

A Review on The Medicinal Plants for The Management of Toothache in Avicenna's *Canon of Medicine*: An Evidence based Review

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ABSTRACT

Toothache is one of the most popular pains which can influence the quality of life which generally refers to pain around the teeth or jaws. Avicenna (980–1032), a Persian scholar, made a great illustration about oral diseases and toothache in book three and the medicinal plants which used to relieve toothache in book two of *Canon of Medicine*. Current investigations show that most medicinal plants mentioned by Avicenna for the treatment of toothache could have significant potential effects, including anti-inflammatory, analgesic, anti-nociceptive, antimicrobial and anti-plaque activities, inhibition of the biofilm formation, and mechanical plaque control in the prevention of plaque and gingivitis. This study suggests that indigenous knowledge and traditional practice can make valuable contributions to the pharmaceutical industry and the production of new effects with less adverse effects drugs.

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Introduction

Pain is one of the most common medical challenges among the people globally and is hard to treat. People have almost always attempted to decrease or kill the pain [1]. Toothache is one of the most popular pains which can influence the quality of life [2] which generally refers to pain around the teeth or jaws. In most cases, toothaches are originated by tooth problems, such as a dental cavity, an exposed tooth root, a cracked tooth, or gum disease. The severity of a toothache could differ from chronic and mild to sharp and severe [3]. Today, drugs such as Analgesics, including non-steroidal anti-inflammatory drugs, opioids and corticosteroids, which are the most commonly used drug, antiulcer, antimicrobial and antibiotics, mouthwashes and multivitamins are applied to relieve this pain. (The aim of applying anti ulcers drugs was to prevent the side effects of Analgesics [3].) These available drugs have many side effects. On the other side, medicinal plants comprise important part of traditional medicine in many societies, and have a special place and value in modern therapeutic approaches [2]. Therefore, use of medicinal plants which have the prior choice to treat diseases could be an alternative therapy for different problems like toothache.

Persian medicine (PM) is one of the traditional systems of medicine that predates thousands of years ago [4]. It was developed during the Islamic golden age in the early medieval period. Many of the medical books of Persian doctors, such as *Liber Regius* (Royal Book or *al-Maliki*) of Haly, *Liber Continent* (*al-Hawi*) of Rhazes, and *Canon* (*al-Qanun fi-Teb*) of Avicenna were taught in western universities until the seventeenth century AD. Among the Persian physicians in the middle Ages, Avicenna (Ibn Sina, 980–1032 AD) was one of the most well-known and influential figures in the history of medicine. His knowledge of medicine, mainly what he had collected in his medical encyclopedia, the *Canon of Medicine* could be considered as an index of medical knowledge of his time [5]. So this review attempted to work on Avicenna's *Canon of Medicine* and found Avicenna's points of view about the toothache. In addition the information of *Canon of Medicine* was compared with current concepts of medicine to

evaluate Avicenna knowledge status about 1000 years ago. Finally, the treatments mentioned by Avicenna to manage toothache were considered and the noticed medicinal plants were evaluated for approaches as possible sources for future studies. Some previous investigations discussed about dental and oral diseases in traditional PM [6,7], but it is the first study investigated comprehensively on all aspects of toothache in *Canon of Medicine*, specially focused on Avicenna's views on treatments.

Study design

To find the medicinal plants which Avicenna recommended for toothache, the second book of the *Canon of Medicine* was reviewed [8]. He introduced all the *Materia Medica* in PM in this book with their morphology, their temperament, general characteristics, and detailed properties in different parts of the body. Each plant was checked for its property in relieving toothache. 23 plants were noticed. The PM name, part used, mode of application, and temperament of each medicinal plants were collected. The information about the way of preparing and application of the plant was completed from the famous Persian Medicine *Materia Medica* "Makhzan-ol-Adviah" [9]. Besides, scientific reports derived from modern medical databases like PubMed, Scirus, ScienceDirect, Google Scholar, and Scopus important added to PM information. All of the retrieved articles were published between 2000 and 2016, and any in vitro, in vivo, or clinical evidence for related efficacy and pharmacological mechanisms were considered for inclusion. The scientific name of medicinal plants, or its common name, with the key words include: toothache, oral problems, gingivitis, dental, analgesic, antinociceptive, anti-inflammatory, antibacterial, antimicrobial, plaque, anti-plaque, and biofilm were used to search for modern data. Only published articles written in English were included in this review. Those articles in languages other than English, review studies, papers that evaluated a mixture of the plant with drugs other than herbs, case reports, and case control studies were excluded. The references of the included papers were also reviewed for

additional, suitable studies. Finally, the included papers were reviewed for mention of the scientific names of the plant, their parts, as well as the active components and pharmacological effect.

Traditional medicinal plants for toothache

Avicenna's treatment views: it mentioned that toothache is originated from a problem in tooth nerve or in gum or infection in the teeth or gum. Each of these sources of pain has their own reasons and treatments. For example Avicenna

said: if the patient feels beating pain, the main reason of toothache is in dental root and tooth nerve. The medicinal plants which are introduced by Canon of Medicine, book 2, are gathered in Table 1. For each plant data, including scientific name, family, Persian name, parts used, mode of application, and temperament were recorded in Table 1. The pharmacological effects of these plants, type of study, and active components also has been gathered in Table 2.

Table 1. Medicinal plants mentioned in *Canon of Medicine* for managing toothache and their mode of application

Scientific name	Family	Persian name	Parts used	Mode of application	Temperament*
<i>Cedrus libani</i> Barrel.	Pinaceae	<i>Sherbin</i>	Leaves	Mouthwash with vinegar and leaves decoction.	Hot, dry
<i>Chelidonium majus</i> L.	Papaveraceae	<i>Māmirān</i>	Root	Chewing	Hot, dry
<i>Citrullus colocynthis</i> (L.) Schrad.	Cucurbitaceae	<i>Ḥanzal</i>	Root, fruit	To rinse (mouthwash) with the root decoction. Rubbing the oil on teeth	Hot, dry
<i>Cnicus benedictus</i> L.	Asteraceae	<i>Baadaavar d</i>	Aerial parts	Chewing	Hot, dry
<i>Cuperessus sp.</i> <i>Cuperessus sempervirens</i> L.	Cupressaceae	<i>Sarw</i>	Aerial parts	Gargling with the decoction of aerial part	Hot, dry
<i>Curcuma longa</i> L.	Zingiberaceae	<i>Orūqoṣeba ghin</i>	Rhizome	Chewing	Hot, dry
<i>Drimia maritima</i> (L.) Stearn	Asparagaceae	<i>Esghil</i>	Root	Mouthwash	Hot, dry
<i>Delphinium staphisagria</i> L.	Ranunculaceae	Mavizaj	Fuit	Mouthwash	Hot, dry
<i>Ecballium elaterium</i> (L.) A.Rich.	Cucurbitaceae	<i>Ghesa ol Hemar</i>	Root	Gargling with the decoction, extract or its decoction with Syrian Rue and vinegar.	Hot, dry
<i>Hyoscyamus niger</i> L.	Solanaceae	<i>Banj</i>	Root, seed	The incense of seeds. To rinse (mouthwash) with the extract and root extract	Hot, dry
<i>Iris jermanica</i> L.	Iridaceae	<i>Irsā</i>	Root	To rinse (mouthwash) with the root decoction	Hot, dry
<i>Moringa peregrine</i> (Forssk.) fiori.	moringaceae	<i>Baan</i>	Root	To rinse (mouthwash) with the root decoction	Hot, dry
<i>Nigella sativa</i> L.	Ranunculaceae	<i>Shūniz</i>	Seed	To rinse (mouthwash) with the seeds decoction	Hot, dry

Continue of Table 1. Medicinal plants mentioned in *Canon of Medicine* for managing toothache and their mode of application

Scientific name	Family	Persian name	Parts used	Mode of application	Temperament*
<i>Olea europaea</i> L.	Oleaceae	<i>Zaytūn</i>	Root, fruit, gum	To rinse (mouthwash) with the root extract. To rub (toothbrush) the fruit on teeth. To put the gum on dental caries	Hot, dry
<i>Onopordum acanthium</i> L.	Asteraceae	<i>shokae</i>	Aerial parts	Chewing	Hot, dry
<i>Opopanax chironium</i> (L.)Koch.	Apiaceae	<i>Jāvshir</i>	Gum	To rub the gum on teeth or to fill dental caries	Hot, dry
<i>Pinus orientalis</i> Link <i>Pinus</i> sp.	Pinaceae	<i>Şenobar</i>	Bark	To rinse (mouthwash) with the bark extract with vinegar	Hot, dry
<i>Plantago major</i> L.	Plantaginaceae	<i>Lesan-ol-ḥamal</i>	Root	To rinse (mouthwash) with the root decoction. Chewing the root	Cold, dry
<i>Platanus orientalis</i> L.	Platanaceae	<i>Dolb</i>	Bark	To rinse (mouthwash) with the decoction of bark and vinegar	Cold, dry
<i>Rhus coriaria</i> L.	Anacardiaceae	<i>Somaq</i>	Seed, root	To rub (toothbrush) the powder of seeds on teeth. To put the gum on teeth	Cold, dry
<i>Rumex conglomeratus</i> L.	Polygonaceae	<i>Ḥammāq</i>	Fruit	To rinse (mouthwash) with the plant extract	Cold, dry
<i>Solanum nigrum</i> L.	Solanaceae	<i>ʿEnabotha ʿlab</i>	Leaf	To rinse (mouthwash) with the leaf extract	Cold, dry
<i>Tamarix gallica</i> L.	Tamaricaceae	<i>Athl</i>	Aerial part	To rinse (mouthwash) with the aerial part extract	Cold, dry

* Entire world is made of quadratic elements and the diversities among objects derive from different ratios of these four elements used in their structures. This quality has been known as temperament (Midzaj).

Historical points of view

Mankind had suffered from toothache since the prehistoric era. In ancient Egypt, there are remedies for relieving this pain [10]. Dental diseases have been mentioned in Sumerian records too. During late antiquity, oral care and even prosthetic dentistry gained better development in the Roman period [1, 6]. Historically, the main available toothache treatment was restricted to medicinal plant preparations that were administered to the gingival and mucosal tissues or used as mouthwashes [10].

In PM, toothache was known as a main problem in oral cavity and it was attempted to realize the causes and treatment of it. In the *Canon of Medicine*, toothache is originated from a problem in tooth nerve or in gum or infection in the teeth

or gum. Each of these sources of pain has their own reasons and treatments.

Pharmacological mechanisms of action

The most common causes of a toothache are included, dental cavity, gum disease, tooth root sensitivities, and cracked tooth syndrome. Dental cavity is a condition where bacterial processes cause hard damage in to tooth structure leading to breakdown and producing dental caries. These bacteria are *Streptococcus mutans* and *Lactobacillus*. Gum disease refers to inflammation of the soft tissue and abnormal loss of bone that surrounds the teeth. It is caused by toxins secreted by certain bacteria in "plaque" which gather over time along and under the gum line.

This plaque is a mixture of food, saliva, and bacteria. Gingivitis, inflammation of the gum tissue, is described non-destructive periodontal disease that is almost caused by adhesion of bacterial biofilms (plaque) to tooth surfaces. Toothache could also be caused by exposing tooth roots due to the bacterial toxins which dissolve the bone around the roots and cause the gum and the bone to recede. In this condition the exposed roots can become exceedingly sensitive to cold, hot, and sour foods. Cracked tooth syndrome refers to tooth fracture without associated cavity or advanced gum disease that is most common in lower back teeth (molars). For these reasons of causing pain in teeth, different kinds of drug group are applied such as Analgesics, anti-inflammatory and antimicrobial and antibiotics. As seen in Table 2, many of the mentioned medicinal plants possess the above pharmacological properties. The medicinal plants which have noticed in section 2 of *Canon of Medicine* for relieving toothache were investigated in scientific reports derived from modern medical databases. The results showed that many of these plants have the potential to use as new pharmaceutical products for managing toothache due to their pharmacological effects, including anti-inflammatory, analgesic, and anti-nociceptive properties, antimicrobial and anti-plaque activities, inhibition of the biofilm formation, and mechanical plaque control in the prevention of plaque and gingivitis (Fig.1). 14 plants among 24 showed anti-inflammatory effect (58%) and 16 medicinal plants possess antimicrobial activity (66%). In the *Canon of Medicine*, Avicenna wrote that chewing the root of *Chelidonium majus* L. relieve toothache. New investigation showed this plant had Antibacterial [11-15], Anti-inflammatory [1, 4, 7, 16-19], and Analgesic activity [7, 20-24] activities. *Curcuma longa* L. (turmeric) had shown many pharmacological activities which can confirm its use as an effective medicinal plant for toothache. The rhizome that is prescribed to chew in the PM was revealed to have antibiofilm, antioxidant and activities against bacteria isolated from dental

plaques and dental unit [25]. It had also shown antibacterial effect against the anaerobic bacteria isolated from the root canals of infected primary teeth, including *Porphyromonas sp.*, *Bacteroides fragilis*, *Peptostreptococcus*, and *Staphylococcus aureus* [26]. Anti-plaque and anti-gingivitis properties of this plant had been shown in different articles [27-31, 38]. It had also revealed mechanical plaque control [30,31] in the prevention of plaque and gingivitis [31] and reducing plaque index (PI) [29,30], gingival index (GI), and probing depth (PD) [29]. Improvement of plaque index and gingival index scores from baseline through the end of the study was investigated through in vitro and in vivo study [32]. The plant antimicrobial property has been studied in various articles too [31,33-37] and showed antibacterial activity against *Enterococcus faecalis* [33-35] in extracted teeth samples [33, 34], intracanal medicament in endodontic failure cases [35], inhibitory effect on the cariogenic properties of *Streptococcus mutans* and inhibit the formation of *S. mutans* biofilms [36]. Against Methicillin-resistant *Staphylococcus aureus* [37] reduce total microbial count [30]. The rhizome of turmeric had anti-inflammatory effect [29, 31,38, 39,40] which can cause toothache relief. It had exhibited treatment of gingivitis [39, 41], by reducing its inflammatory components [39], and periodontal pockets [32,41]. Analgesic and antinociceptive effects were the other potencies of this medicinal plant which can apply for managing of toothache [40]. *Nigella sativa* L. (black cumin) is applied in Canon of medicine for toothache through rinsing (mouthwash) with the seed decoction. The seeds showed many effective pharmacological effects such as Anti-inflammatory [2-49], anti-nociceptive [50] analgesic [51, 52], antimicrobial [53, 54], a broad antimicrobial spectrum, including Gram-negative, Gram-positive bacteria, viruses, parasites, Schistosoma and fungi [53], antibacterial [55-57] properties. It also could inhibit the biofilm formation of *S. aureus*. The main active component of black cumin is Thymoquinone [44, 46, 47, 50, 52, 53, 55, 57-61].



Fig.1. A summarize of traditional medicinal plants for managing toothache and their current pharmacological effects.

The Antinociceptive [62], Anti-inflammatory [63-66], antinociceptive, and analgesic [67] activities of *Olea europaea* L. can make it as an important medicinal plant to relieve toothache which had noticed in Avicenna's manuscripts too. *Plantago major* L. that is applied in PM, rinsing (mouthwash) with the root decoction and chewing the root, has been showed antimicrobial activity [68] against *Streptococcus mutans*, the main bacteria to

produce dental caries [69], *Streptococcus pneumonia* [70], anti-inflammatory [71], cox-2 inhibitory, and antinociceptive effects [72]. In addition, treating oral inflammation [73], *Candida albicans* biofilm-related infections [74], and oral wounds [75] which were noticed in research articles can demonstrate its effectiveness in toothache relief.

Table 2. The list of medicinal plants by Avicenna for managing toothache and their current pharmacological effects.

Scientific name	Family	Persian name	Pharmacological effect	Type of study	Active components
<i>Cedrus libani</i> Barrel.	Pinaceae	<i>Sherbin</i>	Anti-inflammatory activity [76], antibacterial efficacy against <i>Bacillus megaterium</i> , <i>B. subtilis</i> , <i>B. cereus</i> , <i>Klebsiella pneumonia</i> , <i>Enterobacter aerogenes</i> , <i>Staphylococcus aureus</i> , <i>Mycobacterium smegmatis</i> , <i>Proteus vulgaris</i> , <i>Listeria monocytogenes</i> , <i>Pseudomonas aeruginosa</i> [77], antimicrobial activity [78]	In vivo [76] in vitro [77,78]	- [76-78]

Continue of Table 2. The list of medicinal plants by Avicenna for managing toothache and their current pharmacological effects.

Scientific name	Family	Persian name	Pharmacological effect	Type of study	Active components
<i>Chelidonium majus</i> L.	Papaveraceae	<i>Māmirān</i>	Antibacterial activity [11-15] on <i>Streptococcus mutans</i> [11], clinical strains of methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) [12], methicillin and vancomycin resistant <i>Enterococci</i> and <i>Staphylococci</i> [14], <i>S.aureus</i> , <i>E. coli</i> and <i>A. hydrophila</i> [15]. antimicrobial activity [13], Anti-inflammatory effect [1,4,7,16-19] ; reduce carrageenan-induced rat paw oedema [4], reduce the levels of serum immunoglobulin E (IgE), tumor necrosis factor- α (TNF- α), and interleukin-4 (IL-4) , itching behavior, and ear thickness in atopic dermatitis mice [1], inhibit the production of interleukin-6 (IL-6) and the expression of IL-6 mRNA by regulation of nuclear factor- κ B [16], suppress the NO and PGE2 production in macrophages by inhibiting the iNOS and COX-2 expressions [17], inhibition on LPS-induced NO production in macrophage RAW264.7 cells and inductions of COX-2 and iNOS mRNA [18], increasing in COX-2 and HIF-1 α levels [20]. Analgesic activity [7,21-25] more than aspirine [21], inhibitory modulation of <i>Chelidonium herba</i> on GABA [21], suppress glycine-induced response and elevated glutamate-induced response which may increase neuronal excitability in PAG, results in activation of descending pain control system [21], selectively inhibit the glycine transporter GlyT1 [21]	In vitro [11-18,22-24] In vivo [1,4,7,19-21]	Chelerythrine [11] benzo[c]phenanthridine-type alkaloids 8-hydroxydihydrosanguinarine (hhS), 8-hydroxydihydrochelerythrine (hhC) [12] --- [1,13,20,22,23] immunoactive lectin of <i>C. majus</i> [14] sanguinarine and chelerythrine [15] sanguinarine, chelerythrine [4,24] and quaternary benzophenanthridine [4] Chelidonic acid [16,19] Stylopine [17] chelidonine and 8-hydroxydihydrosanguinarine [18] Chelidonine [21] Proteins [7]
<i>Citrullus colocynthis</i> (L.) Schrad.	Cucurbitaceae	<i>Ḥanzāl</i>	Analgesic and anti-inflammatory activities [79,80] Antimicrobial activities against foodborne bacteria [81] <i>Pseudomonas aeruginosa</i> [82], Treatment of toothache [83]	In vivo [79,80] In vitro [81,82] historic al use [83]	--- [79,80,82] 4-Methylquinoline [81]

Continue of Table 2. The list of medicinal plants by Avicenna for managing toothache and their current pharmacological effects.

Scientific name	Family	Persian name	Pharmacological effect	Type of study	Active components
<i>Cyperus sp.</i> <i>Cyperus sempervirens</i> L.	Cyperaceae	Sarw	Antimicrobial (against <i>Klebsiella pneumoniae</i>) and antibiofilm properties (<i>Cyperus sempervirens</i>) Reduce the rate of dental plaque formation by decreasing the virulence of these periodontopathic bacteria (<i>Cyperus hisitanica</i>) ^[85]	In vitro ^[84] In vitro ^[85]	--- ^[84] tannic acid ^[85]
<i>Curcuma longa</i> L.	Zingiberaceae	'orūqoş ebaghin	Antibiofilm, antioxidant and activities against bacteria isolated from dental plaques and dental unit Antibacterial effectiveness ^[26] . Anti-plaque and anti-gingivitis ^[27-32] due to its anti-inflammatory action ^[28] . Mechanical plaque control ^[30,31] . Reduce plaque index (PI) ^[29,30] , gingival index (GI), probing depth (PD) ^[29] . improvement of plaque index and gingival index scores from baseline through the end of the study ^[32] Antimicrobial property ^[31,33-37] , inhibitory effect on the cariogenic properties of <i>Streptococcus mutans</i> , inhibit the formation of <i>S. mutans</i> biofilms ^[36] . reduce total microbial count ^[30] Anti-inflammatory effect ^[29,31,38-40] treatment of gingivitis ^[39] Anti-inflammatory, subgingival scaling and root planning effectiveness, reduce plaque index (PI), gingival index (GI), probing depth (PD). ^[29] Analgesic and antinociceptive effects ^[40] . Treating periodontal pockets ^[32] , gingival healing or periodontal repair ^[41] .	In vitro ^[25] human study or clinical trial ^[26,27,28,29,38,87,39,30,31] In vitro ^[28,29,32,37,39,41,42] In vivo ^[36] In vitro and In vivo ^[38]	--- ^[25,26,27,33,34,28,87,39,35,41,37,31] Curcumin ^[29,86,38,32] curcumin derivative (KMS4034) ^[40] α -turmerone, germacrone, α -zingiberene, α -turmerone, trans- β -elemenone, curlone, and β -sesquiphellandrene in essential oil ^[36]

Continue of Table 2. The list of medicinal plants by Avicenna for managing toothache and their current pharmacological effects.

Scientific name	Family	Persian name	Pharmacological effect	Type of study	Active components
<i>Ecballium elaterium</i>	Cucurbitaceae	<i>Ghesa ol Hemar</i>	Anti-inflammatory activity [88] Antimicrobial activity [89] against <i>Staphylococcus aureus</i> and <i>Candida albicans</i> [89]	In vivo [88] In vitro [89]	— [88]
<i>Hyoscyamus niger</i> L.	Solanaceae	<i>Banj</i>	Analgesic [90,91] on acute and chronic pain thresholds [91]. Anti-inflammatory (both acute and chronic inflammation) and antipyretic activities [90] treatment of toothache [92,93]. Antibacterial activity against <i>Staphylococcus aureus</i> (strong effect), <i>Bacillus subtilis</i> , <i>Bacillus cereus</i> , <i>Escherichia coli</i> , <i>Proteus vulgaris</i> , <i>Salmonella typhimurium</i> and <i>Pseudomonas aeruginosa</i> [94]	In vivo [90,91] Historical use [92,93] In vitro [94]	cleomiscosin A (coumarinolignan) [90] --- [94]
<i>Iris jermanica</i> L.	Iridaceae	<i>Irsā</i>	Anti-inflammatory activity [95,96] anti-microbial effect [96] against <i>Staphylococcus aureus</i> [96], <i>Serratia marcescens</i> , <i>Escherichia coli</i> , <i>Candida albicans</i> [96] and <i>Aspergillus flavus</i> [96], <i>Bacillus subtilis</i> [97]	In vitro [95-98] In vivo [96]	Isoflaonoids [95,96] Irigenin S [96] --- [98, 97]
<i>Moringa peregrina</i> (Forssk.) Fiori	moringaceae	<i>Baan</i>	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Enterobacter cloacae</i> , <i>Klebsiella pneumoniae</i> , <i>Candida albicans</i> , <i>C. tropicalis</i> and <i>C. glabrata</i> [99]	In vitro [99]	— [99]
<i>Nigella sativa</i> L.	Ranunculaceae	<i>Shūniz</i>	Anti-inflammatory [42-49] anti-nociceptive [50,51] analgesic [52,53] antimicrobial [55] a broad antimicrobial spectrum including Gram-negative, Gram-positive bacteria, viruses, parasites, schistosoma and fungi [54] antibacterial [56,57] against <i>Staphylococcus aureus</i> [56] antimethicillin-resistant <i>Staphylococcus aureus</i> (MRSA) [59,57] <i>E. coli</i> , <i>S. typhimurium</i> , and <i>S. aureus</i> [60] <i>B. subtilis</i> , <i>B.cereus</i> , and <i>S. aureus</i> [61] inhibit the biofilm formation of <i>S. aureus</i> [58] <i>Staphylococcus epidermidis</i> , <i>Enterococcus faecalis</i> [60] <i>candida albicans</i> [100]	In vivo [42,43,47,50-52] in vitro [44-46,48,55-61,100] Human study [49]	--- [42,43,48,49,52,54,55,57,100] Thymoquinone [44,46,47,50,51,53,54,56,58-61] and thymol [60] melanin [56]

Continue of Table 2. The list of medicinal plants by Avicenna for managing toothache and their current pharmacological effects.

Scientific name	Family	Persian name	Pharmacological effect	Type of study	Active components
<i>Olea europaea</i> L.	Oleaceae	<i>Zaytūn</i>	Gram-negative, anaerobic periodontal pathogens such as <i>Porphyromonas gingivalis</i> , <i>Prevotella intermedia</i> , and <i>Fusobacterium nucleatum</i> (oral pathogens) [62]. Anti-inflammatory [63-65] and analgesic [67]	In vitro [62,64-66,75] In vivo [64,67], Human study [63]	Unsaponifiable fraction [63] maslinic acid [64] nocellaralactone [65], oleocanthal [66]
<i>Onopordum acanthium</i> L.	Asteraceae	<i>shokae</i>	Anti-inflammatory effect, inhibition of cyclooxygenase-2 [101]	In vitro [101]	Lignans, flavonoids, and sesquiterpenes, 4 β ,15-Dihydro-3-dehydrozaluzanin C and zaluzanin C [101]
<i>Plantago major</i> L.	Plantaginaceae	<i>Lesanol-hamal</i>	Antimicrobial activity [68] against <i>Streptococcus mutans</i> [69] <i>Streptococcus pneumonia</i> [70]. Anti-inflammatory [71]. Treatment of oral inflammation [73] treatment of <i>Candida albicans</i> biofilm-related infections [74]. Oral wound healing properties [75]. Anti-nociceptive [72].	in vitro [68,69,74,75] in vivo [70-72] historical use [73]	aucubin, and baicalein [74], alpha-linolenic acid and (Z)-5-thia-8,11,14,17-icosatetraenoic acid [11] pectin polysaccharide, PMII [70]
<i>Platanus orientalis</i> L.	Platanaceae	<i>Dolb</i>	Anti-inflammatory [102] and analgesic [102,103]	In vivo [102,103]	--[102,103]
<i>Rhus coriaria</i> L.	Anacardiaceae	<i>Somaq</i>	Antibacterial effect [105] against five common oral bacteria, inhibit bacterial biofilm formation [105] against <i>Streptococcus mutans</i> , <i>Lactobacillus rhamnosus</i> and <i>Actinomyces viscosus</i> [106]. Analgesic effect [104]	In vitro [105,106] in vivo [104]	--[105,106] Favonoids [104]
<i>Solanum nigrum</i> L.	Solanaceae	<i>'Enabot ha 'lab</i>	Antimicrobial [142] Antibacterial activity against multi-drug resistant <i>Salmonella typhi</i> [108]. Anti-inflammatory effect [109] antinociceptive [109]	In vivo [109] In vitro [110, 107,108]	--[108-110]
<i>Tamarix gallica</i> L.	Tamaricaceae	<i>Athl</i>	Anti-inflammatory [111]. Antibacterial properties against human pathogen strains [111]	Historical use [111] In vitro [111]	

Discussion

In Persian Pharmacy there were different and board ways of drug application for oral and dental problems. The most popular routes of administration in the oral cavity or particularly teeth were rinsing or mouthwash (*maḍmaḍat*), gargling (*ghargharah*), toothbrush (*meswak*), rubbing on teeth (*sanūn*), chewing (*maḍgh*), sprinkling on teeth (*dharūr*), inhaling incense (*bakhūr*), and to apply directly on the teeth. All of these routes are topical and used in the oral cavity to affect the teeth, gum, and nerves. There are a few occasions in which the formulation should be drunk and act systematically to relieve toothache. Among these routes of administration, rinsing or mouthwash was the most common (44%), followed by rubbing or toothbrush and chewing (17%). 69 preparations are applied externally in the form of decoction [12], crude part of a plant [11], extract [18], powder [15], and oil [13], whereas one is taken orally in the form of an extract. In 10 prescriptions, vinegar accompanied the medicinal plant in the mixture. Vinegar in PM is a well-known *materia medica* and has an important role in traditional pharmacy. It is an astringent and desiccating agent in PM possessing rapid penetrating properties and accelerates reach of accompanying medicine to its target organ [16-20]. Consequently, it is used in some of drug formulations in this review to accelerate drug penetration in different parts of the body.

The philosophy of PM is based on quadratic elements. These elements are air, fire, water, and soil with specific qualities. For example, fire is hot and dry, the air is hot and moist, water is cold and moist, and soil is cold and dry. Followers of this ideology believe that the entire world is made of quadratic elements and the diversities among objects derive from different ratios of these four elements used in their structures. This quality has been known as temperament (*Midzaj*). Theory of temperament also existed in many other traditional medical theories, including Chinese, Greek (*Unani*), Indian, Arabic, Roman, and European [19]. Based on this theory, the temperament of choosed ethnomedicinal plants was collected. The majority of traditional medicinal plants in this study had "hot, dry"

temperament (78%) and then "cold, dry" (22%). According to PM theory the temperament of tooth is dry, so the drugs used for treatment should be dry, too. The heat or the cold of drugs is determined by the cause of disease which reverses the cold or heat of the disease [24]. In PM there are some plants which are mentioned as harmful for teeth or can cause toothache such as *Raphanus sativus* L. (radish), *Vigna mungo* (L.) Hepper. (black gram), *Juglans regia* L. (walnut), *Phoenix dactylifera* L. (date), *Ficus carica* L. (fig), and *Allium ampelopersum* L. (leek) [16-20]. These medicinal plants could be avoided during the period of suffering from toothache.

Conclusion

Results obtained from this review showed that several plants have been applied in *Canon of Medicine* for relieving toothache. Recent investigations support the claims of the PM about the efficacy of many of these plants, including *Cedrus libani*, *Chelidonium majus*, *Citrullus colocynthis*, *Cyperus sempervirens*, *Curcuma longa*, *Ecballium elaterium*, *Hyoscyamus niger*, *Iris germanica*, *moringa peregrine*, *Nigella sativa*, *Olea europaea*, *Onopordum acanthium*, *Plantago major*, *Platanus orientalis*, *Rhus coriaria*, *Solanum nigrum*, and *Tamarix gallica*.

For some of the herbal products used in PM, such as *Cnicus benedictus*, *Drimia maritime*, *Delphinium staphisagria*, *Opopanax chironium*, *Pinus orientalis*, and *Rumex conglomeratus*, there are no (or not enough) studies to confirm their properties to manage toothache. These plants could be studied for their pharmacological potencies in controlling this pain or treating toothache.

In current years, there was a great interest in herbal and traditional medicine for the management and treatment of a variety of diseases. These studies suggest that indigenous knowledge and traditional practice can make valuable contributions to the pharmaceutical industry and the production of new effects with less adverse effects drugs.

Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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