environment and the structural integrity resulting in an immediate short-sharp sensation. Dentin hypersensitivity is the term used when this phenomenon cannot be linked to another particular or evident dental condition [41].

## 2.9. Attrition, abrasion, and erosion in teeth wear

Tooth wear is the total surface loss of the mineralized tooth material as a result of chemophysical or physical processes (dental

erosion, attrition, abrasion). Dental caries, resorption, or trauma are not thought to be the cause of tooth wear. Tooth wear with dental erosion as the main etiological aspect is referred to as erosive tooth wear. While the chemical loss of mineralized tooth material brought on by exposure to acids that are not produced by oral microorganisms is known as dental erosion. The physical loss of mineralized tooth material brought on by tooth-to-tooth contact is known as dental attrition. While the physical loss of mineralized tooth substance brought on by non-tooth-related things is known as dental abrasion. Accurate diagnosis and understanding of etiological variables are required for successful therapy [42].

### 2.10. Halitosis

Halitosis is a word derived from the Latin "halitus" (breath) and Greek "osis" (pathological process) that refers to an unpleasant odor from the mouth, sometimes known as "bad breath." Understandably, it is a severe problem for the patient because it may cause social humiliation, leading to reclusiveness or, in some cases, stigma. It is infrequently detected by a dental practitioner or primary care physician during a regular checkup, and the patient may be unaware. As social awareness of oral hygiene develops, more people seek medical attention to manage this unpleasant disease [43,44]. This disease is caused by volatile molecules (such as sulfur compounds, aromatic compounds, and nitrogen-containing compounds), which can be created by pathogenic or non-pathological sources [45].

Treatment is best accomplished with tongue scrapers rather than toothbrushes. Flossing teeth helps prevent halitosis by removing plaque and food particles from interdental spaces [46]. One study found that tea tree oil can successfully prevent malodor caused by the bacteria *Solobacterium moorei* strain [47]. Masking substances such as mint or fluoride in toothpaste or flavored chewing gum can be helpful, but they only provide a temporary solution. It is encouraged to make lifestyle changes such as quitting smoking, tobacco, and alcohol, as well as reducing the number of onions, garlic, and spices consumed [48].

### 2.11. Dental abscess

Oral decay, trauma, and poor oral care are the most common causes of dental abscesses. Breakdown in the protective enamel of teeth allows oropharyngeal bacteria to enter the tooth cavity, resulting in a local infection. As the infection spreads in the pulp cavity, it compresses the inner dentin walls and causes extreme discomfort [49]. Depending on where the infected tooth is located, the infection travels down the root canal and into the mandible or the maxilla. Another parameter that predisposes people to dental abscesses is a partly erupted tooth, usually a wisdom tooth, in which bacteria become trapped between the crown and soft tissues, irritating. Other causes include hereditary factors like amelogenesis imperfect, which predisposes people to weaker enamel that is more prone to wear [50,51].

### 2.12. Oral cavity flora

Many bacteria live in the mouth, the majority of which are gram-negative and facultative anaerobes. *Streptococcus mitis* is commonly found on tooth surfaces, but its distribution varies throughout the oral cavity. This is not always the causal organism in a dental abscess, as other oral bacterial species can enter the tooth through many mechanisms, including but not limited to trauma [52].

The treatment consists of draining the abscess, administering antibiotics, managing discomfort, and removing the infectious tooth source. Often, oral antibiotics combined with a prompt dentist appointment for dental treatment intervention are sufficient. Dental abscesses may not necessitate hospitalization or the administration of intravenous antibiotics until the patient exhibits alarming symptoms such as dyspnea, fever, or airway compromise due to swelling. Antibiotics can be used to treat most dental abscesses, including those caused by gram-negative, facultative, and strictly anaerobic bacteria [52,53].

Penicillin and cephalosporins can be used in odontogenic infections, although antibiotic resistance is rising due to  $\beta$ -lactamase development. Penicillin may be more effective when combined with metronidazole or extended-spectrum antibiotics like ampicillin-sulbactam and ampicillin-clavulanate due to increased resistance [52].

### 2.13. Root canal infection

It is an infection in the inner core of the tooth that affects the root part, usually because of decay, gum disease, or trauma. This sort of infection can cause severe pain and discomfort, and if not treated, it can lead to tooth loss. Root canal infections are caused by bacteria that have penetrated the dental pulp and colonized the root canal system. Inflammatory responses are brought on by bacterial populations and metabolic byproducts that enter periradicular tissues through apical or lateral foramina. These reactions result in the lysis of both hard and soft periradicular tissues, mostly as a result of the recruitment of osteoclasts and immune cell proteolytic activity (mast cells, neutrophils, and macrophages) [54]. This eventually generates a bone cavity filled with cellular debris, cholesterol crystals, osteoclasts, fibroblasts, and varying proportions of immune cells, depending on the severity of inflammation [55].

There are numerous potential routes for pathogens to enter the root canal system, the most prevalent of which is dental caries. Other common sources of infection include fractures, trauma, exposed dentinal tubules, and iatrogenic causes [56]. The treatment sequence eliminates infection and protects the tooth from future microbial invasion.

## 3. Material and methods

A search was conducted using the databases PubMed, Elsevier, Scopus, Google Scholar, and Web of Science to find the most recent

research on the therapeutic potential of medicinal plants and their active principles in dental care. Original, peer-reviewed studies and reviews that were published in English over the almost preceding 25 years (1999–2024) were considered. Papers lacking a clear scientific foundation, and notable practical characteristics were eliminated by the authors.

#### 4. Search strategy

To examine the most recent studies on dental problems, phytoconstituents, and herbal remedies that have been published. Most available databases, including PubMed, Elsevier, Scopus, Google Scholar, and Web of Science, were checked up until April 2024 to make sure the data was accurate. The search parameters included terms like periodontitis, gingivitis, dentistry, dental problems, mechanism, phytochemicals, antioxidant, antiplaque, anti-inflammatory, analgesic, and halitosis. Unpublished research and commercial materials were excluded from this examination; instead, all publications that were received were thoroughly researched and examined to get comprehensive information about herbs that naturally occur and are beneficial in treating oral disorders.

#### 5. Herbs used in dental therapy

Since ancient eras, people have utilized herbs to prevent and manage several ailments. It’s critical for consumers’ health that the true effects of natural medicine be established by science, along with any potential therapeutic uses that may be identified. Herbal medicine has been used for generations to cure tooth discoloration, gum disease, periodontitis, and oral infections.

In the following section of this review, we are discussing some of the most important herbs commonly used by many nations for the treatment of oral disorders and their mechanisms of action. These are summarized in Figure (2) and Table 1.

##### 5.1. *Acacia arabica*

*Acacia* is one of the most important genera in the Leguminosae family which is commonly known as Babul, Kikar, or Indian Gum Arabic tree [57]. With around 1350 species, *Acacia* is the second biggest genus in the Leguminosae family. It can be found in tropical and warm temperate regions around the world, with the highest number of species found in the Americas (185 species), Australia (957 species), Asia (89 species), and Africa (144 species). *A. arabica* gum as one of its members has been utilized in many communities for regular oral hygiene regimens. The principal component of *A. arabica* is a complex mixture of the potassium, magnesium, and calcium salts of arabic acid. Moreover, there are antimicrobial tannins, cyanogenic glycosides, oxidases, peroxidases, and pectinases [58]. *A. arabica* chewing stick is commonly used in India and has long been used for dental hygiene and periodontal diseases. For almost a century, Indian traditional tooth remedies have included the dried powders of *A. arabica* (bark) [59,60]. A clinical study conducted found that *A. arabica* gel has a positive impact on gingivitis and plaque in patients with mild to moderate chronic periodontitis [61].

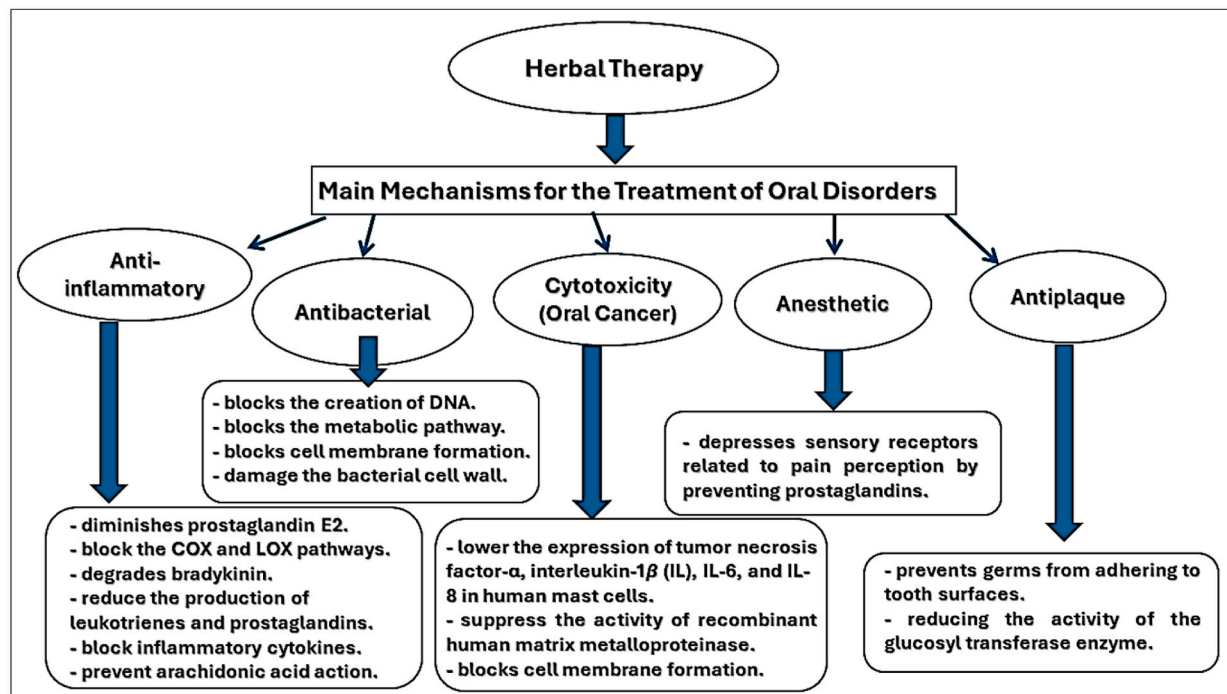


Fig. (2). Main mechanisms of Natural Herbs in treating dental disorders.

Table (1)

List of some medicinal herbs used for dental therapy and their mechanism of action.

No.	Medicinal Herbs	Main dental use	Mechanism of action	Parts used	Formulations used	Ref.
1	<i>Acacia arabica</i>	<ul style="list-style-type: none"> <li>- mild to moderate chronic periodontitis.</li> <li>- controlling plaque.</li> <li>- gingivitis, daily.</li> <li>- oral hygiene.</li> <li>- enamel hardness.</li> </ul>	<ul style="list-style-type: none"> <li>- Reduction and/or eradication of bacteria.</li> <li>- improves the remineralization of teeth.</li> </ul>	bark	<ul style="list-style-type: none"> <li>- toothpaste.</li> <li>- gel.</li> <li>- dried powder.</li> <li>- chewing stick.</li> </ul>	[60–62,64, 302–304]
2	<i>Achillea millefolium</i>	<ul style="list-style-type: none"> <li>- hemorrhages.</li> <li>- oral ulcers.</li> <li>- improve blood clotting.</li> <li>- healing of oral wounds due to surgery.</li> <li>- healing of oral mucositis.</li> <li>- teeth cleaning and braces.</li> </ul>	<ul style="list-style-type: none"> <li>- Antibacterial.</li> <li>- decreases the severity of oral mucositis.</li> </ul>	herb	<ul style="list-style-type: none"> <li>- mouthwash.</li> </ul>	[67]
3	<i>Allium sativum</i>	<ul style="list-style-type: none"> <li>- periodontitis.</li> <li>- dental caries.</li> <li>- endodontitis.</li> <li>- irrigant for pulpectomy of primary molar root canals.</li> </ul>	<ul style="list-style-type: none"> <li>- broad-spectrum antibacterial.</li> </ul>	bulbs	<ul style="list-style-type: none"> <li>- Paste of the bulb.</li> <li>- mouthwash.</li> <li>- root canal irrigant.</li> </ul>	[70,71, 74–76,305, 306]
4	<i>Aloe vera</i>	<ul style="list-style-type: none"> <li>- oral lichen planus.</li> <li>- stomatitis.</li> <li>- oral mucositis.</li> <li>- alveolar osteitis.</li> <li>- oral submucosal fibrosis.</li> <li>- gingivitis.</li> <li>- periodontitis.</li> <li>- surgical extraction.</li> </ul>	<ul style="list-style-type: none"> <li>- diminishes prostaglandin E2.</li> <li>- blocks the COX pathway.</li> <li>- degrades bradykinin.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- mouthwash.</li> <li>- toothpaste.</li> <li>- gel.</li> </ul>	[79–87,307]
5	<i>Artemisia herba alba, and Artemisia Siberia</i>	<ul style="list-style-type: none"> <li>- cleans the teeth.</li> <li>- prevents decay.</li> <li>- halitosis.</li> <li>- protects oral hygiene.</li> </ul>	<ul style="list-style-type: none"> <li>- antimicrobial</li> <li>- blocks the creation of DNA.</li> <li>- blocks the metabolic pathway.</li> <li>- blocks cell membrane formation.</li> </ul>	essential oil	<ul style="list-style-type: none"> <li>- toothpaste.</li> <li>- mouthwash.</li> <li>- gum paint.</li> </ul>	[91,92,308]
6	<i>Azadirachta indica</i>	<ul style="list-style-type: none"> <li>- dental plaque.</li> <li>- oral epithelial cell carcinoma.</li> <li>- reducing the plaque index and salivary bacterial count</li> </ul>	<ul style="list-style-type: none"> <li>- interaction with hydroxyl-apatite, it fully inhibits the growth of <i>C. albicans</i>.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- endodontic irrigation solution.</li> <li>- local drug delivery.</li> </ul>	[96,98,100, 103,309]
7	<i>Calendula officinalis</i>	<ul style="list-style-type: none"> <li>- plaque.</li> <li>- gingivitis.</li> <li>- oral candidiasis.</li> <li>- oropharyngeal mucositis in patients undergoing radiotherapy.</li> </ul>	<ul style="list-style-type: none"> <li>- anti-inflammatory.</li> <li>- Quercetin minimizes osteoporosis bone loss and periodontal cases.</li> <li>- suppresses the activity of recombinant human matrix metalloproteinase and lowers the expression of tumor necrosis factor-<math>\alpha</math>, interleukin-1<math>\beta</math> (IL), IL-6, and IL- 8 in human mast cells.</li> </ul>	flowers	<ul style="list-style-type: none"> <li>- mouthwash.</li> </ul>	[105–108, 310,311]
8	<i>Camellia sinensis</i>	<ul style="list-style-type: none"> <li>- gingivitis.</li> <li>- periodontitis.</li> <li>- dental caries.</li> <li>- halitosis.</li> <li>- oral cancer</li> </ul>	<ul style="list-style-type: none"> <li>- direct bactericidal against <i>S. mutans</i> and <i>S.sobrinus</i>;</li> <li>- inhibits bacterial and human amylases.</li> <li>- prevents bacteria from adhering to teeth.</li> <li>- inhibits glucosyl transferase, which limits the creation of sticky glucan.</li> <li>- minimizes bone loss in osteoporosis and periodontal diseases.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- mouth rinse.</li> <li>- local drug delivery.</li> <li>- chewing gum.</li> </ul>	[109,111, 112,312]
9	<i>Carica papaya</i>	<ul style="list-style-type: none"> <li>- plaque-induced gingivitis.</li> <li>- periodontitis.</li> <li>- oral ulcer.</li> </ul>	<ul style="list-style-type: none"> <li>- Antibacterial against <i>Salmonella</i>, <i>Staphylococcus</i>, and <i>E. coli</i>.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- mouthwash.</li> <li>- toothpaste.</li> </ul>	[121–123]
10	<i>Carum carvi</i>	<ul style="list-style-type: none"> <li>- gingivitis.</li> <li>- periodontal diseases.</li> <li>- flavoring agents in toothpaste and mouthwash formulations.</li> </ul>	<ul style="list-style-type: none"> <li>- Carvone present in the volatile oil has been shown to suppress 5- COX and COX activity, which can reduce the production of leukotrienes and prostaglandins.</li> </ul>	essential oil	<ul style="list-style-type: none"> <li>- toothpaste.</li> <li>- mouthwash.</li> </ul>	[126,127, 313]
11	<i>Casearia sylvestris</i>	<ul style="list-style-type: none"> <li>- alternative intracanal medicament/- denture stomatitis.</li> </ul>	<ul style="list-style-type: none"> <li>- irreversible structural damage and altering the expression of particular virulence genes of the bacteria.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- root canal irrigation solution.</li> <li>- ethanolic extract.</li> </ul>	[130,133, 314,315]

(continued on next page)

Table (1) (continued)

No.	Medicinal Herbs	Main dental use	Mechanism of action	Parts used	Formulations used	Ref.
12	<i>Citrullus colocynthis</i>	- periodontitis. - dental caries. - cariogenic bacteria	Antibacterial against teeth infected with <i>Enterococcus faecalis</i>	seeds	Aqueous and ethanolic extracts	[316]
13	<i>Cinnamon zeylanicum or Cinnamon cassia</i>	- dental caries. - halitosis.	- block the LOX pathway, which results in the production of leukotrienes that trigger inflammation. - alteration of bacterial cell membranes.	Bark	- chewing gum. - endodontic irrigate solution.	[98,136, 317]
14	<i>Citrus aurantifolia</i>	- periodontal diseases - improve oral wound healing. - dental caries.	Essential cell contents leak out of the respiratory chain because of the oils' partitioning into the lipid bilayer of the cell membrane.	Peels	- mouthwash.	[142,143, 318]
15	<i>Citrus sinensis</i>	- dental caries. - an alternative to xylene in dissolving different endodontic sealers. - orthodontic bracket friction.	- inhibits cell protein synthesis.	Peels	- peel extract. - gel.	[147-149, 173]
16	<i>Cocos nucifera</i>	- decrease plaque formation. - gingivitis.	- cell walls of bacteria, viruses, and fungi break down, killing them.	Oil	- Coconut oil. - Coconut water.	[152,319, 320]
17	<i>Commiphora myrrha</i>	- gingivitis. - oral ulcers. - root canal irrigant. - post-operative antimicrobial.	- damage the bacterial cell wall. - activates macrophages.	tree phoem	- mouthwash. - root canal irrigant.	[154,156, 321,322]
18	<i>Curcuma longa</i>	- dental caries. - gingivitis. - periodontitis. - radiation-induced oral mucositis. - subgingival irrigant. - oral cancer. - oral submucous fibrosis. - oral ulcer. - oral submucous fibrosis. - halitosis.	- essential oil inhibited the adherence of <i>S. mutans</i> to the saliva-coated hydroxyapatite beads. - inhibited the formation of <i>S. mutans</i> biofilm. - reduces inflammation by lowering histamine levels and increasing the production of natural cortisone by adrenal glands. - reduces pain. - hinders the biosynthesis of inflammatory prostaglandins.	rhizome	- topical application. - mouthwash. - subgingival irrigant. - local drug delivery system.	[157-165, 323]
19	<i>Elettaria cardamomum</i>	- cariogenic bacteria. - Toothache.	- lower the release of a few inflammatory intermediates that are triggered by LPS, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-8. Evidence suggested that blocking nuclear factor kappa B (NF- $\kappa$ B) signalling may have caused the anti-inflammatory action. - Anti-inflammatory by blocking nuclear factor kappa B (NF- $\kappa$ B) signalling.	Fruits & seeds	- essential oil.	[167,324, 325]
20	<i>Eucalyptus globulus</i>	- promising alternative to antibiotics. - prevent oral infection. - dissolve root canal sealer.	- slowed the development of periodontopathic bacteria.	leaf	- eucalyptus oil	[172,173, 326]
21	<i>Glycyrrhiza glabra</i>	- dental caries. - gingival diseases. - periodontal diseases. - oral candidiasis. - oral cancer. - an endodontic treatment.	- precipitate nucleic acids and cytoplasmic proteins. - completely stops the phosphoenol pyruvate-phosphotransferase sugar transport system's function. - significantly reduces the amount of acid produced by oral <i>streptococci</i> and cariogenic bacteria. - inhibit tumor angiogenesis.	root s	- candy. - herbal lollipop. - root Extract	[175,176, 327]
22	<i>Hypericum perforatum</i>	- periodontal diseases.	- antibacterial.	flowering aerial parts	<i>Hypericum perforatum</i> extract	[181,183]
23	<i>Mangifera indica</i>	- oral hygiene. - toothache.	- prevention of arachidonic acid action.	leaf	- mouthwash. - alternatives to CHX in mouthwashes for children.	[189-191, 328]

(continued on next page)



Table (1) (continued)

No.	Medicinal Herbs	Main dental use	Mechanism of action	Parts used	Formulations used	Ref.
24	<i>Matricaria chamomilla</i>	<ul style="list-style-type: none"> <li>- gingivitis.</li> <li>- periodontal disease.</li> <li>- burning mouth syndrome. - oral mucositis.</li> </ul>	<ul style="list-style-type: none"> <li>- constriction of blood vessels and activation of platelets (synthesis and release of TXA2 and release of several chemical mediators such as ADH 5-HT and PAF.</li> </ul>	flowers	<ul style="list-style-type: none"> <li>- mouthwash.</li> <li>- an irrigate solution.</li> </ul>	[195–197, 329]
25	<i>Mentha piperita</i>	<ul style="list-style-type: none"> <li>- reduce gingival inflammation.</li> <li>- stop toothache.</li> </ul>	<ul style="list-style-type: none"> <li>- a cooling effect that serves as an analgesic and lessens discomfort.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- toothpaste.</li> <li>- mouthwash.</li> </ul>	[125,199]
26	<i>Nigella sativa</i>	<ul style="list-style-type: none"> <li>- toothache.</li> <li>- periodontitis.</li> <li>- improve peri-implant tissues.</li> <li>- promising remineralizing agent in treating non-cavitated demineralized carious lesions.</li> <li>- gingivitis.</li> </ul>	<ul style="list-style-type: none"> <li>- inhibition of COX and LOX molecular pathways.</li> <li>- lipid peroxidation suppression.</li> <li>- eicosanoid production, notably thromboxane B and leukotriene B4.</li> <li>- antioxidant.</li> <li>- anti-inflammatory.</li> <li>- bactericidal capacity.</li> </ul>	seeds	<ul style="list-style-type: none"> <li>- seeds oil.</li> <li>- toothpaste.</li> </ul>	[203–207, 330]
27	<i>Ocimum tenuiflorum</i>	<ul style="list-style-type: none"> <li>- maintenance of oral hygiene,</li> <li>- reducing plaque</li> <li>- gingivitis,</li> <li>- periodontal conditions.</li> </ul>	<ul style="list-style-type: none"> <li>- antibacterial against <i>E. coli</i>, <i>B. anthracis</i>, and <i>P. aeruginosa in vitro</i>.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- chewing Tulsi leaves.</li> <li>- toothpaste.</li> <li>- mouthwash.</li> </ul>	[209,210, 212,331]
28	<i>Pimpinella anisum</i>	<ul style="list-style-type: none"> <li>- maintain oral hygiene.</li> </ul>	<ul style="list-style-type: none"> <li>- inhibits the growth of early Gram-positive facultative aerobes and promotes the growth of predominantly Gram-negative obligatory anaerobes.</li> </ul>	Leaves and Seeds	<ul style="list-style-type: none"> <li>- mouth rinse</li> </ul>	[214,332]
29	<i>Pistacia lentiscus</i>	<ul style="list-style-type: none"> <li>- cleansing of teeth.</li> <li>- halitosis.</li> <li>- filler for carious teeth.</li> <li>- preventing caries lesions.</li> </ul>	<ul style="list-style-type: none"> <li>- prevents the buildup of plaque.</li> <li>- antimicrobial.</li> </ul>	trunk and branches	<ul style="list-style-type: none"> <li>- dental powder</li> <li>- chewing mastic gum</li> <li>- mastic oil</li> </ul>	[218,221, 333]
30	<i>Propolis</i>	<ul style="list-style-type: none"> <li>- stomatitis.</li> <li>- periodontitis.</li> <li>- halitosis.</li> <li>- dental caries.</li> <li>- traumatic ulcers.</li> <li>- dental hypersensitivity.</li> <li>- candidal infections.</li> </ul>	<ul style="list-style-type: none"> <li>- reducing the activity of the glucosyl transferase enzyme.</li> </ul>	resin-like material	<ul style="list-style-type: none"> <li>- gel</li> <li>- mouth rinses.</li> <li>- toothpastes.</li> <li>- tooth coating preparations.</li> </ul>	[224–226, 334]
31	<i>Rosmarinus officinalis</i>	<ul style="list-style-type: none"> <li>- gingival diseases.</li> <li>- halitosis.</li> <li>- dental caries.</li> <li>- periodontitis.</li> </ul>	<ul style="list-style-type: none"> <li>- suppress the growth of periodontal bacteria through biofilm control.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- toothpaste.</li> </ul>	[199,231, 234,335]
32	<i>Salvia officinalis</i>	<ul style="list-style-type: none"> <li>- mouth inflammation.</li> <li>- gingivitis.</li> <li>- dental caries.</li> <li>- halitosis.</li> <li>- reduce <i>Candida</i>-associated denture stomatitis risk.</li> </ul>	<ul style="list-style-type: none"> <li>- antibacterial.</li> <li>- inhibits induction of catalase in <i>S. aureus</i> in response to the oxidative burst of phagocytes.</li> <li>- indirect antibacterial by preventing bacteria from defending themselves against phagocytes.</li> <li>- an anti-inflammatory by reducing the antibacterial response.</li> </ul>	leaf	<ul style="list-style-type: none"> <li>- mouthwash.</li> <li>- gargle.</li> </ul>	[237,240, 336,337]
33	<i>Salvadora persica</i>	<ul style="list-style-type: none"> <li>- reduce plaque.</li> <li>- reduce bacterial oral germs.</li> <li>- halitosis.</li> <li>- remineralization effects following dental caries.</li> <li>- accelerate wound healing after oral/periodontal surgery or extraction.</li> <li>- whitening properties and orthodontic chain preservation.</li> <li>- good natural substitute for sodium hypochlorite.</li> </ul>	<ul style="list-style-type: none"> <li>Alternative treatments for <i>Candidiasis</i> and natural inhibitors of the most significant pathogenic species of <i>Candida</i> using its alcoholic extract.</li> </ul>	roots	<ul style="list-style-type: none"> <li>- chewing stick.</li> <li>- mouthwash.</li> <li>- root canal irrigant.</li> </ul>	[244,245, 338,339]
34	<i>Sanguinaria canadensis</i>	<ul style="list-style-type: none"> <li>- gingivitis.</li> <li>- periodontal disease.</li> <li>- halitosis</li> </ul>	<ul style="list-style-type: none"> <li>- reduces inflammation by preventing the synthesis of PGE-2 and COX-2.</li> <li>- causes the release of autolytic enzymes that are attached to bacterial membranes, which act</li> </ul>	rhizomes	<ul style="list-style-type: none"> <li>- toothpaste.</li> <li>- chewing gum.</li> <li>- mouthwash.</li> </ul>	[248–251, 340]

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Table (1) (continued)

No.	Medicinal Herbs	Main dental use	Mechanism of action	Parts used	Formulations used	Ref.
35	<i>Syzygium aromaticum</i>	<ul style="list-style-type: none"> <li>- minor oral wounds.</li> <li>- analgesic.</li> <li>- infective diseases of the oral cavity.</li> <li>- general oral hygiene.</li> <li>- dental caries.</li> <li>- halitosis.</li> </ul>	<p>against Methicillin-resistant <i>Staphylococcus aureus</i>.</p> <ul style="list-style-type: none"> <li>- inhibits COX-2 and LOX enzymes.</li> <li>- Eugenol, in clove oil used as an anesthetic in dentistry, depresses the sensory receptors related to pain perception by preventing prostaglandin.</li> </ul>	buds	<ul style="list-style-type: none"> <li>- mouthwashes.</li> <li>- toothpastes.</li> <li>- topical agents.</li> </ul>	[254–257, 341,342]
36	<i>Terminalia chebula</i>	<ul style="list-style-type: none"> <li>- periodontal diseases such as gingivitis.</li> <li>- anticaries agent.</li> <li>- anti-cariogenic.</li> </ul>	<ul style="list-style-type: none"> <li>- anti-inflammatory by protease inhibition.</li> <li>- inhibits the formation of glucan and amylases.</li> <li>- prevents germs from adhering to tooth surfaces.</li> <li>- bactericidal effects on oral microorganisms.</li> </ul>	fruits	<ul style="list-style-type: none"> <li>- mouthwash.</li> </ul>	[259,260, 264,343]
37	<i>Thymus vulgaris</i>	<ul style="list-style-type: none"> <li>- dental caries.</li> <li>- oral herpes.</li> <li>- chronic candidiasis.</li> <li>- halitosis.</li> <li>- root canal irrigation.</li> </ul>	<ul style="list-style-type: none"> <li>- effective action on microbial biofilms by breaking the cell membrane and releasing the cell contents.</li> </ul>	essential oil	<ul style="list-style-type: none"> <li>- gingival mucoadhesive patch from the essential oil.</li> <li>- Thyme water extract</li> </ul>	[266–268, 271,272, 344]
38	<i>Trigonella foenum-graecum</i>	<ul style="list-style-type: none"> <li>- irrigation agent for root canals.</li> <li>- an alternative periodontal dressing to reduce postoperative inflammation.</li> <li>- recurrent aphthous.</li> <li>- stomatitis.</li> <li>- gingivitis.</li> </ul>	<ul style="list-style-type: none"> <li>- Anti-inflammatory.</li> </ul>	seeds	<ul style="list-style-type: none"> <li>- seeds extract.</li> <li>- root canal irrigant.</li> <li>- gel.</li> <li>- bucco-adhesive paste.</li> <li>- toothpaste.</li> </ul>	[274–277, 345]
39	<i>Vitis vinifera</i>	<ul style="list-style-type: none"> <li>- prevention of dental caries.</li> <li>- decreasing dentine degradation.</li> <li>- remineralize tooth surfaces.</li> <li>- root canal irrigation.</li> </ul>	<ul style="list-style-type: none"> <li>- Antibacterial.</li> <li>- Antifungal.</li> <li>- Antiviral.</li> <li>- control the imbalance of oxidative stress and the inflammatory response caused by bacteria in periodontal disease.</li> </ul>	seeds	<ul style="list-style-type: none"> <li>- Grapes seeds extract.</li> <li>- 3 % v/v Grapes seeds oil- modified conventional glass ionomer cement.</li> <li>- root canal irrigant.</li> </ul>	[279,281, 283,285, 346]
40	<i>Zingiber officinale</i>	<ul style="list-style-type: none"> <li>- intracanal dressing.</li> <li>- recurrent aphthous.</li> <li>- stomatitis.</li> <li>- denture stomatitis.</li> <li>- analgesic in controlling pain after periodontal flap.</li> <li>- dental caries.</li> <li>- potential root canal irrigation solution.</li> <li>- improving chronic periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>- interferes with the inflammatory cascade.</li> <li>- inhibits prostaglandin biosynthesis.</li> <li>- inhibits the growth of <i>A. flavus</i>, <i>A. moniliforme</i>, and <i>A. fumigatus</i>.</li> </ul>	rhizomes	<ul style="list-style-type: none"> <li>- mouthwash.</li> <li>- root canal irrigant.</li> <li>- toothpaste.</li> </ul>	[288–290, 293–296, 347,348]

For patients with mild to moderate chronic periodontitis, it might be suggested as an adjunct to scaling and root planning (SRP) for maintenance [61]. The impact of Gum Arabic on plaque-induced gingivitis was evaluated in a different clinical trial and they found that Gum Arabic was useful in reducing gingivitis and plaque [62]. Additionally, a study was carried out to evaluate the impact of using Gum Arabic topical gel on demineralized enamel hardness [63]. The findings showed that while the initial hardness could not entirely be restored, there was an increase in tooth enamel hardness following gel application. The 96-min exposure duration group showed the largest increase in enamel hardness. Moreover, assessing in an adult population the anti-plaque and anti-gingivitis qualities of toothpaste containing *A. arabica*, and reductions in plaque index (PI), gingival index (GI), and bleeding on probing index (BOP%) were observed in the test group compared with the control group, so brushing with *A. arabica* containing toothpaste may help inhibit gingivitis. It can be recommended for daily oral hygiene procedures [64].

## 5.2. *Achillea millefolium*

*Achillea millefolium* L. belongs to the Asteraceae family and is commonly known as Yarrow. Asteraceae plants are distributed throughout the world and are most common in the arid and semi-arid regions of subtropical and lower temperate latitudes. *Achillea* contains around 130 flowering and perennial species, found in Europe and temperate areas of Asia and America. *Achillea* is represented

in Turkey with 46 taxa, of which 25 are endemic, and in Iran with 19 species, of which seven species are endemic. *A. millefolium* is native to Europe and western Asia but is also widespread in most temperate regions including North America and is represented by about 85 species mostly found in Europe, Asia and in North America. In dentistry, Yarrow is used to treat hemorrhages, and ulcers and to improve blood clotting, it is also used as mouthwash to promote the healing of cuts in the mouth due to surgery, teeth cleaning, and braces [65]. Responsible for this therapeutic effect is considered to be the flavonoids and tannins contained in *A. millefolium* [66]. In a clinical study conducted, it has been observed that the extract has beneficial effects in the healing of oral mucositis, a major complication of classical antitumor chemotherapy [67]. In an *in vitro* investigation to assess the antibacterial activity of hydroalcoholic extract of *Salvia officinalis* and *A. millefolium* against cariogenic microorganisms, they found that the MIC of *S. officinalis* and *A. millefolium* for *Streptococcus mutans* were 6.25 and 50 µg/mL, respectively [68].

### 5.3. *Allium sativum*

Garlic, or *Allium sativum* L., is a member of the Alliaceae family and genus *Allium*. It mainly produced in Mediterranean and European Union countries, India, China, and the USA. In 2011, Turkey produced about 79000 tons garlic and was the fourteenth largest garlic producer in the world, producing 0.33 % of the world and 10.23 % of Europe's total garlic production. Its primary components, alliin, methiin, and S-allyl cysteine, are responsible for many of its well-known medicinal qualities [69]. In dentistry, Garlic finds its utility due to its antibacterial effects in the treatment of periodontitis, and dental caries, and recent studies have also shown the beneficial effect of Garlic in the treatment of oral cancer [70]. Mainly, the bulb's paste is applied to the gum to treat infections [71]. Research has been done on both *in vitro* and *in vivo* dental pathogens and *A. sativum*'s antibacterial properties. The antibacterial activity of several garlic types against cariogenic bacteria (*S. mutans* and *L. acidophilus*) was assessed and compared in an *in vitro* investigation that revealed a maximal zone of inhibition (ZOI) of 24 mm [72]. Another *in vivo* study conducted to assess the antimicrobial activity of garlic against oral *Streptococci* 5 % Garlic solution was used as a mouthwash showed that Garlic mouthwash solution had good antimicrobial activity against *S. mutans* and oral microorganisms [73,74]. Besides, a clinical study showed that *A. sativum* extract can be used efficiently as an irrigant for pulpectomy of primary molar root canals [75]. Garlic's antifungal action is one of its other therapeutic benefits in dental pathology. Consequently, nystatin and fluconazole were used to compare the antifungal effects of garlic extract, and it was found that the antifungal impact of the garlic extract was stronger than that of the traditional antifungal medications [76,77].

### 5.4. *Aloe vera*

*Aloe vera* L. is a plant that belongs to the Liliaceae family. Currently, *A. vera* is found as a wild plant or cultivated in North Africa, from Morocco to Egypt, in the Middle East, in Asia (especially in India) throughout the southern Mediterranean, in Madeira, Cape Verde, and the Canary Islands. It is also reported in Central and South America, especially in the Antilles, Puerto Rico, Jamaica, Mexico, and in the Andes mountains.

*A. vera* is effective in periodontal disease conditions such as oral lichen planus, stomatitis, oral mucositis, alveolar osteitis, oral submucosal fibrosis, gingivitis, and periodontitis [78–86]. In addition, it accelerates healing after surgical extraction including the third molar. It is available in several forms, such as mouthwash, toothpaste, or gel [87]. *A. vera* toothpaste is effective on PI and GI and is suggested as an alternative to traditional toothpaste [88]. In a clinical study to evaluate the effect of *A. vera* mouth rinse in reducing plaque and gingival inflammation, negligible or very minimal adverse effects were observed compared to CHX [87]. Another clinical study conducted to study its inhibitory activity on some clinically isolated cariogenic and periodontopathic bacteria showed that *A. vera* gel had inhibitory activities on some cariogenic organisms (*S. mutans*), periodontopathic (*A. actinomycetemcomitans*, *P. gingivalis*) and an opportunistic periodontal-pathogen (*Bacteroides fragilis*) [89]. *A. vera* also can be used as an intracanal medicament against *E. faecalis* [90].

### 5.5. *Artemisia herba alba*, *Artemisia sieberi*

*Artemisia sieberi*, Asteraceae family, grows wild in desert and semi-desert climates. It has forage value for animals and medicinal properties for humans [91]. The genus is widely distributed in all continents except Antarctica. The distribution of the genus from Northern Asia primarily follows the main three routes: (1) in the West, it migrates into Europe, Western Asia, Mediterranean Basin, and Africa; (2) Siberia and into western North America; and (3) further south into Asia. Only a few number of species, not exceeding 25 taxa, have been reported from the Southern Hemisphere although a small diversity center occurs in South America and it is found in Oceania as allochthonous taxa. The main center of species diversity of *Artemisia* is located in Central Asia consisting the region of Uzbekistan, Tadjikistan, Turkmenistan, Kazakhstan, Kyrgyzstan, parts of Russia, China, and Mongolia. Other relevant centers of diversity include the territory of Iran-Turanian and Mediterranean regions and in western North America *Artemisia herba-alba* (Shih – An Arabic term used locally “shih” is an aromatic herb known for its bitter-tasting leaves commonly known as Wormwood [92]. *A. herba alba*, and *A. sieberi* extracts can be used in toothpaste, which not only cleans the teeth but also prevents decay, treats bad breath, and protects oral hygiene [92]. The antimicrobial activity of *A. sieberi* essential oil was assessed using the disc diffusion method and micro broth dilution assay against various microorganisms, including yeast, fungi, and Gram-positive and Gram-negative bacteria. The oil, primarily containing camphor,  $\beta$ -thujone, and  $\beta$ -thujone, demonstrated antimicrobial activity against these pathogens. The sensitivity of Gram-positive bacteria and fungi was higher than that of Gram-negative ones.

Among Gram-positive bacilli, *Listeria monocytogenes*, *Bacillus cereus*, and Gram-positive cocci, *S. mutans* were more sensitive than

others [91]. There was a significant degree of inhibition in the nucleic acid production in another investigation to evaluate the prevention and treatment of dental caries caused by *S. mutans*, suggesting that this crude extract interferes with DNA replication. Shih possesses potentially efficient antibacterial action; consequently, it may be recommended as a possibly useful antiplaque and anti-cariogenic agent in the form of mouthwash or gum paint. Inhibition of glucan formation was 45 % as compared to control [93].

#### 5.6. *Azadirachta indica*

*Azadirachta indica*, referred to as Neem, is a plant widely utilized in Ayurvedic, Unani, and Homoeopathic medicine. It is believed to be native to the whole Indo-Pakistan sub-continent, especially southeast Asia (India, Burma/Myanmar, Sri Lanka, Thailand, Malaysia and Indonesia), from where it was introduced to Nigeria in 1928 through Ghana by a man named 'Dogon Yaro' and hence its local name in northern Nigeria.

It is currently regarded as a wonder tree in modern medicine [94]. In dentistry, Neem stick aqueous extract inhibits streptococci's ability to colonize tooth surfaces [95]. Neem oil has been recommended for the treatment of dental plaque due to its strong antibacterial properties [96]. Neem leaf chloroform extract inhibits *S. mutans* and *Streptococcus salivarius* and is useful in the treatment of dental caries [97]. Neem may be used as an endodontic irrigation solution to decrease *E. faecalis*, which is equivalent to 3 % sodium hypochlorite (NaOCl) [98]. It has been demonstrated that Neem effectively compacts *Candida albicans* [99]. The extremely pure Neem leaf extract has demonstrated the ability to inhibit oral epithelial cell cancer by suppressing intra-tumor pro-inflammatory pathways [100]. Mouthwashes containing *A. indica* have been shown in numerous studies to be quite effective and to be a viable alternative for treating periodontal disorders [101]. A clinical study was conducted to assess *A. indica* leaf extract gel for its antiplaque action against CHX gluconate mouthwash [102]. It was found that mucoadhesive dental gel containing Neem is superior to CHX gluconate mouthwash in decreasing the PI and salivary bacterial count. Additionally, a clinical and microbiological study demonstrated that a local application method utilizing 10 % Neem oil has the intended effects on *Porphyromonas gingivalis*. More investigation is required to assess the effectiveness of neem oil against additional periodontal infections [103].

#### 5.7. *Calendula officinalis*

*Calendula officinalis* L., a member of the Asteraceae family, is commonly referred to as English marigold or "pot marigold." [104]. It is widely distributed in Mediterranean countries and the southern region of Europe. In dentistry, *C. officinalis* can be used for gingivitis and plaque. This is supported by the randomized study evaluating *C. officinalis* as an anti-plaque and anti-gingivitis agent and demonstrated the efficacy of *calendula* mouthwash as a scaling adjunct in reducing tooth plaque and gingivitis [105]. Additionally, a study to investigate the anti-microbial effect of different concentrations of *calendula* extract on periodontal pathogens, demonstrated that the total microbial count in patients with gingivitis and periodontitis can be effectively reduced by using different concentrations of *C. officinalis* mouthwash [106]. *Calendula* is beneficial in oral candidiasis. The evidence for this is a study conducted to assess the antifungal activity of *C. officinalis* volatile oil and revealed that *Calendula* helps treat oral candidiasis and has antifungal properties similar to nystatin [107]. *Calendula* is also helpful in reducing oropharyngeal mucositis in radiation therapy patients [108].

#### 5.8. *Camellia sinensis*

*Camellia sinensis* L. also referred to as "Green tea", belongs to the Theaceae family. It was extensively cultivated in Asian, African, Latin American, and Oceanian countries, which was believed to originate from northeast India, north Myanmar, and southwest China. Green tea has several medicinal benefits in dentistry that might help with conditions like periodontitis, gingivitis, tooth caries, and halitosis [109]. A four-week mouthwash routine with diluted tea catechin solution decreased periodontal disease-related halitosis [110]. It is useful in a variety of applications, including mouthwash, chewing gum, and local drug delivery. Catechins included in it exhibit antibacterial properties against *Streptococcus sobrin*, *Porphyromonas melaninogenicus*, *Porphyromonas gingivalis*, and *S. mutans* [111]. Green tea and its main ingredient, flavonoid epigallocatechin-3-gallate, induce osteoclasts and osteoclast-like cells to undergo apoptosis, which reduces bone loss in cases of osteoporosis and periodontal disease [112].

#### 5.9. *Carica papaya*

*Carica papaya*, commonly known as Papaya, belongs to the Caricaceae family and is extensively grown in tropical and subtropical regions, where it is used as food and traditional medicine to treat several illnesses [113]. It is indigenous to Central America and the South of Mexico and cultivated in many countries worldwide. Because of its wide range of pharmacological effects, fermented papaya preparation has proved helpful in treating the following conditions: gingival irritation and the progression of oral cavity disorders such as caries [114]. The seeds of *C. papaya* are rich in chemical components that have antibacterial and anti-inflammatory properties, including tannin, alkaloid, and flavonoid. Also, a proteolytic enzyme called Papain is extracted from the Papaya fruit's latex [115] which has been claimed to affect dentistry in the eradication of dental caries [116,117]. A double-blinded parallel designed a randomized controlled trial study to compare the antibacterial efficacy of *C. papaya* leaf extract mouthwashes about the reduction of *S. mutans* counts in saliva from 8- to 12-year-old schoolchildren. The results indicated that *C. papaya* leaf extract mouthwashes were effective suggesting that *C. papaya* leaf extract mouthwashes may be useful in reducing *S. mutans* [118]. Another clinical trial investigation showed that patients with gingivitis might lower their dental plaque score by rinsing with mouthwash containing 10 % extract from *C. papaya* L. seeds [119]. The same effect as 0.2 % CHX in reducing PI and GI in mild gingivitis is seen with 2.5 % papaya

leaf extract solution [120]. Additionally, a randomized controlled trial study to compare the effectiveness in reducing interdental gingival bleeding between a natural dentifrice or mouthwash containing leaf extract of *C. papaya* and a classical sodium lauryl sulfate (SLS)-free enzyme-containing dentifrice, either alone or in combination with a volatile oil (VO) mouthwash demonstrated that leaf extract of *C. papaya* dentifrice or mouthwash provides an effective and natural alternative to SLS-free dentifrice +/VO-containing mouthwash when used as an adjunctive to mechanical oral care to reduce interdental gingival inflammation [121]. Moreover, a clinical study to evaluate the *C. papaya* seed extract's clinical and microbiological efficacy on clinical parameters, including GI, probing pocket depth (PPD), and papillary bleeding index (PBI), as well as on organisms that cause oral malodor, revealed that using dried Papaya seeds as an herbal mouthwash in addition to scaling is a more beneficial approach for treating periodontitis, plaque-induced gingivitis, and oral malodor in all groups [122]. On the other hand, a study to assess the efficacy of the topical application of the ethanolic extract of *C. papaya* L. on the healing process of rat mouth ulcers demonstrated that the ethanolic extract of Papaya leaf could accelerate the healing of oral ulcers on the buccal mucosa of Wistar rats [123].

### 5.10. *Carum carvi*

*Carum carvi*, commonly known as Caraway, belongs to the family Apiaceae and is among the oldest spices grown in Europe. Today, it is cultivated in nations including Australia, Jamaica, India, Canada, and the United States. Carvone and limonene are the principal constituents of the volatile oil of *C. carvi* [124]. In dentistry, it can be used as a mouthwash for periodontal disease or gingivitis [125]. It can also be added to toothpaste and mouthwash products as a flavoring [126]. A clinical study investigating the efficacy of hydro-alcoholic extract of Caraway (HEOC) on 5-fluorouracil (5-FU)-induced oral mucositis in male golden hamsters, indicated that HEOC was more effective against *S. intermedius* and *S. epidermidis*, and the use of HEOC topically may be linked with a reduction in the severity of oral mucositis [127]. Adverse effects of the use of caraway is typically safe. However, since oil from caraway and other Umbelliferous plants might irritate skin and mucous membranes, children under the age of two should not use pure volatile oil [125].

### 5.11. *Casearia sylvestris*

*Casearia sylvestris* is an American shrub or small tree that is a member of the Flacourtiaceae family. It is commonly recognized in Brazil by terms like Guaçatonga or Porangaba, which are derived from the original Tupi-guarani language and indicate the plant's long history of use by native Brazilian communities [128]. *Casearia* species are found in the America, Africa, Asia, and Australia. In folk medicine, this plant species has been widely utilized as an antiseptic, topical anesthetic, anti-tumor, anti-ulcer, and anti-ophidian agent [129]. It is an excellent anti-inflammatory medication to be used for intracanal medication because it is high in phospholipase A-2 inhibitors, which inhibit the acute phase of the inflammatory process and extend the regenerative phase [130]. A study to assess the impact of *C. sylvestris* on dentinal tubule obliteration and dental sensitivity control resulted in a favorable correlation between dentinal tubule obliteration and *C. sylvestris* use [131]. Another study evaluated *C. sylvestris* leaf extracts' antimicrobial potential against oral bacteria using various extraction techniques, including the extraction of essential oil, and to contrast their antibacterial properties with those of traditional mouthwash CHX. All extracts examined showed MIC values higher than 400 µg/mL and few indicated bactericidal action. The antibacterial activity of the essential oil was higher than the activity of the extracts; therefore, the essential oil of *C. sylvestris* has strong antimicrobial action against oral pathogens [132]. Additionally, a study to evaluate the *in vitro* activity of an ethanolic leaf extract against oral pathogenic bacterial and fungal infections where results indicated that all the microorganisms that were tested were susceptible. These findings point to the possibility of using *C. sylvestris* ethanolic extract as a novel treatment for oral infectious diseases such as dental caries, periodontitis, and denture stomatitis [133].

### 5.12. *Cinnamon zeylanicum* or *Cinnamon cassia*

There are more than 250 types of *Cinnamon* (*Cinnamomum* spp., Lauraceae family, mostly found in Asia, China, and Australia [134]. *Cinnamon cassia* or *Cinnamon zeylanicum* are frequently used names for *Cinnamon*. It possesses significant antibacterial properties against cariogenic bacteria, such as *L. casei* and *S. mutans* [98]. It can also be used to minimize the count of bacteria in the water lines of the dental unit [135]. Furthermore, *Cinnamon* exhibits fungicidal properties against both *Candida glabrata* and *Candida tropicalis* [98]. *Cinnamon*-containing chewing gum with cinnamon can reduce the concentration of volatile sulfur compounds in the mouth, which can aid in the treatment of halitosis cases [136]. An *in vitro* study for evaluating the antibacterial efficacy of Neem extract, *Cinnamon* extract in comparison to NaOCl as an irrigant against *E. faecalis* indicated that *Cinnamon* extract had the greatest reduction in colony-forming units (CFU) colonies. The *E. faecalis* colonies showed the least reduction in Neem extract irrigant [98]. Another *in vitro* study demonstrated that *C. zeylanicum* ethanolic extracts have antibacterial efficacy against each periodontal pathogen tested [137].

### 5.13. *Citrullus colocynthis*

*Citrullus colocynthis* L. Schrader is an annual plant belonging to the Cucurbitaceae family and grows in arid and semi-arid regions. Native to tropical Asia and Africa, *C. colocynthis* is now widely distributed in the desert areas of the Mediterranean basin (in Italy the only known population is located in the Aeolian Island of Vulcano). Aqueous and ethanolic extracts of *C. colocynthis* were tested for their ability to inhibit *C. albicans* and *S. mutans*. Test results for minimal bactericidal concentration (MBCs)/minimal fungicidal concentration (MFCs) and minimum inhibitory concentration (MICs) were obtained. A comparison of the aqueous and ethanolic extracts revealed that the former had MICs of 0.75 mg/mL and MBCs of 1.5 mg/mL against *S. mutans* and 3.0 mg/mL and MFCs of 12.0

mg/mL against *C. albicans*, respectively, while the latter had MICs of 0.37 mg/mL and MBCs of 1.5 mg/mL against *S. mutans* and 3.0 mg/mL and MFCs of 3.0 mg/mL against *C. albicans*. Extracts of *C. colocynthis* significantly suppressed the growth of *S. mutans* and *C. albicans* [138].

#### 5.14. *Citrus aurantifolia*

*Citrus aurantifolia*, also referred to as Lime, is a member of the Rutaceae family. It is native to the tropical regions of Southeastern Asia, such as Malaysia and Indonesia but it has been carried and cultivated throughout the tropical regions of the world. When used as recommended, Lime offers positive medical and cosmetic effects [139]. *C. aurantifolia* is native to Southeast Asia and Asia's tropical and subtropical regions, including China and India [140]. Lime also promotes the body's health, particularly that of the mouth and teeth. Natural antibacterial, anti-inflammatory, and antioxidant properties are found in the lime peel [141]. The polyphenolic components of these species have been demonstrated to promote oral wound healing in dentistry applications. To promote oral wound healing in patients with periodontal diseases, these polyphenols may be added as extra ingredients to mouthwash [142]. In a study, the antibacterial effects of volatile lime oil have been tested in dentistry against *S. mutans* species, and the results indicated that volatile lime oil exhibits the highest antibacterial activity when compared to volatile oils from *Citrus limon*, *Citrus hystrix*, *Citrus sinensis*, and *Citrus nobilis* [143]. Dental caries can be efficiently treated using its antibacterial properties. Similarly, research to investigate the antibacterial impact of aqueous and alcoholic Lime extracts against the principal bacterial species causing caries revealed that *C. aurantifolia* exhibits antibacterial effects on *S. aureus*, *K. pneumonia*, and *Proteus mirabilis* species [139]. Additionally, *Escherichia coli* species were proven to be susceptible to its antibacterial actions [144].

#### 5.15. *Citrus sinensis*

*Citrus sinensis*, often referred to as orange, is a delicious and juicy fruit that is cultivated worldwide. It is a major crop in the Rutaceae family and is estimated to produce 120 million tons annually. In tropical and subtropical regions, orange trees are commonly grown for their delicious juice and potential medical benefits [145]. It is native to China and Vietnam. Orange oil is a naturally occurring product that is obtained from the peel of *Citrus sinensis* fruits. The oil's extensive composition includes alcohols, esters, aldehydes, and hydrocarbons; D-limonene is the most significant phytoconstituent [146]. Regarding its use in dentistry, it was observed that *C. sinensis* oil is efficient against dental caries bacteria, supported by several *in vitro* studies. An *in vitro* study was conducted to assess the antimicrobial potential of *C. sinensis* peel extracts against *S. mutans* and *L. acidophilus* using the agar well diffusion method [147]. The results indicated that the hot ethanolic extract of *C. sinensis* peel was the most effective in inhibiting dental caries pathogens, followed by the cold extract where the efficacy of aqueous extracts increased with increasing their concentrations. The MIC of *C. sinensis* peel ethanolic extracts, both hot and cold, was found to be between 12 and 15 mg/ml against the two dental caries pathogens [147]. In another study, it was found that eucalyptus and orange oils can be used as substitutes for xylene to dissolve various endodontic sealers for the healing of periodontal diseases in rat models [148]. Moreover, in a study to evaluate the antibacterial activity of *C. sinensis* on organisms isolated from human teeth, it was found that the ethanolic extracts of *C. sinensis* tree stem on *S. aureus* had the greatest ZOI values, measuring 7 mm [139]. On the other hand, a study to evaluate the effectiveness of sweet orange peel extract (*C. sinensis*) in reducing friction on orthodontic wire and brackets resulted in a difference in bracket friction values between the treated and control groups suggesting that the extract maintains orthodontic bracket friction [149].

#### 5.16. *Cocos nucifera*

*Cocos nucifera* L., often referred to as Coconut, is a member of the Arecaceae family. Coconut palm is cultivated in 93 countries, including Central and South America, East and West Africa, Southeast Asia and the Pacific Islands, with a total growth area of more than 12 million hectares. Because of its many uses in nutrition, medicine, and cosmetics, Coconut is renowned as the tree of abundance, heaven, and life [150]. Coconut proteins, oil, and water besides derived products like coconut palm sugar (a value-added product) can help prevent vitamin deficiencies and offer beneficial health benefits [151]. It consists mainly of medium-chain fatty acids, of which lauric acid, which has antibacterial and anti-inflammatory properties, makes up about 50 % [152]. In dentistry, Coconut oil is used to clean the mouth since it has a dense quality that helps remove food particles, germs, and other microbes from the oral cavity [152]. To evaluate the impact of coconut oil on plaque-induced gingivitis, a study demonstrated a statistically significant decline in the gingival and plaque indices starting on day seven of administration. Therefore, Coconut oil may be a useful adjuvant technique for reducing the development of plaque and gingivitis associated with it [152].

#### 5.17. *Commiphora myrrha*

*Commiphora myrrha*, also known as *Commiphora molmol* or *Balsamdendron myrrha*, is a tiny tree that is often found in the Middle East (Saudi Arabia, Oman, Somalia, Sudan, northern Kenya, and Ethiopia). The yellowish-resinous fluid known as myrrh is exuded from the tree's phloem. Furthermore, the Arabic word murr, which means bitter, is the source of the name Myrrh [153]. Resin, gum, and volatile oil are the three products of *C. myrrha* that possess wound-healing and antibacterial properties and can be applied as a mouthwash to treat ulcers, gingivitis, and tonsillitis [154]. A study carried out to compare *C. myrrha* and NaOCl for their antibacterial activity against *E. faecalis* and *Fusobacterium nucleatum* as root canal irrigants [155]. Results showed that there was no difference between their antibacterial activity, indicating that myrrh is a suitable option for this purpose. In another randomized controlled clinical trial to

assess *C. myrrha*'s clinical implications after tooth extractions, it was noted after testing *Myrrha* in the form of a mouthwash that most patients did not have serious side effects or problems during the postoperative evaluation. This leads to the conclusion that *C. myrrha*'s antimicrobial characteristics make it safe to use after dental surgeries [156].

#### 5.18. *Curcuma longa*

*Curcuma longa* L., commonly referred to as turmeric, is a member of the Zingiberaceae family [157]. It is cultivated extensively in Asia mostly in India and China. Probably originated from India, turmeric has been used in India for at least 2500 years. Turmeric plant is distributed throughout tropic and subtropical region of the world. The origin of the plant is not certain, but it is thought to be originated from Southeastern Asia, most probably from India. *C. longa* has been utilized traditionally as a medicinal herb in Asian countries because of its antioxidant, anti-inflammatory, and antibacterial properties [157]. In dentistry, it is applied in various situations, including dental caries [158], gingivitis, periodontitis [159], oral lichen planus [160], radiation-induced oral mucositis in head and neck cancer patients receiving therapy [161], as a subgingival irrigant [162], and oral submucous fibrosis [163]. A study conducted for the evaluation of *C. longa* essential oil's antibacterial efficacy against *S. mutans* revealed that, at high concentrations, turmeric can reduce the growth of *S. mutans* biofilm, hence preventing the development of dental caries [158]. Turmeric can be used topically, as a subgingival irrigant, as a mouthwash, or as a local drug delivery method to treat periodontal illnesses with similar or even greater efficacy than chlorhexidine in terms of reducing periodontopathic bacteria [164]. Besides, turmeric extract gel can be applied topically to relieve pain, ulceration, and erythematous areas [165,166].

#### 5.19. *Elettaria cardamomum*

*E. cardamomum* (L.) Maton, belonging to the Zingiberaceae family (local name: Cardamom), is an expensive and commercially significant spice that is in demand worldwide. Although it is native to India and Sri Lanka, it is also grown in Guatemala, Thailand, El Salvador, Malay Archipelago, Vietnam, Papua New Guinea, Cambodia, Laos, and Tanzania, with Guatemala being the largest producer of *E. cardamomum* in the world. Numerous monoterpenes, including  $\alpha$ -pinene,  $\alpha$ -terpineol, nerol, linalool, and sabinene, are found in *E. cardamomum* seeds essential oil. Primary periodontal pathogens were used to test the fruits and seeds extracts' antibacterial properties. Extracts stopped the growth of bacterial biofilms. Furthermore, cardamom extract could dramatically lower the release of a few inflammatory intermediates that are triggered by LPS, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-8. Evidence suggested that blocking nuclear factor kappa B (NF- $\kappa$ B) signalling may have caused the anti-inflammatory action [167].

#### 5.20. *Eucalyptus globulus*

*Eucalyptus globulus* is a member of the family Myrtaceae. There are around 700 species and variants in the genus *Eucalyptus* that are native to the tropical regions of southern temperate America, Africa, Australia, and Tasmania [168]. It is called "Ban" or "Kafur" in the Arabic language [169]. Although the market for *Eucalyptus* oil is limited, it has many traditional uses, particularly as a non-prescription medication [170]. In dentistry, *Eucalyptus* oil is utilized for its antibacterial properties against a variety of pathogens, including *S. aureus*, *P. aeruginosa*, MRSA biofilm cultures, *E. coli*, and *C. albicans* [171]. Evaluation of the antibacterial efficacy of different concentrations of *E. globulus* leaf extract on periodontal pathogens that at 100 % concentration the highest ZOI against *A. actinomycetemcomitans* and *P. gingivalis* (5.38  $\pm$  0.32 mm, 4.82  $\pm$  0.11 mm) was obtained, followed by 50 % and 10 % concentrations. Therefore, it can be used as a promising substitute for antibiotics and in the prevention of oral infections [172]. Root canal sealers can be dissolved by *Eucalyptus* oil so it can be used as a natural substitute for xylene [173].

#### 5.21. *Glycyrrhiza glabra*

*Glycyrrhiza glabra* L., a member of the Leguminosae family, has been extensively utilized for more than 4000 years in Ayurvedic and traditional medicine. It is native to Eurasia, in central and south-western Asia and the Mediterranean region. Roots are the most commonly used portion of plants in medicine [174]. In dentistry, it is used to treat oral candidiasis, dental caries, gingival and periodontal disorders, oral cancer, and endodontic conditions [175]. Licorice extracts exhibit a significant inhibitory effect on the development of dental caries in human subjects, especially when manufactured as candies, lollipops, or similar items. These extracts can be incorporated into oral hygiene products to prevent gingival disorders and enhance oral health [176]. In a study, the antibacterial and anti-proteolytic properties of licorice root extract were evaluated against *P. gingivalis* in both planktonic and biofilm cells. The results indicated that the extract exhibited antimicrobial activity against *P. gingivalis* with MIC and MBC values of 62.5  $\mu$ g/ml and 25  $\mu$ g/ml, respectively [177]. Additionally, *G. glabra* inhibits oral *C. albicans* with a mean ZOI of 19.8  $\pm$  0.83 at 24, 48, and 72 h [178]. A randomized clinical trial to assess the preventing effect of *Glycyrrhiza* aqueous extract on oral mucositis in cancer patients receiving head and neck radiation demonstrated that it can be useful in reducing the severity of oral mucositis in head and neck cancer patients receiving radiation therapy [179].

#### 5.22. *Hypericum perforatum*

*Hypericum perforatum* L., commonly referred to as St. John's wort, is an herbaceous perennial plant native to Europe and Asia that has been brought to the United States and is a member of the Hypericaceae family [180]. In dentistry, *H. perforatum* extract is primarily

used for its antibacterial properties. The aqueous fraction was found to have strong antibacterial effects (MIC values of 8 µg/ml) against *L. plantarum* and *S. sobrinus*, as well as moderate activity against *S. mutans* and *E. faecalis*. Sub-extracts showed antibacterial activity against *S. sobrinus* at a concentration of 16 µg/mL, suggesting its potential application as a natural antibacterial agent in oral care products [181]. The antimicrobial activity of its flowers' essential oil showed antibacterial activity against *A. actinomycetemcomitans* which was comparable to that of the CHX solution, while it was less effective against *P. gingivalis*. The essential oil's antibacterial activity was enhanced when it was combined with CHX and povidone-iodine solutions [182]. Additionally, *H. perforatum* has strong anti-inflammatory properties that drastically lower all of the indices of inflammation in a rodent model of periodontitis [183].

### 5.23. *Mangifera indica*

*Mangifera indica*, commonly known as Mango, is a family member of the Anacardiaceae. It grows in various world regions, particularly tropical climates [184]. *M. indica* L. is considered as one of the main tropical fruits in the world, believed to be originated from Asia. It has been reported that China, India, Brazil, Nigeria, Pakistan, Mexico, Thailand, and Philippine are well-known for mango cultivation with India being the highest mango cultivating country. Mango fruit is a well-known source of phytochemicals, health-promoting compounds, and vitamins. Mango fruit additionally has vital phenolic chemicals and energy [185]. Mango has anti-inflammatory, antibacterial, anti-tumor, anti-oxidant, and anti-diabetic properties due to its polyphenol content [186]. Regarding the use of *M. indica* in dentistry, it has been observed that the phytochemicals in *M. indica* leaf extracts have a strong antibacterial impact, particularly on microorganisms that cause tooth decay [187]. Herbal extracts of *M. indica* have been demonstrated in numerous studies to have anti-inflammatory and anti-oral pathogen properties. Additionally, they can stop histamine from releasing [188]. Additionally, A study conducted by Ref. [189], investigated the effectiveness of mango leaf as a tool for oral hygiene and found that the group that used the leaf and the group that used a toothbrush were identical. Moreover, a study conducted examined the effectiveness of Mango stem extract against two human pathogens: the fungus *Aspergillus niger*, which causes toothaches in humans, and the bacterial infection *S. mutans* [190]. Mango bark extract was found to be highly effective in treating toothaches when ethanol was utilized as the extraction solvent and amoxicillin and fluconazole were used as the control antibiotic and antifungal, respectively. Mango extract mouthwashes against *S. mutans* at a 25 % concentration showed significant reductions in PI, GI, and salivary pH after 21 days of use [191]. This indicates that mango mouthwashes can be used as successful substitutes for CHX in children.

### 5.24. *Matricaria chamomilla*

*Matricaria chamomilla*, commonly known as German Chamomile, is a well-known Asteraceae family medicinal herb. It is native to northern and western Asia, as well as southern and eastern Europe [192]. Several phytochemicals have been detected in *M. chamomilla*; its main classes include flavonoids, coumarins, sesquiterpenes, volatile terpenoids, and phenolic acids [193]. Usually, chamomile is consumed as a liquid extract or as tea. Three times a day, 1–4 ml of chamomile extract in water is the common regimen [194]. In dentistry, Chamomile can be used effectively as a mouthwash for gingivitis and periodontal problems. This is supported by a study that demonstrated that at 100 % concentration, Chamomile essential oil exhibited antibacterial action against *P. gingivalis* [195]. Furthermore, it can be used to alleviate burning mouth syndrome and as an irrigation solution [196]. Additionally, chamomile might be a promising substitute for treating oral mucositis [197].

### 5.25. *Mentha piperita*

The genus *Mentha* is a significant taxon in the Lamiaceae family commonly known as Peppermint. It consists of 25–30 species that spread all over the world, particularly in temperate parts of Eurasia, Australia, and South Africa [198]. This naturally occurring genus is native to the Mediterranean region and has been used for flavor, aroma, and therapeutic purposes all over the world. *M. piperita* oil has been used in folk medicine for managing toothaches and decreasing gingival inflammation [199].

In dentistry, the anti-biofilm activities of *M. piperita* against *S. mutans* and dental plaque make it suitable for use in toothpaste and mouthwashes. To investigate the inhibitory impact of *M. piperita* volatile oils loaded in chitosan nano-gels (MPVO-CNs) against *S. mutans* on the dental surface revealed that MPVO-CNs might be used as an antibiofilm agent in toothpaste or mouthwash formulations [200]. In an *in vitro* study *M. piperita* leaf extract showed antimicrobial activity against the oral microorganisms, oral microbes, such as *S. mutans*, *A. actinomycetemcomitans*, and *C. albicans* [201].

### 5.26. *Nigella sativa*

*Nigella sativa*, an annual flowering plant in the Ranunculaceae family, is native to south and southwest Asia and is grown in several Mediterranean nations, including South Europe, Syria, Turkey, and Saudi Arabia. It is also known by the name Black cumin, Black seed, and Habbatul Barakah [202]. *N. sativa* seeds were employed by Greek physicians to treat a variety of illnesses, including toothaches and headaches, nasal congestion, intestinal worms, menstrual irregularities, and increased milk supply [203].

In dentistry, *N. sativa* is useful in treating periodontitis and this is supported by an *in vivo* study carried out in which *N. sativa* toothpaste showed anti-inflammatory effects by reducing both inflammatory cell counts and activity as well as anti-destructive effects on the periodontal extracellular matrix in an *in vivo* evaluation of its effects on periodontitis tissue repair based on inflammation and extracellular matrix [204]. Consequently, the treatment of periodontitis may benefit from the usage of *N. sativa* toothpaste. Additionally, pre-implant tissues are improved by *N. sativa* when applied topically where it showed an improvement in peri-implant tissues



delayed dental implant [205]. Furthermore, an *in vitro* study showed that *N. sativa* can be regarded as a promising remineralizing agent in treating non-cavitated demineralized carious lesions [206].

On the other hand, a randomized active-control trial evaluated the antimicrobial and anti-inflammatory efficacy of *N. sativa* oil in comparison to CHX in patients with gingivitis. The results showed that *N. sativa* oil possessed antibacterial and anti-inflammatory properties, preventing the formation of biofilms, and interfering with the colonization of pathogenic bacteria (*Streptococcus mitis*, *S. sanguinis*, and *S. parasanguinis*), which causes periodontal disorder [207]. As a result, *N. sativa* oil could serve as a safe substitute treatment for gingivitis and enhance overall health outcomes.

### 5.27. *Ocimum tenuiflorum* or *Ocimum sanctum*

*Ocimum tenuiflorum* or *Ocimum sanctum*, often known as Tulsi, is a fragrant shrub belonging to the Lamiaceae (tribe *Ocimeae*) family. It is believed to have originated in north-central India and is currently native to the tropical regions of eastern Europe [208]. Tulsi is an herb that shows great promise for treating dental and oral conditions, common mouth infections can be effectively treated with Tulsi leaves are suitable for use as mouthwash or toothpaste [209]. *O. sanctum* mouth rinse is equally effective as CHX in reducing plaque and gingivitis, and reducing gingival bleeding and plaque through randomized controlled clinical trial evaluation [210]. An *in vitro* study showed that *O. sanctum* aqueous extract was found to be effective against all caries-causing microorganisms when tested at three different concentrations against a variety of caries-causing micro-organisms, including *S. mutans*, *S. mitis*, *S. sanguis*, and *L. acidophilus* [211].

On the other hand, the *in vitro* antimicrobial effect of Tulsi leaf extract on periodontal pathogens using doxycycline as standard, and doxycycline has been used as an adjunct to nonsurgical therapy in patients with periodontitis. It was observed that Tulsi extracts showed antimicrobial activity against *A. actinomycetemcomitans* at 5 % and 10 % concentrations, like doxycycline with similar inhibition zones ( $p > 0.05$ ) [212] to evaluate. However, Tulsi extract could be used as an inexpensive and useful “adjunct” in addition to standard care to treat periodontal conditions.

### 5.28. *Pimpinella anisum*

*Pimpinella anisum* L., commonly known as Anise, is a member of the Umbelliferae family. It is an annual grassy herb that grows in Mexico, Egypt, Spain, the Middle East, West Asia, and the Eastern Mediterranean Region [213].

Regarding its use in dentistry, the antibacterial properties of Anise extract make it a useful home preventative therapy for maintaining dental hygiene which is supported by several studies. The antibacterial efficacy of anise extract as a mouthwash in children against *Lactobacilli* and *S. mutans*, possessed a statistically significant decrease in the number of *Lactobacilli* and *S. mutans* in groups that received a 40 ml Anise extract rinse with a concentration of 10 g anise extract/40 ml [214]. Additionally, in an *in vivo* evaluation of *P. anisum* ethanol extract was found to be efficient against *Streptococci mutans* when tested for its effects on the viability counts of salivary *Streptococci* and *S. mutans* in comparison to CHX [215]. Moreover, an *in vitro* study conducted to examine *P. anisum* essential oil's antibacterial efficacy against *Actinomyces naeslundii*, *E. faecalis*, *L. casei*, and *A. actinomycetemcomitans*, revealed that it was successful against each of the four species [216].

### 5.29. *Pistacia lentiscus*

The evergreen shrub *Pistacia lentiscus* L., sometimes referred to as the Mastic tree, is a member of the Anacardiaceae family and is extensively found in Mediterranean nations [217]. Mastic is a naturally occurring fragrant resin that is extracted from the mastic tree's trunk and branches (*P. lentiscus* L.). In dentistry, it is utilized to prepare dental powder due to resin which contains 12 % essential oil. It smells pleasant and can be used as a filler for cavities, to clean teeth, and to get rid of bad breath odor [218]. The antibacterial activity of chewing mastic gum was tested against the levels of *S. mutans*, total viable bacteria, and *Lactobacilli* in patients' saliva receiving therapy with fixed orthodontic appliances [219]. It demonstrated that chewing mastic gum reduced these levels in the saliva of orthodontically treated patients with fixed appliances, suggesting that chewing mastic gum could help prevent caries lesions. Additionally, *P. lentiscus* essential oil exhibits a broad-spectrum activity against periodontal bacteria and *Candida* with a desirable dual inhibitory capacity toward Cyclooxygenase 2 (COX-2) and Lipoxygenase (LOX) inflammatory enzymes, and without producing any adverse effects against oral cells [220]. Furthermore, more than 0.1 %–0.4 % of mastic oil possessed significant antibacterial activity that suppressed the growth of *S. mutans* responsible for dental caries [221]. Thus, it was claimed that mastic oil could be employed as a prophylactic measure against dental caries since it generated an anti-adhesive capacity in *S. mutans*.

### 5.30. Propolis

Propolis is a resinous substance extracted by bees from a variety of plants [222]. Propolis has great promise in dentistry, oral health care, and medicine because of its qualities [223]. Propolis is usually accessible in a variety of forms, such as lozenges, pills, creams, gels, mouthwashes, and toothpaste [224]. It is used in dentistry for a variety of conditions, including halitosis, periodontitis, and stomatitis. Moreover, it can be utilized in tooth coating preparations, dental caries, traumatic ulcers, dentinal hypersensitivity, and candidal infections [225,226]. Propolis rinse was found to be useful in reducing cariogenic infections in patients with dental caries caused by *Lactobacilli* and *S. mutans* [55]. application of topical Propolis medication to the periodontal pockets of patients with periodontitis demonstrated a tendency toward a decrease in *P. gingivalis* burden in gingival crevicular fluid, as well as a significant

improvement in PPD and clinical attachment level [227]. During supportive periodontal therapy, Propolis-based therapy is probably going to become an alternate treatment option for chronic periodontitis. The ethanol and hexane extracts of propolis demonstrated cytotoxicity towards murine macrophages, and anticancer activity in the tongue cancer cells. However, at the lowest dose tested, neither extract showed any cytotoxic effects on normal gingival fibroblasts [228]. Moreover, Toothpaste containing propolis has been proven to be very successful in enhancing oral health and reducing the incidence of dental plaque-induced gingivitis [229].

### 5.31. *Rosmarinus officinalis*

*Rosmarinus officinalis* L., commonly referred to as Rosemary, is a widely distributed shrub in the Lamiaceae family [230]. It is native to the Mediterranean region and cultivated around the world. In dental practice, *R. officinalis* is mainly used as a freshener for the mouth and to treat gingivitis [199]. An *in vitro* study examined *R. officinalis* extract's antibacterial properties against oral microorganisms within *in situ* initial oral biofilms and showed that *R. officinalis* extract treatment has a considerable potential to eradicate microbial oral initial biofilms. These findings support the use of *R. officinalis* extracts as an herbal adjuvant to synthetic drugs in the treatment of periodontitis and caries by controlling biofilm [231]. Additionally, the viability of monomicrobial biofilms made of *C. albicans*, *S. aureus*, *E. faecalis*, *S. mutans*, and *P. aeruginosa*, as well as those made of *C. albicans* associated with *S. aureus*, *E. faecalis*, *S. mutans*, or *P. aeruginosa* in polymicrobial biofilms were found to be significantly reduced upon application of rosemary extract, except for the *E. faecalis* biofilm [232]. Furthermore, *R. officinalis* extract has a statistically significant antibacterial effect against *S. mutans* in a group of Egyptian children when compared to the gold standard, chlorhexidine. However, the reduction in *S. mutans* counts was found to be slightly higher in CHX, indicating that the use of *R. officinalis* extract in children is safer than CHX due to the natural herb's lack of chemicals [233]. On the other hand, in a randomized controlled double-blind study, a toothpaste derived from *R. officinalis* extract showed efficiently healed gingival bleeding and decreased bacterial plaque in comparison to conventional toothpaste [234].

### 5.32. *Salvia officinalis*

*Salvia officinalis* L., often referred to as Sage, is one of the Lamiaceae family's most commercially significant species [235]. It is a subshrub that is perennial and evergreen, indigenous to the Mediterranean region. Regarding its use in dentistry, a gargle of Sage tea is commonly recommended in modern European herbal medicine for treatment of inflammations in the mouth, and gingivitis. The antiplaque and anti-inflammatory properties of *S. officinalis* herbal mouthwash demonstrated that it successfully reduced the patients' GI and PI [236]. Besides, dental caries can be treated with *S. officinalis* mouthwash which efficiently decreases the count of *S. mutans* in dental plaque in school children [237]. Additionally, when the antibacterial properties of *S. officinalis* and commercial mouthwashes were compared, it was found that the plant extract of *S. officinalis* had the same antibacterial properties as *S. mutans* and *P. gingivalis* [238].

Furthermore, *S. officinalis* is sufficient to eradicate germs responsible for halitosis. To make mouthwashes using *S. officinalis*, infuse one spoonful of dried plant material into one cup of water [239]. On the other hand, *S. officinalis* essential oil demonstrated anti-candidal action against all strains of *C. albicans*, with an inhibition zone ranging from 40.5 mm to 19.5 mm. As a consequence, its volatile oil can be used as an antifungal denture cleaning to prevent candidal adhesion, lowering the risk of Candida-associated denture stomatitis [240].

Sage infusion or fractions comprising its volatile components and either water or its dry matter were applied to human gingival fibroblasts (HGF-1) for 6 h. A mean phorbol-12-myristate-13-acetate/ionomycin (PMA/I)-stimulated production of pro-inflammatory interleukins IL-6 and IL-8 was reduced by more than 50 % ( $p < 0.05$ ) by SI, AD, and DM. In SI-treated cells, the presence of 1,8-cineole, borneol, camphor, and  $\alpha$ -/ $\beta$ -thujone was revealed by cellular uptake studies. Applying the volatile borneol at concentrations typical of sage infusion showed more than 50 % mean reduction of PMA/I-induced IL-6 and IL-8 release [241].

### 5.33. *Salvadora persica*

*Salvadora persica*, a member of the Salvadoraceae family, is more often known as the Arak tree. It is the most commonly used to make chewing sticks, especially in the Middle East's most prevalent source of Miswak [242]. This plant's sticks are typically chewed or tapered on one end until they shred into a brush-like form, which is then used to clean teeth in a way that's comparable to that of a toothbrush [243]. *S. persica* may be beneficial for halitosis, cavity prevention, plaque reduction, and bacterial oral germs [244]. It can also hasten the healing of wounds following extractions or oral or periodontal surgery and has whitening and orthodontic chain preservation qualities.

Further, after dental caries, it has remineralization properties and can be applied as toothpaste, chewing gum, mouthwash, and chewing sticks [245]. *S. persica* chewing sticks and toothbrushes are just as effective in maintaining gingival health and controlling plaque as standard toothbrushes, which confirms their anti-plaque and anti-gingivitis properties [246].

### 5.34. *Sanguinaria canadensis*

*Sanguinaria canadensis*, often referred to as Bloodroot is a member of the Papaveraceae family and is primarily found in the region between the east coast and the Midwest of North America. When *S. canadensis* root extract was introduced to toothpaste and mouthwash in the early 1980s, the products quickly became well-known all over the world [247]. In dentistry, it is used to treat periodontal disease and gingivitis. Because it prevents oral germs from growing, it is also occasionally added to toothpaste and other

oral hygiene products [248,249]. Furthermore, using 15 mL of mouthwash for 15 s twice a day was linked to a 65 % decrease in sulfur compounds breathed into the air, suggesting that *Sanguinaria* extract oral rinses could be useful in the treatment of halitosis [250]. *S. canadensis* tincture linked to chewing gum significantly reduced dental plaque scores and the number of *Streptococcus* species when compared to placebo chewing gums, according to a double-blind, placebo-control study evaluating the effect of the chewing gum on dental plaque scores and *Streptococcus* species [251]. The therapeutic efficacy of a natural Mexican *Sanguinaria* extract against gingivitis was confirmed and the extract can be used as a supportive treatment in the form of an oral rinse [252].

### 5.35. *Syzygium aromaticum*

*Syzygium aromaticum* L., sometimes referred to as Clove is a member of the Myrtaceae family [253]. *Syzygium* is a vast family of plants that ranges from Southern India and Southeast China to Southeast Australia and New Zealand. However, whereas Malaysia is the center of the genus in terms of species richness, it appears that the Malaysian-Australian region is the center of the genus in terms of its basic evolutionary diversity. Multiple species belong to this genus, which extends from southern East Asia and the Pacific to Africa and Madagascar. Eugenol, one of the constituents of the volatile oil of Clove buds has been used in dentistry to heal minor oral wounds, as an analgesic in painful and infectious disorders of the oral cavity and oropharynx, and for general oral hygiene additionally, it can be used for treating gingival bleeding [194,254]. Clove can be applied topically or used as toothpaste and mouthwash [255]. A study carried out for the evaluation of *S. aromaticum* and its bud oil's antimicrobial activity against dental caries-causing microorganisms, such as *S. mutans*, *S. aureus*, *L. acidophilus*, *C. albicans*, and *Saccharomyces cerevisiae*, revealed that cloves and clove oil possess strong antimicrobial properties against the tested microorganisms [256]. On the other hand, a study was conducted to evaluate the potential of *S. aromaticum* volatile oil as a viable option for developing oral care functional items for the treatment of halitosis. It was found to be effective in preventing halitosis triggered by the oral bacterium *S. sanguinis* [257].

### 5.36. *Terminalia chebula*

*Terminalia chebula*, a member of the Combretaceae family, is also referred to as Black myrobalan. In India and other countries in Asia and Africa, *T. chebula* is widely utilized for its wide range of significant phytoconstituents, including polyphenols, terpenes, anthocyanins, flavonoids, alkaloids, and glycosides, it displays a wide range of therapeutic properties [258]. In dentistry, *T. chebula* extract is utilized to treat gingivitis by reducing inflammation, thereby preventing periodontal disorders, by providing anti-inflammatory effects in gingivitis [259].

After clinical evaluation of *T. chebula* aqueous extract as a mouth rinse, it was efficient as an antibacterial agent as it decreased the number of microorganisms by increasing the pH and buffering capacity [260]. *T. chebula* aqueous extract suppresses *S. mutans* with great potency by preventing it from adhering to oral surfaces, aggregating glucan, and growing where its effect lasted for as long as 90 min after rinsing [261].

Additionally, *T. chebula* fruit different extracts exhibited high activity against five dental caries-causing microorganisms, namely *S. mutans*, *L. acidophilus*, *S. aureus*, and two yeasts, *Saccharomyces cerevisiae* and *C. albicans* with MIC ranging from 12.5 to 25 mg/ml [262]. As a result, *T. chebula* fruit extracts can be employed as an alternative antimicrobial agent against dental caries-causing microorganisms. Moreover, *T. chebula* ethanol extract revealed a potent antimicrobial agent to treat tooth caries caused by *S. mutans* which may be helpful in antibacterial oral hygiene products [263]. Besides, *T. chebula*'s aqueous extracts have the potential to be used as kid-friendly anti-cariogenic mouthwashes due to their acceptable tastes [264].

### 5.37. *Thymus vulgaris*

Among the members of the Lamiaceae family, *Thymus vulgaris*, is better known by its common name, Thyme. This herb is native to the Mediterranean region (Spain, Italy, France, Greece, Egypt, Lebanon, and Turkey), used for culinary and medicinal purposes [265]. The antibacterial activity of its volatile oil has been proven, even against *S. mutans*, one of the main causes of dental caries, indicating the efficacy of *T. vulgaris* extracts in treating dental illnesses. In addition, Thyme extract can be used to treat oral *Herpes*, chronic *Candidiasis*, and halitosis due to the presence of carvacrol and thymol [266,267]. *T. vulgaris* essential oil exhibits good antimicrobial action against *C. albicans* and may be used at a concentration of 2 % to ensure that orthodontic appliances are free of fungal infection [268]. *T. vulgaris* extract was effective against the viable count of salivary *Streptococci* as *S. mutans* [269]. Additionally, thyme oil as root canal irrigants to the *E. faecalis* bacteria showed activity of 55.6 % [270]. Moreover, thyme water extract showed antimicrobial activity on a variety of bacterial isolates, including *S. aureus*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*, as well as cultivated root canal swabs where it exhibited the greatest antimicrobial activity against *M. catarrhalis* [271]. As a result, thyme water extracts could be beneficial for irrigation purposes in root canals due to their antibacterial properties. On the other hand, research on the potential of a gingival mucoadhesive patch derived from *T. vulgaris* essential oil to suppress the growth of *A. actinomycetemcomitans* and *F. nucleatum* bacteria revealed that the growth of these bacteria can be suppressed by its use [272].

### 5.38. *Trigonella foenum-graecum*

*Trigonella foenum-graecum*, known by most as Fenugreek, is an annual plant that belongs to the Leguminosae family and is extensively grown in Asia and the Mediterranean region. Due to the dried seeds' numerous health benefits, including their galactagogue, antibacterial, anti-inflammatory, insulinotropic, and restorative properties, they have been utilized for centuries in Egypt,

India, China, and some regions of Europe [273]. Regarding its use in dentistry, seed extract of *T. foenum-graecum* (SETFG) is a suitable substitute irrigation agent for root canals [274].

Additionally, Fenugreek can be utilized as a substitute periodontal dressing to lessen inflammation following surgery [275]. Fenugreek gel possessed antimicrobial and anti-inflammatory activity against *S. mutans*, *Lactobacillus*, *E. faecalis*, and *C. albicans* oral microbes where at a concentration of 100 µg/ml, Fenugreek gel had a higher ZOI ( $5.39 \pm 0.05$ ) than doxycycline ( $1.1 \pm 0.08$ ), indicating a high level of antimicrobial potential against all oral microorganisms. When Fenugreek extract was compared to aspirin at 100 µg/ml, the anti-inflammatory activity of the gel revealed a greater inhibition zone ( $67.15 \pm 1.36$ ), indicating that fenugreek gel possesses higher antimicrobial and anti-inflammatory properties than aspirin and doxycycline. Fenugreek also helps with recurrent aphthous stomatitis as it can improve recurrent aphthous stomatitis using bucco adhesive paste of fenugreek because of the paste's strong adhesion to the ulcer's surface, which creates a barrier that protects against most mechanical irritations or infections [276]. On the other hand, Fenugreek toothpaste was found to be beneficial in treating gingivitis, as evidenced by a reduction in the clinical characteristics of gingivitis when compared to ordinary toothpaste in the control of mild gingivitis [277].

### 5.39. *Vitis vinifera*

*Vitis vinifera* L., Grapes, is one of the oldest varieties used in wineries and other applications. It originated in Europe [278]. Grapes seeds obtained from *V. vinifera* are naturally occurring and have numerous biological and dental uses. It is mostly used in dentistry to prevent tooth cavities and perform restorative dentistry. The proanthocyanidin group is the primary grapes seeds phytoconstituent that has positive effects on dental diseases [279].

According to *in vivo* experimental studies, Grapes seeds extract can decrease *S. mutans* colonization, which is the primary bacterium that causes dental cavities, and lessens dentine deterioration by strengthening the collagenous tissues through the formation of crosslinks [280]. It also promotes the synthesis of collagen [281]. In comparison to other scavenging agents like sodium ascorbate, the bleached enamel treated with Grapes seeds extract gains a noticeably stronger connection [282]. In addition, through mineral deposition, Grapes seeds extract can help restore the mineral content of tooth surfaces [283].

Furthermore, the antifungal activity of acrylic soft liners and their adherence to denture base material may be enhanced by grape seed extract [284]. According to a study carried out to assess the ability of different Grapes seeds formulations to influence the physical properties of conventional glass ionomer cement (GIC), it was found that the traditional GIC modified with 3 % v/v grape seed oil is a promising restorative material with improved physical properties and a pleasing appearance [285]. On the other hand, an *in vitro* study evaluated the antibacterial efficacy of red Grape ethanol extract (red Grapes) as a root canal irrigation material against *Actinomyces* spp. bacterial growth. The results indicated that there were notable variations in the ethanol extract of red Grapes' ability to inhibit *Actinomyces* spp. bacterial growth at each concentration, indicating its effectiveness as a root canal irrigation material [286].

### 5.40. *Zingiber officinale*

*Zingiber officinale* Roscoe, frequently referred to as Ginger, is a member of the Zingiberaceae family and genus. It is seasonally cultivated in many tropical and subtropical regions worldwide, including Australia, China, Indonesia, India, Malaysia, Nigeria, Spain, and others. For a very long time, humanity has used ginger as a spice and an herbal remedy. It has oleoresins, sesquiterpene hydrocarbons, and phenolic substances such as shogaol and gingerol [287]. In the dental field, it can be applied as an intracanal dressing [288] and can be employed in patients with recurrent aphthous and denture stomatitis [289,290]. Plaque can be effectively controlled during the periodontal maintenance phase with a natural gel that contains *Z. officinale* and honey [291]. Ginger reduces pain nearly as effectively as Ibuprofen even though it has fewer adverse effects, it is preferable to use it as an analgesic to manage pain during periodontal flap surgery [292]. Another *in vitro* study showed that *Z. officinale* extract had strong antibacterial activity against *S. mutans* and *S. sanguinis* cariogenic microorganisms, as evidenced by the effects of varying concentrations of the extract on their proliferation. The MIC was 0.02 mg/mL for *S. mutans* and 0.3 mg/mL for *S. sanguinis*, and the MBC was 0.04 mg for *S. mutans* and 0.6 mg for *S. sanguinis* [293]. Additionally, to ascertain and formulate the antibacterial activity of *Z. officinale* extract against *E. faecalis* as a possible cost-effective and readily available irrigating solution, it was found that the extract possesses antimicrobial activity against *E. faecalis* with an MBC of 15.625 mg/mL ( $p < 0.05$ ) and can be further developed as a potential root canal irrigation solution [294].

Moreover, a study to investigate the relationship between oxidative stress, antioxidant enzymes, total antioxidant capacity, and periodontal parameters; and evaluate *Z. officinale* mouthwash effects and periodontal therapy on oxidative stress, total antioxidant capacity, and antioxidant enzyme activities in the saliva of patients with periodontitis showed that, in addition to periodontal therapy, the mouthwash can be useful in managing inflammation, lowering oxidative stress, according to clinical and biochemical markers that primarily showed positive correlations [295]. On the other hand, the degree of salivary acidity before and after brushing the teeth with ginger extract toothpaste had an impact on the effectiveness of the toothpaste in reducing the formation of bacteria that cause dental cavities [296].

### 5.41. Miscellaneous herbal preparations

The antibacterial activity of extracts from *Echinacea purpura*, *Arctium lappa*, and *Zataria multiflora* was tested as a herbal mouthwash ingredient. The combination of Echinacea and Burdock extracts (5.86 mg/ml) with Zataria essential oil (0.08 µl/ml) showed bactericidal action against *S. mutans*. The formulation produced biofilm destruction and had a substantial impact on microbial biofilm development [297]. *S. mutans*, *L. acidophilus*, *S. salivarius*, *S. mitis*, *S. aureus*, *E. coli*, and *C. albicans* were used to test the antimicrobial

and antibiofilm activities of propolis extracts from various areas. These were the range of MIC values, expressed in  $\text{mg mL}^{-1}$ : *S. mutans* (0.003–0.029), *L. acidophilus* (0.007–0.117), *S. salivarius* (0.003–0.048), *S. mitis* (0.007–0.058), *S. aureus* (0.007–0.058), *E. coli* (0.007–0.058), and *C. albicans* (0.014–0.234) [298]. Amla seed extract was utilized in a study to create graphene oxide (GO)-silver (Ag) nanocomposite mouthwash. The study's findings demonstrated that in individuals with plaque-induced gingivitis, amla seed extract effectively decreased plaque, gingival inflammation, and colony-forming units [299]. When *Aloe vera*, povidone-iodine, and probiotic mouthwash were compared against chlorhexidine mouthwashes in a clinical investigation to see which was more effective in lowering bleeding and plaque scores in individuals with gingivitis, the results showed that probiotic demonstrated superior outcomes across all clinical criteria more than *Aloe vera* and povidone-iodine [300]. *Actinidia deliciosa* (kiwifruit) extract has been shown to stimulate angiogenesis and increase the migration and proliferation of human gingival fibroblasts, making it a viable agent for healing oral wounds [301].

## 6. Secondary metabolites used in dental care

Numerous beneficial antimicrobial phytochemicals, including simple phenols, phenolic acids, quinones, flavones, flavonoids, flavonols, tannins, coumarins, terpenoids, essential oils, alkaloids, lectins, and antimicrobial peptides, are embedded in a variety of plants that are employed in the treatment of oral infections. Antioxidant qualities are the traditional explanation for the effects of flavonoids. Besides, Different forms of oral malignancies can be treated *in vitro* and *in vivo* by several alkaloids that are derived from natural herbs. These effects include anti-proliferation, antibacterial, antiviral, and anti-metastatic benefits. The following are some classes of natural compounds that treat many dental disorders and are summarized with their mechanism of action in Table 2.

### 6.1. Terpenes

#### 6.1.1. Monoterpenes

6.1.1.1.  *$\alpha$ -Pinene*. It is a bicyclic monoterpene of *Curcuma* spp. Pretreating HSV-1 for 1 h before infection with oils or monoterpene compounds significantly reduced the amount of plaque that formed. Alpha-pinene, showed a reduction in infectivity of >96 % [349]. Additionally, it was effective against *Candida* species responsible for oral candidiasis [319].

6.1.1.2.  *$\alpha$ -terpineol*. It is a monoterpene of *Citrus* spp. Through quantitative real-time reverse transcription polymerase chain reaction tests,  *$\alpha$ -terpineol* blocked the IL-6 receptor gene expression, confirming the anti-inflammatory effect of  *$\alpha$ -terpineol* on IL-6 production [350].

6.1.1.3. *Carvacrol*. It is a natural monoterpene of Oregano and Thyme essential oils. Formalin, Capsaicin, and glutamate-induced orofacial nociception were examined in mice pretreated with carvacrol and  $\beta$ -cyclodextrin complex containing carvacrol to explore their antinociceptive impact. The effects of capsaicin or glutamate injection-induced nociception were significantly reduced by carvacrol preparations. Therefore, the carvacrol encapsulation in  $\beta$ -cyclodextrin can function as a significant therapeutic agent of pharmacological interest for the treatment of pain in the orofacial region [351].

6.1.1.4. *Eugenol*. It is a monoterpene of *Eugenia aromatica* (Clove). Clove oil demonstrated antibacterial activity against all tested oral bacteria that were comparable to eugenol. Additionally, when clove oil or eugenol was combined with antibiotics, the MIC and MBC were lowered to one-half-one sixteenth. Time-kill tests employing clove oil or eugenol with antibiotics confirmed the synergistic effect. When ampicillin or gentamicin was added to clove oil or eugenol at a minimum inhibitory concentration (MIC) for 60 min, the rate of CFU/mL killing increased more than when the antibiotic was used alone [352].

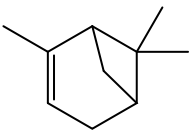
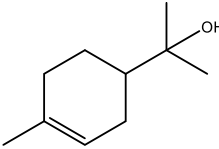
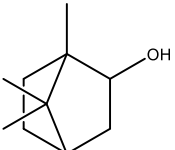
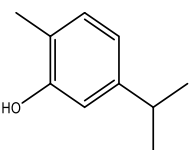
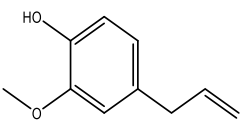
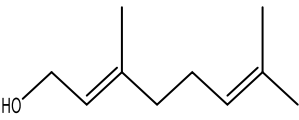
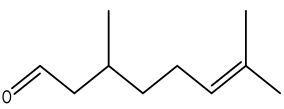
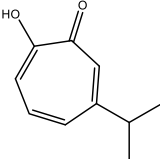
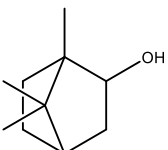
Eugenol has extensive usage in several dental applications, including as a local anesthetic and a component in dental cement for temporary fillings [353]. Compared to other local anesthetics, it is more user-friendly and can be used at a lower dosage [354]. Also, it is quickly metabolized and eliminated, negating the need for a withdrawal period [355]. In juvenile and sub-adult Tambaqui fish, eugenol at 65 mg/L was demonstrated to safely and successfully induce all stages of anesthesia within the necessary time frame [356].

The study examined the antibacterial properties and mechanism of eugenol derived from the leaves of *Syzygium aromaticum* L. (Clove) essential oil (CLEO) about *Porphyromonas gingivalis*, an oral anaerobe. At a concentration of 31.25  $\mu\text{M}$ , the results demonstrated that eugenol, which made up 90.84 % of clove volatile oil, had antibacterial activity against *P. gingivalis*. Additionally, at various concentrations, eugenol decreased the preformed biofilm of *P. gingivalis* and prevented the formation of new biofilm. Eugenol suppressed biofilm formation at the initial stage, which was explained by the downregulation of biofilm-related virulence factor genes (*fimA*, *hagA*, *hagB*, *rgpA*, *rgpB*, *kgp*). These results point to the possibility of using clove essential oil and eugenol as food and personal hygiene product additives as a preventative measure against periodontitis [357].

6.1.1.5. *Geraniol*. It has been demonstrated that geraniol, an acyclic monoterpene present in lemongrass volatile oil, has antioxidant and anticancer properties against a variety of cancer forms. A study examined the putative chemoprotective function of geraniol against oral carcinogenesis in male Wistar rats. Additionally, the study aimed to evaluate the anti-inflammatory mechanisms of action through potential NF- $\kappa$ B signaling. By upregulating the expressions of tumor necrosis factor (TNF- $\alpha$ ), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-1 $\beta$  (IL-1 $\beta$ ), and nuclear factor kappa- $\beta$  (NF- $\kappa$ B).

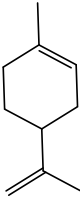
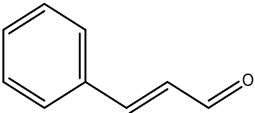
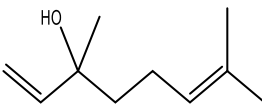
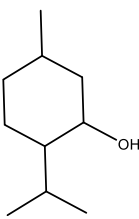
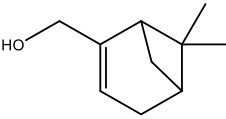
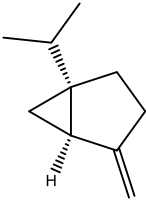
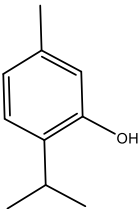
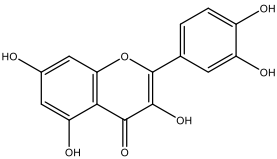
**Table (2)**

List of some natural phytoconstituents used for dental therapy and their mechanism of action.

No.	Phytoconstituents	Chemical structure	Natural source	Mechanism of action	Ref.
<b>A- Terpenes</b>					
<b>I- Monoterpenes</b>					
1	$\alpha$ -Pinene		<i>Cannabis sativa</i> L. <i>Curcuma</i> spp. <i>Daucus carota</i> . <i>Juniperus</i> spp. <i>Pinophyta</i> spp. <i>Piper nigrum</i> .	- Analgesic. - Antinociceptive. - Antifungal. - Anti viral.	[319,349, 387,388]
2	$\alpha$ -Terpineol		<i>Citrus aurantium</i> ssp. <i>Melaleuca</i> spp. <i>Origanum vulgare</i> L. <i>Pinus</i> spp. <i>Salvia rosmarinus</i> . <i>Vitex agnus-castus</i> . <i>Zingiber officinale</i> .	- Anti-inflammatory.	[350,388]
3	Borneol		<i>Daucus carota</i> . <i>Mentha spicata</i> . <i>Salvia officinalis</i> . <i>Salvia rosmarinus</i> . <i>Thymus vulgaris</i> . <i>Zingiber</i> spp.	- Anti-inflammatory.	[241,388]
4	Carvacrol		<i>Lippia origanoides</i> . <i>Origanum dictamnus</i> . <i>Origanum vulgare</i> . <i>Satureja thymbra</i> . <i>Thymus capitatus</i> . <i>Thymus serpyllum</i> . <i>Thymus vulgaris</i> .	- Analgesic. - Antinociceptive.	[351,388]
5	Eugenol		<i>Cinnamomum</i> spp. <i>Myristica fragrans</i> . <i>Ocimum</i> spp. <i>Pimenta dioica</i> <i>Syzygium aromaticum</i> .	- Antibacterial. - Local anesthetic.	[352,357, 389]
6	Geraniol		<i>Camellia sinensis</i> . <i>Citrus</i> $\times$ <i>deliciosa</i> . <i>Cymbopogon</i> spp. <i>Vitis vinifera</i> . <i>Humulus lupulus</i> . <i>Pelargonium</i> spp. <i>Rosa</i> spp. <i>Zingiber officinale</i> .	- Anti-cancer. - Anti-inflammatory.	[358,388]
7	Citronellal		<i>Corymbia citriodora</i> . <i>Cymbopogon</i> spp. <i>Ocimum</i> spp. <i>Zingiber</i> spp.	- Analgesic. - Antinociceptive.	[388,390]
8	Hinokitiol ( $\beta$ -thujaplicin)		<i>Chamaecyparis</i> spp. <i>Cupressus</i> spp. <i>Thuja</i> spp. <i>Thujopsis dolabrata</i> .	- Anticancer. - Antifungal. - Antibacterial. - Anti-inflammatory.	[360-362, 388]
9	Isoborneol		<i>Artemisia annua</i> . <i>Curcuma amada</i> . <i>Cinnamomum camphora</i> . <i>Salvia fruticose</i> . <i>Salvia officinalis</i> . <i>Thymus vulgaris</i> . <i>Zingiber officinale</i> .	- Antiviral.	[363,388]

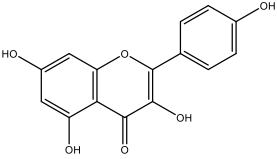
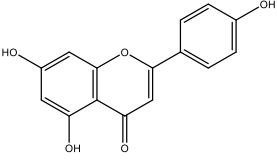
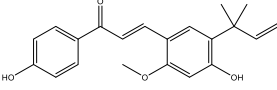
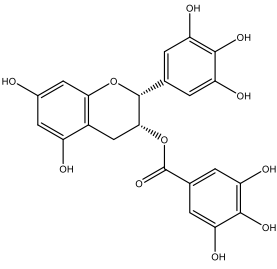
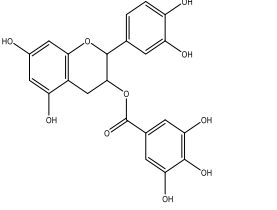
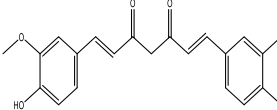
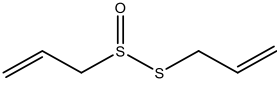
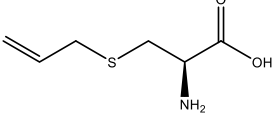
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Table (2) (continued)

No.	Phytoconstituents	Chemical structure	Natural source	Mechanism of action	Ref.
10	Limonene		<i>anethum graveolens</i> . <i>Citrus</i> spp. <i>Eucalyptus globulus</i> .  <i>Melaleuca alternifolia</i> . <i>Salvia officinalis</i> . <i>Salvia rosmarinus</i> . <i>Vitex agnus-castus</i> .	- Antibacterial. - Antiviral.	[365,366,388]
11	Trans-Cinnamaldehyde		<i>Cinamommum zeylanicum</i> .	- Antibacterial.	[367,391]
12	Linalool		<i>Lavendula officinalis</i> .	- periodontal pathogens.	[368,392]
13	Menthol		<i>Mentha</i> spp.	- Antiviral. - significant decrease in plaque. - reduction in gingival and bleeding indices.	[369,388,393]
14	Myrtenol		<i>Achillea</i> spp. <i>Eucalyptus</i> spp. <i>Myrtus communis</i> . <i>Taxus</i> spp.	- Analgesic. - Antinociceptive.	[370,388]
15	Sabinene		<i>Artemisia annua</i> . <i>Juniperus communis</i> . <i>Mesosphaerum suaveolens</i> . <i>Piper nigrum</i> . <i>Salvia Rosmarinus</i> . <i>Vitex agnus-castus</i> . <i>Zingiber montanum</i> .	- Antibacterial.	[388]
16	Thymol		<i>Lippia</i> spp. <i>Nigella sativa</i> . <i>Ocimum</i> spp. <i>Origanum</i> spp. <i>Satureja thymbra</i> . <i>Thymus</i> spp. <i>Trachyspermum ammi</i> .	- Anti-cancer. - Antifungal. - Antibacterial.	[372,373,388]
<b>B- Flavonoids</b>					
17	Quercetin (Flavonol)		<i>Calendula officinalis</i> . <i>Phytolacca americana</i> .	- squamous cell carcinoma. - Anti-inflammatory. - Antibacterial. - recurrent aphthous oral cancer.	[310,374,375,394,395]

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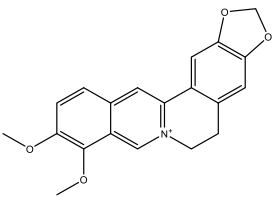
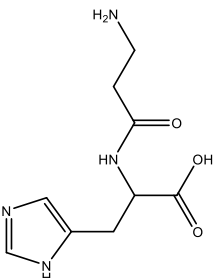
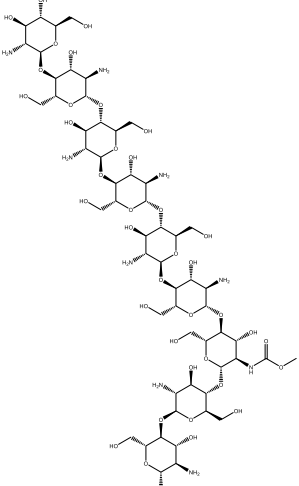
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No.	Phytoconstituents	Chemical structure	Natural source	Mechanism of action	Ref.
18	Kaempferol (flavonol)		<i>Phytolacca americana</i> . <i>Camellia sinensis</i> .	- Antibacterial against <i>S.aureus</i> and <i>P.gingivalis</i> .	[375]
19	Apigenin (flavone)		<i>Matricaria chamomilla</i> .	- promotes human oral osteoblasts proliferation. - promotes mineralization.	[376,396]
20	Licochalcone A (Chalcones)		<i>Glycyrrhiza glabra</i> .	- Antibacterial against <i>P.gingivalis</i> .	[176]
<b>C- Polyphenolics</b>					
21	Epigallocatechin 3-gallate		<i>Camellia sinensis</i> .	- prevents dental caries. - Antibacterial.	[377,378, 397]
22	Epicatechin gallate				
23	Curcumin		<i>Curcuma longa</i> .	- Anti-cariogenic against <i>S.aureus</i> . - prevention of plaque and gingivitis. - Anti-inflammatory	[379]
<b>D- Sulfur-containing compounds</b>					
24	Allicin		<i>Allium sativum</i> .	- decreasing oral ulcers. - Antimicrobial. - Antioxidant.	[396,398, 399]
25	S-allyl cysteine			- Human oral cancer.	[381]
<b>E- Alkaloids</b>					

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Table (2) (continued)

No.	Phytoconstituents	Chemical structure	Natural source	Mechanism of action	Ref.
26	Berberine		<i>Coptidis</i> rhizome.	- Anti-inflammatory. - Antibacterial.	[382,383]
<b>F- Enzymes</b>					
27	Papain		- latex of <i>Carica papaya</i> .	- dental caries for removing debris without any harmful effect on the surrounding tissues.	[384]
<b>G- Polysaccharides</b>					
28	Chitosan		- natural cationic polymer extracted from the shells of Crustaceans and shellfish	- Anti-inflammatory. - Antibacterial. - Antifungal.	[385,386,388]

Furthermore, there was a greater increase in the cancer niche when toluidine blue and alcian blue-safranin staining were used to detect immature and mature mast cells. When geraniol 200 mg/kg b. w. was administered concurrently, there was a noticeable drop in the amount of p65 NF- $\kappa$ B in the nucleus. This could be because NF- $\kappa$ B activation and translocation into the nucleus are inhibited. This was further supported by a decrease in the density of immature and mature mast cells as well as the expression of inflammatory downstream mediators like TNF- $\alpha$ , IL-1 $\beta$ , COX-2, and iNOS. As a result, geraniol can be considered a possible anti-inflammatory drug, which activates NF- $\kappa$ B, and changes the expression of inflammatory mediators [358].

**6.1.1.6. Citronella.** Citronellal is a monoterpene that is mostly produced by plants' secondary metabolism, the main component of citronella oil which gives it its distinctive lemon aroma. The antinociceptive effects of citronellal on orofacial nociception showed a reduction in nociceptive face-rubbing behavior after pretreatment. According to these findings, citronellal may be a valuable tool for the management and/or therapy of orofacial discomfort [359].

**6.1.1.7. Hinokitiol.** Hinokitiol is an essential oil constituent extracted from the Cupressaceae family. It was found to have antibacterial properties against a variety of pathogenic bacteria that can infect the mouth, nose, and nasopharynx, such as *S. mutans*, *S. sobrinus*, *P. gingivalis*, *A. actinomycetemcomitans*, *Prevotella intermedia*, *Fusobacterium nucleatum*, methicillin-resistant and -susceptible *S. aureus*, antibiotic-resistant and -susceptible *S. pneumoniae*, and *S. pyogenes*. Hinokitiol significantly inhibited the growth of all of these

bacterial strains; the minimal inhibitory concentrations of hinokitiol were against *S. mutans*, *S. sobrinus*, *P. gingivalis*, *P. intermedia*, *A. actinomycetemcomitans*, *F. nucleatum*, methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus*, antibiotic-resistant *S. pneumoniae* isolates, antibiotic-susceptible *S. pneumoniae*, and *S. pyogenes* which were from 0.3 to 50 µg/mL [360].

Local hinokitiol therapy effectively reduced osteoclast differentiation and alveolar bone loss caused by tooth ligation. Furthermore, both *in vitro* and *in vivo*, hinokitiol therapy reduced the oral bacterial load of the silk ligature and downregulated the mRNA levels of genes linked to the inflammatory cytokines. Then hinokitiol possessed anti-inflammatory and antibacterial properties, as well as a protective impact against periodontitis [361].

The growth of *C. albicans* was consistently inhibited by hinokitiol, which was also effective against a panel of *Candida* strains with various azole-resistant mechanisms. Based on its mechanism studies, it was found that hinokitiol did not affect mammalian cells but chelated intracellular iron in fungi and hindered their respiration, decreased intracellular ATP generation, and increased harmful intracellular reductive stress were the results of hinokitiol's further inhibition of the activities of mitochondrial respiratory chain complexes I and II and reduction of mitochondrial membrane potential. Moreover, hinokitiol significantly increased the survival of *Galleria mellonella* infected with *Candida* and showed no tendency to cause resistance in several *Candida* species [362].

**6.1.1.8. Isoborneol.** It is a monoterpene of *Artemisia annua*. Isoborneol has shown dual viricidal action against the *Herpes simplex* virus type 1 (HSV-1) where it inactivated HSV-1 by nearly 4 log<sub>10</sub> values within 30 min of exposure, and at a concentration of 0.06 % it suppressed viral reproduction without influencing viral adsorption [363].

**6.1.1.9. Limonene.** Limonene is a monoterpene, the major component in the oil of oranges. It exerts a considerable reduction in adherence of bacteria to buccal epithelial cells with MIC and MFC values of 300 µg/mL and 400 µg/mL, respectively. Their growth was 100 % inhibited after 9 h of incubation. Proteinases and phospholipases secreted 73 % and 53 % less at MIC, respectively. There was a 91 % reduction in adhesion and an 87 % reduction in biofilm development. On silicon sheets, the formation of biofilm biomass was prevented by 69 %. Biofilm integrity and structure were disturbed by limonene treatment. Studying four distinct hyphae-inducing media, the amount of filamentation was greatly decreased. In summary, limonene inhibits adhesion, biofilm formation, and morphological changes by binding to proteins essential to *Candida* pathogenicity. It shows enormous promise for treating invasive *candidiasis* and is harmless [364].

Using the disk diffusion method, the minimal inhibitory doses of limonene and lemon oil were determined against *S. sobrinus* infection. Lemon oil and limonene had minimum inhibitory values of 4.50 and 21.00 mg/mL, respectively and the caries lesions were found to be lower [365].

The antiviral efficacy of limonene against *Herpes simplex* virus type 1 (HSV-1) was investigated *in vitro*. It eliminated viral infectivity and demonstrated strong anti-HSV-1 efficacy. The viral infection was rendered inactive by the dose-dependent interactions with the virus. According to this limonene may be employed as a future antiviral medicine as it shows antiherpetic activity during the early stages of viral replication [366].

**6.1.1.10. Trans cinnamaldehyde.** (*E*)-cinnamaldehyde is the *E* (trans) stereoisomer of cinnamaldehyde the main active constituent of Cinnamon volatile oil. It demonstrates substantial antibacterial properties where the volatile oil's MIC was 6.25 µg/mL and the cinnamaldehyde's MIC was 2.5 µM. Additionally, it was found that cinnamaldehyde inhibited the *P. gingivalis* biofilm by 67.3 % [367].

**6.1.1.11. Linalool.** It is a monoterpene of the oil of Lavender. The minimum inhibitory concentration (MIC) of linalool against periodontal infections ranged from 0.1 to 1.6 mg/mL. Linalool exhibited reduced antibacterial activity against cariogenic bacteria. Except for the *S. mutans* strain, which is the most sensitive to linalool (MIC and MBC of 0.1 mg/mL), the antibacterial activity against cariogenic bacteria was rather weaker, with values ranging from 0.4 to 1.6 mg/mL. If used in toothpastes or mouthwashes, the maximum concentration of linalool and  $\alpha$ -terpineol should be 0.4 mg/mL and higher due to their increased toxicity on the KB cell line [368].

**6.1.1.12. Menthol.** It is a monoterpene of *Mentha* spp. Menthol mouthwash significantly reduces the plaque, gingival, and bleeding indices, which are 0.56, 0.45, and 0.03, respectively. Menthol mouth rinse (0.018 %) can be used as an effective antiplaque and anti-gingivitis agent [369].

**6.1.1.13. Myrtenol.** It is a monoterpene of *Achillea* spp. Myrtenol therapy has two effects: one is anti-inflammatory because it lowers the levels of IL-1 $\beta$  in the trigeminal ganglia, and the other is antinociceptive because it inhibits the activation of p38-MAPK in these cells. Therefore, myrtenol has the potential to cure orofacial inflammation and pain [370].

**6.1.1.14. Sabinene.** A naturally occurring bicyclic monoterpene that is present in Juniper berries. It exerts inhibitory effects on cariogenic activity when applied to *S. mutans*. Sabinene prevented *S. mutans* from growing and adhering. The glucan-binding protein level dramatically dropped by the inhibitory effects on bacterial adhesion as well as suppression of biofilm development and acid production [371].

**6.1.1.15. Thymol.** It is a monoterpene of Thyme that can be used effectively to manage early childhood caries. Thymol possesses an anti-infective potential against *C. albicans* and *S. mutans*. At a dosage of 300 µg/ml, it fully stopped the development and multiplication

of both organisms showing rapid pathogen-killing effectiveness within a 2-min time frame. Furthermore, it successfully reduces the virulence and biofilm formation, including filamentation, yeast-to-hyphal transition, hyphal-to-yeast transition, acidogenicity, and acidity, at sub-inhibitory doses [372].

Thymol also exhibits *in vitro* cytotoxicity when applied to acute promyelocytic leukemia cells and oral squamous cell carcinoma. Thymol causes apoptosis and mitochondrial malfunction and may be effective against a variety of malignancies [373].

## 6.2. Flavonoids

### 6.2.1. Quercetin (flavonol)

*Calendula officinalis* is a good source of quercetin, a flavonoid component with antibacterial and anti-inflammatory properties that works against *S. aureus* and oral cancer. Annexin V/PI double labeling was used to look at how quercetin affected the apoptotic process in squamous carcinoma cells. The percentage of early apoptotic cells found at 24 h (5.97 %) and 48 h (21.06 %) increased. This indicates that quercetin induces cell apoptosis and time-dependently triggers early-stage apoptosis [374].

At 8 µg/mL, quercetin showed 96 % growth inhibition against *S. mutans*, but at all tested dosages, it did not affect *P. gingivalis* [375].

### 6.2.2. Kaempferol (flavonol)

Kaempferol is a naturally occurring flavonoid that has been extracted from grapefruit, delphinium, and witch hazel. At 8 µg/mL, kaempferol showed 84 % antibacterial activity against *P. gingivalis*; this was decreased to 38 % after the compound's concentration was diluted twice, and additional dilution caused the compound to lose its activity against the pathogen. Comparably, at 8 µg/mL and 4 µg/mL, respectively, kaempferol demonstrated 97 % and 45 % growth inhibition against *S. mutans*. Ferulic acid, quercetin, isoquercitrin, and kaempferol were among the few natural components in *P. americana* L. that have antibacterial properties [375].

### 6.2.3. Apigenin (flavone)

Apigenin is a naturally occurring flavone with anti-inflammatory, antioxidative activities, that accelerates the formation of new bones *in vivo* and promotes osteogenic differentiation *in vitro*. It is a promising molecule in bone repair with potential clinical applications in conditions where bone is deficient. Increasing the amount of bone available for implant placement in the maxilla is especially important in the dental field. Apigenin demonstrated a stimulating impact on cell growth after demonstrating the lack of cytotoxicity and any morphological alterations. Additionally, it markedly increased the expression of the collagen1 and alkaline phosphate genes and expedited the mineralization of osteoblasts. Thus, it can stimulate the growth and mineralization of human oral osteoblasts, indicating its possible application in dentistry [376].

### 6.2.4. Licochalcone A (Chalcones)

Licochalcone A is a derivative of the phenol chalconoid, extracted from the roots of *Glycyrrhiza* species *Glycyrrhiza glabra* and *inflata*. Licochalcone A suppresses the host immune system and *P. gingivalis* biofilm development, which are the two main etiological components of periodontitis [61]. By suppressing NF-κB-dependent endothelial IL-8 production, 18 α-glycyrrhetic acid appears to considerably diminish *P. gingivalis* LPS-induced vascular permeability, suggesting its therapeutic potential in *P. gingivalis*-related vascular disorders [176].

## 6.3. Polyphenols

### 6.3.1. Epigallocatechin and epigallocatechin gallate

It is among the biologically active compounds contained in *Camellia sinensis*; the main antioxidant agents are catechins. The steric structure of the 3-galloyl radical present in its structure is important for the inhibition of collagenase activity. The addition of tea catechins completely inhibited the collagenase activity in the gingival crevicular fluid from highly progressive adult periodontitis. The most potent inhibitory effect on collagenase activity was demonstrated by epigallocatechin and epigallocatechin gallate, which were added to the reaction mixture containing collagenase and collagen at an optimal concentration of 100 µg/ml. This confirms that galloyl radical-containing tea catechins can suppress the production of collagenase in both prokaryotic and eukaryotic cells. Besides, pre-incubation of collagenase with tea catechins also reduced the collagenase activity [377].

The attachment of *S. mutans* to saliva-coated hydroxyapatite discs was found to be effectively inhibited by the crude tea polyphenolic compounds from *Camellia sinensis* leaves. Epigallocatechin gallate and epicatechin gallate representing tea catechins had the strongest inhibition of the glucosyltransferase activity which reduced caries scores [378].

### 6.3.2. Curcumin

Curcumin, diferuloylmethane, is an active component in the golden spice turmeric (*Curcuma longa*). Oral nano-curcumin on gingival inflammation in patients with gingivitis and mild periodontitis was evaluated on forty-eight patients. The results of this study showed a beneficial impact on individuals with gingivitis and mild periodontitis by reducing inflammation and gingival bleeding. Compared to topical formulations, nano-curcumin capsules offer a greater bioavailability at the systemic target location [379].

## 6.4. Sulfur-containing compounds

### 6.4.1. Allicin

Allicin is a sulfoxide isolated from the volatile oil of *Allium sativum*. It has a role as an antibacterial agent in oral adhesive tablets where 5 mg of allicin was given four times a day for five days in a randomized, double-blind, placebo-controlled clinical trial gave efficacy reduction in size, pain, and frequency of oral ulcers. This study demonstrates that the oral adhesive tablets of Allicin greatly reduce ulcer size and alleviate pain [380].

### 6.4.2. S-allyl cysteine

S-allyl cysteine (SAC) isolated from garlic bulb, which is a sulfur-containing amino acid and reported to have antioxidant activity. In human oral squamous carcinoma cells, it efficiently stopped the cells from proliferating, increased the expression of the E-cadherin protein, and stabilized the adherent junction complex between E-cadherin and  $\beta$ -catenin. A portion of the mechanism of action involved down-regulating the SLUG repressor protein and suppressing the MAPK/ERK signaling pathway [381].

## 6.5. Alkaloids

### 6.5.1. Berberine

Berberine in the *Coptidis rhizoma* extract (CRE) has antibacterial properties. Due to its anti-inflammatory properties, it can stop the breakdown of alveolar bone and periodontal tissues by suppressing the expression and synthesis of several pro-inflammatory mediators, such as TNF $\alpha$ , IL-1 $\beta$ , RANKL, MCP-1, MMP-2, and MMP-9 [382]. Besides, it stimulated the osteogenesis of stem cells from apical papilla's in a concentration- and time-dependent way. To up-regulate more runt-related nuclear factor 2 downstream, BBR increased  $\beta$ -catenin entry into the nucleus and promoted the production of  $\beta$ -catenin. In teeth that were still developing and had apical periodontitis, BBR improved root healing by triggering the canonical Wnt/ $\beta$ -catenin pathway in stem cells from apical papilla [383].

## 6.6. Enzymes

### 6.6.1. Papain enzyme

Papain is isolated from the latex of the *Carica papaya*, also referred to as the pawpaw, and is a member of the Caricaceae family. Due to its selectivity, this proteolytic cysteine enzyme serves as a debriding remover without endangering surrounding tissues. It also possesses antibacterial and anti-inflammatory qualities. To investigate the null hypothesis that the shear bond strength of orthodontic brackets bonded with resin-modified glass ionomer cement (RMGIC) is not increased by enamel deproteinization using 10 % papain gel. Results showed that inferred that enamel deproteinization using 10 % papain gel strengthens the shear bond. In the orthodontic clinic, papain gel proved to be a new agent [384].

## 6.7. Polysaccharides

### 6.7.1. Chitosan

Chitosan is a cationic polymer mostly generated from the chitin exoskeleton of marine crustaceans like crabs and shrimps. It is the only positively charged polysaccharide found in nature. A study to ascertain the impact of chewing gum containing chitosan on lowering the salivary pH and *S. mutans* numbers where a double-blind, randomized clinical trial was carried out involving 36 dental students. Chewing gum containing chitosan increased salivary pH by 0.17, a statistically significant rise ( $p = 0.01$ ), and reduced the quantity of salivary *S. mutans* colonies [385].

Another study compared the antifungal properties of nystatin suspension with a low-molecular-weight chitosan solution on *C. albicans* in denture stomatitis. The chitosan solution dramatically reduced the amounts of blastospores and mycelia, the burning sensation, the amount of time needed for clinical improvement, and the erythematous surface area. Chitosan is a good option for use as an antifungal mouthwash because of its antifungal activity and natural biocompatibility [386].

## 7. Limitations and future directions

This review is limited to trusted studies published in high-impact journals. It did not evaluate the included studies' quality or bias risk. Furthermore, relevant papers were reviewed using published literature, and publication bias has been avoided as much as possible. Research yielding unfavorable or negligible results, particularly when assessing the bioactivity of plants, might not be portrayed.

People prefer using medicinal herbs rather than contemporary medications for dental conditions because they think they are easier to use and have fewer negative effects. Nevertheless, the effectiveness of these plants and their constituent parts is not well supported by scientific research. Many therapeutic plants have not received enough attention in carefully monitored, double-blind clinical trials. There isn't enough proof to say they work; therefore, they should be used carefully. There are abundant natural resources for the development of novel chemicals that may be helpful in the treatment of dental disorders because the locals still employ numerous traditional herbal treatments.

Nonetheless, more investigation is required to determine the efficacy and security of plants. It is necessary to clarify the nature of bioactive substances obtained from plants that have anti-inflammatory or antibacterial properties against dental problems, enhance

tooth remineralization, and stop bacteria from sticking to tooth surfaces. Furthermore, the structure and side effects of phytochemicals that prevent the formation of biofilm, decrease prostaglandin synthesis, and block inflammatory cytokines should be studied. The separated active fractions from crude plant extracts should first be tested using *in vitro* and *in vivo* tests before being used to create herbal medications. Clinical trials should be conducted to assess these compounds' efficacy as well. Moreover, hazardous chemical components, impurities, incorrect plant identification, or inappropriate plant usage give rise to safety concerns. The creation of secure and efficient herbal medications might result from a careful evaluation of the toxicity and activity research on plants.

## 8. Conclusion

One of the most significant concerns that nowadays affects not only individuals and families but also the government and the health sector's policymaking is oral and dental hygiene. It is advised to become familiar with and make use of traditional medicine's therapeutic and preventive methods for oral and dental health, as well as the medicinal plants' affordability, in light of the World Health Organization's policies regarding these areas. The use of medicinal plants and herbal remedies for a variety of oral conditions, such as gingivitis, ulcers, plaque, and oral diseases, is presented in this review. Our results show that medicinal products can enhance the clinical outcomes of dental health in adolescents. Minimal unfavorable side effects show that these treatments are generally safe for a variety of oral conditions. The present study's advantage is that it presents the most widely used herbal remedies as substitute treatments for dental disorders. The authors also recommend creating a meta-analysis systematic review and assessing the efficacy of herbal remedies as a form of treatment. As a complementary medicine, the results of this series of investigations will be used to propose herbal regimens for the treatment of dental and oral illnesses. Nonetheless, an abundance of research on the advantages of herbal medicine in dentistry asserts that herbal medicines can be used as stand-ins for conventional medications without examining the *in vivo* and *in vitro* processes of active substances. Consequently, these studies are carried out in preclinical and *in vitro* environments. Consequently, there is a pressing need to boost funding and research efforts for clinical trials on these natural chemicals' efficacy, safety, cost-effectiveness, and characterization.

## Data availability

All data required are presented in the submitted review.

## Funding

No Fund.

## CRediT authorship contribution statement

**Mohamed S. Refaey:** Supervision, Methodology. **Esraa Fawzy Abosalem:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rana Yasser El-Basyouni:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shymaa E. Elsheriri:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sara Hassan Elbehary:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marwa A.A. Fayed:** Writing – review & editing, Supervision, Investigation.

## Declaration of competing interest

We respectfully inform you that the authors of the attached manuscript titled “*Exploring the Therapeutic Potential of Medicinal Plants and Their Active Principles in Dental Care: A Comprehensive Review*” for publication in the Journal of Heliyon have no conflict of interest to report.

## Acknowledgements

We are thankful to Dr. Basma M. Gebri, a dentist at the Medical Administration of University of Sadat City, Menoufia, Egypt for her revision of the manuscript from the perspective of a dentist.

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