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Global use of Ethnomedicinal Plants to Treat Toothache

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Toothache is one of the most common global health problems, and medicinal plants are widely used to relieve the associated pain and inflammation. Several studies have been conducted on the use of plants to treat toothache, but no study has comprehensively assessed the types of plants and the mechanisms of action of the phytochemical compounds involved in their analgesic effect. This review aims to bridge this gap. This is the first review to collect a large volume of data on the global use of medicinal plants used in the treatment of toothache. It presents the relevant information for dentists, researchers, and academics on using medicinal plants to treat toothache. We found that preclinical studies and state-of-the-art technology hold promise for furthering our knowledge of this important topic. In total, 21 species of medicinal plants used to treat toothache were found in America, 29 in Europe, 192 in Africa, 112 in Asia, and 10 in Oceania. The most common species were Allium sativum, Allium cepa, Acmella oleracea, Jatropha curcas, Jatropha gossypiifolia, and Syzygium aromaticum. The most commonly found family of medicinal plants was Asteraceae, followed by Solanaceae, Fabaceae, Lamiaceae, Euphorbiaceae, Rutaceae, and Myrtaceae. The most common phytochemicals found were flavonoids, terpenes, polyphenols, and alkaloids. The reported mechanisms of action involved in toothache analgesia were antioxidant effects, effects mediated by transient receptor potential channels, the ?-aminobutyric acid mechanism, and the cyclooxygenase/lipoxygenase anti-inflammatory mechanism.

Keywords: Dental Pain; Flavonoids; Medicinal Plants; Phytochemicals; Toothache.

Toothache is an unpleasant sensory and emotional experience[1]. originating in the tooth or adjacent structures and is caused by factors such as caries, periodontal disease, trauma, or dentoalveolar abscess[2]. It is one of the most common health problems worldwide[3]. Toothache has a higher prevalence in lower socioeconomic groups, in whom this disease is not always adequately treated[4]., and in developing countries, where access to healthcare is limited. This has led many local communities to resort to using alternatives for toothache relief, such as medicinal plants[3].

Medicinal plants are widely used in dental practices. The World Health Organization has reported that between 65% and 80% of the population in developing countries use them to reduce inflammation, inhibit oral pathogen growth, and trigger anti-inflammatory, antiseptic, antioxidant, and analgesic effects[3, 4]. Several phytochemical studies conducted on these plants have identified compounds such as flavonoids, alkaloids, and terpenes, which reduce toothache through their mechanism of action[3, 5–7].

Phytotherapy is the use of plants to treat diseases or as health-promoting agents. When used for this purpose, their original composition and integrity are generally preserved, so that an entire plant or a desired percentage of its components may be used for medicinal purposes, fulfilling a specific mechanism of action, generally, a specific pathway to relieve pain [8.. However, to our knowledge, no study has comprehensively tackled the mechanisms of action of the phytochemical compounds contained in medicinal plants used to treat toothache. This integrative review aimed to bridge this gap by compiling and analyzing the different studies available in the literature.

MATERIALS AND METHODS

The available literature in PubMed, PMC, and Scopus databases was searched to identify relevant articles on medicinal plants used to relieve toothache, published in English until July 31, 2021, using the search terms toothache, dental pain, medicinal plants, medicinal herbs, and phytochemicals. Articles unrelated to the use of plants that relieved toothache or lacking data for at least one of the following characteristics were excluded: family, scientific name, plant parts used, and method of preparation.

Of a total of 300 articles, 80 met the inclusion criteria and were comprehensively analyzed for this review. In addition, we performed a manual search of the reference lists of the initially selected articles to complement the available information and found 294 additional articles. Ten books with relevant information were also included. Regional medicinal plant types retrieved from the articles and books were summarized by continents. Finally, owing to length restrictions, this review did not include information related to the possible adverse reactions and drug interactions resulting from the use of the plants included in this review.

Medicinal plants for toothache treatment

For several millennia, plants have been used in traditional dentistry to treat toothache, periodontal disease, herpetic ulcers, stomatitis, maxillary sinusitis, and other ailments[6]. In recent years, advances in science and technology have identified the phytochemical compounds in some of these plants and their mechanisms of action[3]. Phytochemicals are a large group of plant-derived chemical substances that have various biochemical and physiological effects that are beneficial for human health and nutrition[6, 9].

Phytochemicals found in plants vary greatly in number, structural heterogeneity, and distribution, and they are classified into polyphenols, carotenoids, alkaloids, terpenes, and terpenoids[10, 11]. All the tables in this review outline the phytochemicals described in previous reports on medicinal plants used to treat toothache, focusing on their analgesic mechanisms of action.

Plant parts and preparation method

As mentioned above, plants are used to treat diseases through phytotherapy, using either the entire plant or a desired percentage of its components [8.. The most commonly used parts of medicinal plants are the leaves, seeds, flowers, and roots. The roots, in particular, are highly important because they are higher in bioactive compound content than other plant parts[3, 12–14].

Leaves contain high concentrations of secondary metabolites, phytochemicals, and essential oils that have various health benefits [14.. Hence, most of the research studies support the use of leaves instead of roots because root extraction threatens the conservation of several plant species, especially those that are widely used[3, 14].

There is considerable variation in the preparation methods of plants used to treat toothache, and the most common methods of administration are: using the plant extract, chewing, crushing, and drinking a decoction[3].

Mechanisms of action of phytochemical compounds

Phytochemicals such as flavonoids, alkaloids, and terpenes[3, 5]. are biologically active compounds found in plants that work through various mechanisms of action[15, 16]. Based on the information gathered in this review, the most salient mechanisms of action of phytochemicals used to treat toothache were antioxidant activity[9, 17]., action on transient receptor potential channels (TRP)[18], ã-aminobutyric acid (GABA) mechanism[19, 20], and anti-inflammatory mechanisms (cyclooxygenase (COX) and lipoxygenase (LOX) pathways)[21].

Antioxidant activity

In living organisms, reactive oxygen species (ROS) are generated during metabolism and do not generally cause oxidative damage to cellular components due to the action of antioxidants present in these organisms[22].

Natural antioxidants are found in various plants and play a key role in stopping the generation of free radicals by preventing the oxidation of biomolecules in the body. Therefore, they are valuable therapeutic agents for preventing diseases caused by oxidative stress. The latter causes an imbalance that favors the production of prooxidants, represented by ROS, such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) [23], which damage key cellular components, such as DNA, proteins, and membrane lipids, and can even trigger cell death[17, 24–27].

Conversely, during inflammatory processes, free radicals balance themselves by attacking the nearest stable molecule and "stealing" an electron. The attacked molecule then becomes a free radical by losing its electron and initiating a cascade of cell-damaging reactions[24]. Additionally, leukocytes present in damaged regions cause a "respiratory burst" from enhanced oxygen uptake, and inflammatory cells generate inflammatory mediators that act on the infection site to release more reactive species[24, 28, 29].

Therefore, the role of antioxidants is to delay, prevent, or eliminate oxidative damage of target molecules by controlling the levels of free radicals and other reactive species[30]. Plants are responsible for our oxygenated environment, and because they are exposed to high intracellular levels of oxygen and ROS, they have developed specialized defense systems (antioxidants) to protect their structures and tissues. Antioxidant activity is inherent to all plants as they act to prevent, destroy, or neutralize free radicals[17].

These antioxidant defense systems can be *enzymatic complexes and non-enzymatic systems.* Some enzymatic complexes are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). *Non-enzymatic systems* consist of low-molecular-weight antioxidants such as ascorbic acid, glutathione, proline, carotenoids, phenolic acids, and flavonoids; and high-molecular-weight secondary metabolites, such as tannins, which efficiently prevent the toxic effects of free radicals[31, 32].

The phytochemicals in plants can act as antioxidants by directly eliminating ROS, chelating metals (Fe, Zn, Mg, and Mn), quenching the mitochondrial respiratory chain, and increasing the levels of endogenous antioxidant enzymes, such as SOD, CAT, and GPx[9, 31].

ROS and reactive nitrogen species (RNS) are key players in various types of pain[33]. Evidence suggests that tissue injury induces the production of both ROS and RNS, which cause pain by promoting neuronal excitability in pain pathways through neural interactions and by triggering mitochondrial dysfunction and neuro-inflammation[26, 34].

Peroxynitrite ($ONOO^-$) (PN) and its precursor superoxide (SO) are critical in the development of chronic pain and in the transition from acute to chronic pain [35.. An increase in SO/PN production triggers thermal hyperalgesia associated with acute and chronic inflammation in response to the activation of the *N*-methyl-D-aspartate receptor (NMDAR), leading to the development of orofacial pain[36].

PN improves protein kinase C (PKC) activity. This kinase is activated by peripheral and central sensitization and optimizes the translocation of regulatory subunits of NADPH oxidase to the cell membrane to increase the production of SO derived from NADPH oxidase. These two mechanisms together amplify the formation of SO-derived PN, leading to the development of central sensitization[35].

Thus, antioxidants can be administered for pain management to prevent the negative impact of ROS and RNS on nociception, both of which play key roles in neuro-inflammatory processes both at the central and peripheral levels, leading to increased nociceptive and inflammatory responses[26, 33, 37, 38].

In addition to their antioxidant activity, flavonoids and phenolic compounds exhibit effective anti-inflammatory biological properties by blocking two main signaling pathways, NF-5ØßB and mitogen-activated protein kinase (MAPK)[24]. These pathways initiate a cascade of phosphorylation events and result in the production of several pro-inflammatory mediators that mediate the transmission of extracellular signals from the membrane to the nucleus[24, 27, 39].

Action on TRP channels

TRP channels are involved in various homeostatic and sensory functions, such as nociception and temperature sensation, and are expressed in both neuronal and non-neuronal cells. They are grouped into six subfamilies: TRP ankyrin (TRPA), TRP canonical (TRPC), TRP melastatin (TRPM), TRP mucolipin (TRPML), TRP polycystin (TRPP), and TRP vanilloid (TRPV). They are mostly non-selective cation channels expressed on the cell membrane, including the TRPA1 channel, a Ca^{2+}-permeable channel expressed in sensory neurons and is activated by phytochemicals and multiple products of oxidative stress[18].

The Ca^{2+}-permeable TRP channels of presynaptic terminals can modulate synaptic transmission independent of action potentials. Thus, the TRP channels, TRPV1, and TRPA1 can cause the release of neurotransmitters at sensory nerve terminals where these channels are highly co-expressed and participate in inflammatory hyperalgesia[18, 40]. Capsaicin (hot pepper), allicin (garlic), camphor (*Cinnamomum camphora)*, rosemary, and menthol (peppermint) are all analgesics that excite and desensitize nociceptive sensory neurons by acting on the TRPA1 and TRPV1 channels[41–43].

Other phytochemicals also activate the TRP channels. For example, curcumin (*Curcuma longa*) activates TRPA1 channels; eugenol activates the TRPV1 and TRPV3 channels; menthol activates TRPM8 channels; ginger components activate the TRPV1 and TRPA1 channels; and the thymol and linalool compounds of thyme (*Thymus vulgaris*) activate the TRPV3 and TRPA1 channels[18].

GABA mechanism

GABA is a major inhibitory neurotransmitter[44]. involved in most inhibitory actions in the central and peripheral nervous systems (CNS and PNS). GABA exerts its action through two types of receptors: ionotropic (GABAA and GABAC) and metabotropic (GABAB) receptors. GABAA and GABAC are ion channels found in CNS neurons that are permeable to chloride ions when activated by GABA. GABAB receptors belong to the superfamily of G protein-coupled receptors and are present at different levels of the pain neuraxis where they regulate nociceptive transmission and pain[19, 45, 46].

Some phytochemicals, including flavonoids and terpenes, modulate the function of ionotropic GABA receptors and can act as positive, negative, and neutralizing allosteric modulators. Thus, herbal preparations such as *Heliopsis longipes*, *Acmella caulirhiza*, *Ginkgo biloba*, *Panax ginseng*, and *Scutellaria lateriflora* may help modulate toothache by crossing the blood–brain barrier and influencing brain function. Past research has suggested that an increase in GABAergic activity in the rostral agranular insular cortex may induce analgesia by enhancing the descending inhibition of spinal cord nociceptive neurons[19, 47].

Spilanthes acmella is a flowering herb species, also known as the "toothache plant"[48–50]. It has been used for centuries to treat oral pain owing to its analgesic, anti-inflammatory, and anesthetic properties attributed to its bioactive compounds, especially phytosterols, phenolic compounds, and *N*-alkylamides[48, 50, 51]. Spilanthol, which is mainly present in the flowers and shoots of *S. acmella*, is the most representative compound found in this genus. This plant species and other species such as *H. longipes* are used worldwide as traditional remedies for their analgesic, antinociceptive, antioxidant, and anti-inflammatory effects. The analgesic effect of this compound is attributed to GABA release in the temporal cerebral cortex, whereas the antinociceptive effect is caused by the activation of the opioid-adrenergic, serotonergic, and GABAergic systems[52].

The flavonoid baicalein, which can be extracted from *S. lateriflora*, exerts sedative and anxiolytic effects by binding to GABAA receptors and, hence, could be used to manage orofacial pain. This flavonoid is also believed to modulate both intra- and extracellular calcium levels, which play key roles in pain signaling and transmission[44].

GABA receptor systems are found in peripheral pathways and the spinal cord, which are both important sites for pain impulse formation and transmission; they are located in the marginal zone and substantia gelatinosa of the dorsal horn, which are essential for interpreting and responding to pain signals. These findings indicate that GABA plays a key role in nociceptive processing. Consequently, agents that modify the function of this inhibitory neurotransmitter are used as analgesics[46].

Anti-inflammatory mechanism (COX and LOX pathways)

Inflammation is mediated by several families of mediators such as eicosanoids, which are lipid mediators produced through arachidonic acid metabolism, primarily in the COX and LOX pathways[53]. The COX pathway leads to the formation of prostanoids (prostaglandins (PG), prostacyclin, and thromboxane), whereas the LOX pathway leads to the production of leukotrienes (LTs)[54].

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the COX pathway, whereas other drugs such as licofelone are dual inhibitors that block both COX and LOX[54, 55]. However, the selective inhibition of the two COX isoforms by NSAIDs has several reported side effects. This has encouraged the search for a dual inhibitor of both COX-2 and 5-LOX that possesses improved anti-inflammatory potency and fewer side effects[53, 56].

This anti-inflammatory effect leads to the elimination of harmful stimuli and the restoration of normal physiology through the complex molecular cascade mentioned above[3, 21]. This is thought to be the mechanism by which herbal extracts act in the treatment of toothache[21]. Accordingly, medicinal plants, particularly herbs whose main component is curcumin, such as *C. longa*, seem to provide several advantages through their mediating action on the COX and LOX pathways. As a dual inhibitor, curcumin exhibits synergistic effects and optimal anti-inflammatory activity[57]. *Allium cepa* (onion), which also contains polyphenols and flavonoids, inhibits the COX and LOX pathways and prevents the formation of LTs, thromboxane B2 (TXB2), and prostaglandin E2 (PGE2)[58, 59].

Additionally, various ginger compounds, such as gingerols, shogaols, zingerones, gingerdiols, and paradols, exhibit antioxidant, analgesic, and anti-inflammatory activities. More specifically, they act through the inhibition of COX and LOX in addition to their antioxidant activity resulting in an analgesic effect[60]. *Allium sativum* also has antioxidant and anti-inflammatory properties, and its efficacy in reducing pro-inflammatory responses is based on its nature as a COX and LOX inhibitor[59].

Bioavailability of medicinal plants

In humans, most phytochemicals exhibit low bioavailability after ingestion[9]. Hence, polyphenols have a rather low bioavailability because they exert most of their antioxidant activity in the gastrointestinal tract[61]. Additionally, a challenge with flavonoids is their low water solubility, which leads to decreased absorption and consequently decreased bioavailability following oral administration[62].

Interindividual variability, which depends on several factors such as diet, genetic background, composition, and activity of the intestinal microbiota, must also be considered. For example, polyphenols are relatively poorly absorbed (0.3–43%), resulting in low circulating plasma concentrations of their metabolites[63]. Additionally, the quantity and composition of phytochemicals in plants are influenced by species, age, plant part, cultivation method, harvesting season, conservation method, and geographic distribution[9, 64].

To improve bioavailability, proper decoction practices and various plants combinations have been suggested[65]. due to their different phytochemical components and because they may provide different health benefits without requiring an increase in the dose[9]. For example, *Piper sarmentosum* combined with ginger is used to soothe toothache[66]. Medicinal plants containing hundreds of phytochemicals can produce many metabolites in the body, exerting more efficient beneficial effects than individual phytochemicals[9]. However, their combination can also directly affect their bioavailability in the body via mechanisms such as the first-pass effect[18, 67].

Medicinal plants vs pharmaceutical drugs

Comparisons between the analgesic effects of medicinal plants and pharmaceutical drugs have shown that the rhizome of *Zingiber officinale* (ginger) has long been used in traditional Chinese and Indian medicine to treat a wide range of ailments, including toothache[68]. Fresh ginger extracts have been subjected to chromatographic purification, and the resulting fractions were analyzed to assess their effect on PG synthesis. Through this method, plant extracts belonging to the Zingiberaceae family were found to inhibit PG synthesis *in vitro*[69].

The rhizome of *Z. officinale* has pharmacological properties similar to those of dual-action NSAIDs [55.. It inhibits both COX and LOX and has significantly fewer side effects than conventional NSAIDs[69, 70]. Licofelone is an example of a dual-action NSAID (5-LOX/COX) that is currently in phase III clinical development[55]. Studies have shown that orally administered dry ginger or ginger extract can reduce acute inflammation[68, 71], *and in vitro* and *in vivo* comparisons have confirmed the anti-inflammatory and analgesic actions of ginger extract[69, 70].

However, most *in vitro* studies analyzed phytochemical profiles using indices such as the half-maximal inhibitory concentration (IC_{50}), and the medicinal plant extracts have been tested for only a single biological target, COX or LOX. This is insufficient to validate their anti-inflammatory and analgesic properties and hinders direct comparisons between plants and dual-action NSAIDs[72].

The anti-inflammatory properties of ginger extracts come from a mixture of biologically active components such as gingerols, shogaols, and paradols, which are phenolic compounds[73]. The inhibitory effects of ginger on PG synthesis can be attributed to the presence of hydroxymethoxyphenyl compounds in gingerols and shogaols, which in turn inhibit arachidonic acid metabolism via the COX pathway[69, 74]. Moreover, ginger components inhibit several genes encoding cytokines and chemokines involved in inflammatory responses[69, 75].

Essential oil from the fruit of the plant *Dennettia tripetala* (DT), commonly known as pepper fruit, has analgesic effects like those induced by opioids morphine, aspirin, and indomethacin. The analgesic mechanism of DT has been inferred from studies showing that naloxone, which inhibits the analgesic effect of morphine, could also inhibit DT. These findings suggest that DT can also be used for toothache relief[22].

Plant combinations

Mixtures of medicinal plants are a key field of research which accounts for a large volume of information because their polyvalent effects can be used to cure multicausal diseases[76]. In different regions and cultures, plants are used as the entire plant, a combination of plants, or a combination of a plant and a drug. When medicinal plants are mixed, side effects are more likely to happen because interactions can occur between individual components. The most desirable interactions provide additional therapeutic benefits. However, natural extracts also contain multiple components. Therefore, the effects of interactions between two plants are often unpredictable and complex[77].

Additionally, a combination of two or more phytochemicals does not always enhance a specific effect. Combining two or more active chemical substances can produce additive, synergistic, or antagonistic effects[9, 78]. An example of synergism in the use of medicinal plants is Iberogast®, a phyto-preparation used in European countries consisting of nine plant extracts. It is considered to have a multi-target effect (at the gastrointestinal level). Such a multi-target effect has advantages over that of synthetic single-target drugs[79, 80].

Another example is the phytotherapeutic drug Lenidase®, which, when compared to ibuprofen, more efficiently and safely controls postoperative pain and discomfort following third molar extraction. Lenidase® contains a blend of herbal extracts, such as baicalin (190 mg), bromelain (50 mg), and escin (30 mg)[81], which exhibit anti-inflammatory activities. Bromelain inhibits pain mediators such as PGE2 and substance P and exhibits anti-edematous activity. Baicalin regulates several genes associated with inflammation, such as *COX*, *LOX*, and the inducible nitric oxide synthase gene. Escin exerts anti-inflammatory and anti-edematous effects through antihistaminic and antiserotonergic activities[81].

RESULTS AND DISCUSSION

As discussed above, medicinal plants, their phytochemicals, and their mechanisms of action are key subjects of scientific research because they are used to treat and prevent various diseases. Further, plants are the basis of many drugs. Although they are highly complex compounds and are not always suitable substitutes for synthetic agents[82], phytochemicals have been used to provide relief from toothache in various regions of the world, as outlined in the five tables included in this review.

The components of the medicinal plants used and their preparations vary by location and between species. For example, a study conducted in America revealed that leaves were the most commonly used plant parts and that the most common preparations were pastes, extracts, and rinses[83]. Another study conducted in Africa found that *Datura stramonium* L. roots, leaves, stems, and seeds were often used to provide relief from toothache[3]. These findings demonstrate the need for further phytochemical and pharmacological studies to identify the plant part that is most effective for toothache treatment and the optimal application

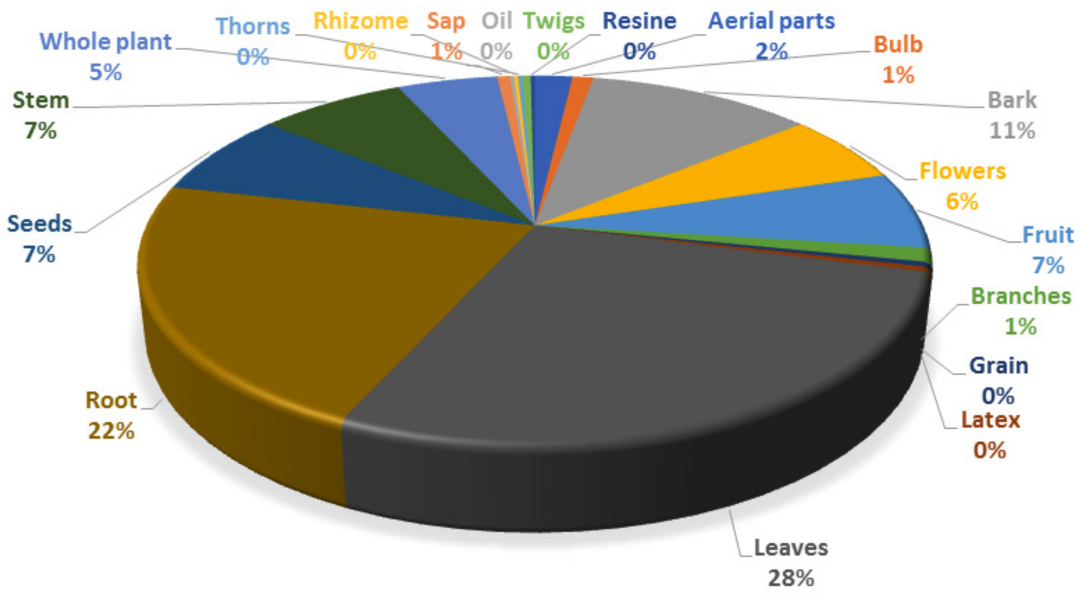

Fig. 1. Relative frequency of the global use of plant parts for the treatment of toothache

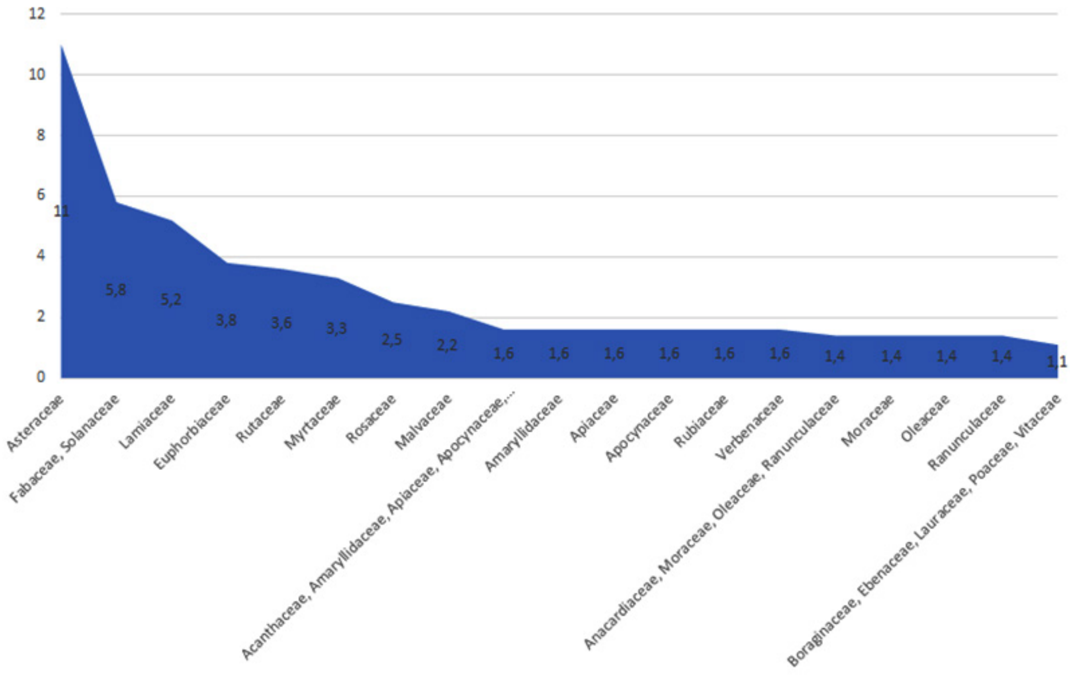

Fig. 2. Families of medicinal plants globally used for the treatment of toothache

Table 1. America

Family	Scientific name	Used part	Preparation	Phytochemicals	Analgesic effect	Anti-inflammatory effect	Mechanism of action	Ref.
Fabaceae	Acacia farnesiana (L.) Willd.	Stem, leaves	Filling, extract, rinse	Diterpenes, flavonoids	x	x	Antioxidant activity	[83]
Asclepiadaceae	Asclepias curassavica L.	Latex, leaves, stem	Filling, extract, rinse	Flavonoids, triterpenes, phenols, quinines, tannins	x	x	N/A	[83, 100]
Malpighiaceae	Byrsonima crassifolia (L.)	Leaves, flowers	Filling, extract, rinse	Triterpenes, sterols, flavonoids	x	x	Antioxidant activity	[83, 101, 102]
Solanaceae	Capsicum frutescens L.	Leaves	Filling, extract, rinse	Alkaloids, tannins, saponins, flavonoids, carotenoids, steroids	x	x	Antioxidant activity	[83, 103]
Chenopodiaceae	Chenopodium graveolens (Willd.)	Leaves	Filling, extract, rinse	Sterols, flavonoids	x	x	N/A	[83]
Sterculiaceae	Chiranthodendron pentadactylon Lam.	Root	Filling, extract, rinse	Flavonoids, phenolic compounds	x	x	Antioxidant activity	[83]
Moraceae	Dorstenia contrajerva L.	Root	Filling, extract, rinse	Flavonoids, alkaloids	x	x	N/A	[83, 104]
Asteraceae	Heliopsis longipes	Root	Filling, extract, rinse	Alkamides, affinin (spilanthol)	x	x	GABA mechanism, anti-inflammatory mechanism (COX and LOX)	[83, 105]
Campanulaceae	Lobelia laxiflora Kunth.	Whole plant	Filling, extract, rinse	N/A	x	x	N/A	[83]
Lauraceae	Persea americana Miller.	Fruit	Filling, extract, rinse	Phenolics, flavonoids	x	x	Antioxidant activity	[83, 106]
Malvaceae	Sida rhombifolia L.	Stem, leaves	Filling, extract, rinse	Flavonoids, terpenoids, alkaloids	x	x	N/A	[83, 107]
Sterculiaceae	Theobroma cacao L.	Grain	Filling, extract, rinse	Polyphenols (flavonoids, lignans, lignins.)	x	x	Antioxidant activity	[83]
Poligonacea	Mexican Sanguinaria	Root	Filling, extract, rinse	Flavonoids	x	x	N/A	[83]
Euphorbiaceae	Jatropha gossypifolia	Whole plant	Decoction	Alkaloids, terpenes, flavonoids, lignans, coumarins, phenolics	-	x	Antioxidant activity	[108]
Euphorbiaceae	Jatropha curcas	Sap	Topical	Alkaloids, terpenes, flavonoids, lignans, coumarins, phenolics	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[108, 109]
Amaryllidaceae	Allium sativum L.	Bulb	Crushed	Steroids, terpenoids, flavonoids, phenols	-	x	Antioxidant activity, TRP mechanism, anti-inflammatory mechanism (COX and LOX)	[18, 59, 110, 111]
Araliaceae	Panax ginseng	Leaves, seeds	Extract	Flavonoids, terpenes	-	x	GABA mechanism	[110]
Zingiberaceae	Zingiber officinale roscoe	Leaves, seeds	Extract	Flavonoids, terpenes	-	x	Anti-inflammatory mechanism (COX and LOX)	[60, 110]
Asteraceae	Tagetes lucida	Aerial parts	Decoction, infusion, rinse, direct application	Carotenoids, flavonoids, thiophenes	-	x	Antioxidant activity	[112, 113]
Onagraceae	Lopezia racemosa	Leaves, seeds	Infusion	Tannins, flavonoids	-	x	Antioxidant activity	[114, 115]
Asteraceae	Acmella oleracea	Flowers	Chewed	Spilanthol, sequesterpenes.	x	x	GABA mechanism, antioxidant activity	[51, 116]

Table 2. Europe

Family	Scientific name	Used part	Preparation	Phytochemicals	Analgesic effect	Anti-inflammatory effect	Mechanism of action	Ref.
Amaryllidaceae	*Allium cepa L.*	Bulb	Bandage	Saponin, quercetin, anthocyanin	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[6, 59, 117]
Amaryllidaceae	*Allium sativum L.*	Bulb	Crushed	Alliin, allicin, flavonoids, terpenes	-	x	Antioxidant activity, TRP mechanism, anti-inflammatory mechanism (COX and LOX)	[6, 18, 59, 76, 111]
Asteraceae.	*Antennaria dioica (L.)*	Leaves	Decoction	Phenolic, ûavonoid	-	x	Antioxidant activity	[6, 118]
Brassicaceae	*Armoracia rusticana P.*	Root	Finely chopped, chew	Flavonoids	-	-	Antioxidant activity	[6, 119]
Brassicaceae	*Brassica oleracea L.*	Leaves	Rinse, gargle	Carotene, tocopherol, ascorbate	-	-	Antioxidant activity	[6, 120]
Lauraceae	*Cinnamomum verum J. Presl*	Bark	Mix with cinnamon powder, honey, rub and spread	Monoterpenes, diterpenes, sesquiterpenes, polyphenols	-	x	Antioxidant activity	[6, 121]
Myrtaceae	*Eucalyptus globulus Labill.*	Leaves	Infusion mixed with lemon, inhalation	Flavonoids	-	x	Antioxidant activity	[6, 122]
Solanaceae	*Hyoscyamus niger L.*	Leaves	Infusion, gargle	Alkaloids	x	x	Antioxidant activity	[6, 123]
Asteraceae	*Matricaria chamomilla L.*	Flowers	Infusion, gargle	Flavonoids, coumarins, sesquiterpenes, and polyacetylenes	-	x	Antioxidant activity	[6, 124, 125]
Ranunculaceae	*Nigella sativa L.*	Oil, seed	Dissolved in hot water	Phenols	-	x	Antioxidant activity	[6, 126]
Plantaginaceae	*Plantago lanceolata L.*	Leaves	Gargle	Phenolic compounds	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[6, 127, 128]
Lamiaceae	*Salvia officinalis L.*	Leaves	Decoction, gargle	Phenolic compounds	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[6, 129, 130]
Myrtaceae	*Syzygium aromaticum L.*	Flowers	Chewed	Phenolic compounds	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[6, 131, 132]
Asteraceae	*Taraxacum sp.*	Leaves, root	Boil, drop, or chew	Phenolic compounds	x	x	Antioxidant activity	[6, 133]
Vitaceae	*Vitis vinifera L*	Fruit	Decoction, gargle	Polyphenols	-	x	Antioxidant activity	[6, 134]
Poaceae	*Zea mays L.*	Grain	Boil, gargle	Flavonoids, alkaloids, phenols, steroids, terpenoids, tannins.	x	X	Antioxidant activity	[6]
Malvaceae	*Althaea officinalis L*	Root	Tisane	N/A	-	-	N/A	[76]
Oleaceae	*Olea europaea L*	Fruit	Juice, aerosol	Phenolic compounds	x	X	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[76, 135]
Asteraceae	*Calendula arvensis L*	Flowers	Poultice	N/A	-	-	N/A	[76]
Apiaceae	*Eryngium campestre L*	Root	Tisane	N/A	-	X	N/A	[76]
Anacardiaceae	*Pistacia lentiscus L*	Leaves	Mouthwash	N/A	x	X	N/A	[76]
Lamiaceae	*Origanum vulgare L.*	Flowers	Tisane	N/A	x	X	N/A	[76]
Rutaceae	*Ruta chalepensis L*	Aerial parts	Tisane	Alkaloids, flavonoids, phenols, saponins.	x	x	N/A	[76, 136]
Rosaceae	*Crataegus monogyna Jacq.*	Flowers	Poultice	N/A	-	x	N/A	[76]
Apiaceae	*Foeniculum vulgare Mill.*	Seed	Poultice	Flavonoids, phenolic compounds.	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[76, 137, 138]
Fabaceae	*Glycyrrhiza glabra L.*	Root	Poultice	N/A	-	-	N/A	[76]
Papaveraceae	*Papaver rhoeas L*	Flowers	Poultice	N/A	-	-	N/A	[76]
Lamiaceae	*Thymus vulgaris L.*	Aerial parts	Fumigation	N/A	-	-	TRP mechanism	[18, 76]
Rutaceae	*Citrus limon L.*	Fruit	Juice, mouthwash	N/A	-	-	N/A	[76]

Table 3. Africa.

Familia	Scientific name	Used part	Preparation	Phytochemicals	Analgesic effect	Anti-inflammatory effect	Mechanism of action	Ref.
Ebenaceae	Euclea undulata thunb.	Root, bark	Powder rubbed or root chewed	Flavonoids, saponins, diterpenes, alkaloids	-	x	Antioxidant activity	[139]
Fabaceae	Millettia ferruginea (hochst.)	Bark	Grind, mix with water, chew	Flavonoids	-	-	N/A	[140, 141]
Lamiaceae	Salvia nilotica juss.	Leaves, root, bark	Chewing, grinding, rubbing	N/A	-	x	N/A	[140, 142]
Lamiaceae	Rotheca myricoides (hochst.)	Leaves, root, bark	Rubbing, grinding, eating, boiling	N/A	-	-	N/A	[140]
Malvaceae	Ceiba pentandra L. Gaertn	Fruit	Grinding, hold on teeth	Flavonoids	x	x	N/A	[140, 143]
Acanthaceae	Blepharis linariifolia pers.	Aerial part	Filling with powder	Flavonoids, phenolic acids	-	x	N/A	[144, 145]
Acanthaceae	Barleria homoiotricha c. B. Clarke	Bark	Drink	N/A	-	-	N/A	[3]
Acanthaceae	Dyschoriste radicans (hochst. Ex. Rich.) Nees	Whole plant	N/A	N/A	-	-	N/A	[3]
Acanthaceae	Justicia Schimperiana (Hochst. ex Nees) T. Anderson	Twigs	Chewed	Saponins, alkaloids, terpenoids and ?avonoids	-	-	Antioxidant activity	[3, 146]
Amaryllidaceae	Allium sativum L.	Bulb	Crushed	Alliin, allicin, flavonoids, terpenes	-	x	Antioxidant activity, TRP mechanism, anti-inflammatory mechanism (COX and LOX)	[3, 18, 111]
Amaranthaceae	Amaranthus caudatus L.	Bark, leaves	Chewed	Flavonoids, phenols	-	-	Antioxidant activity	[140, 147]
Amaryllidaceae	Allium cepa L.	Leaves	Paste	Flavonoids, saponin	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[59, 148, 149]
Anacardiaceae	Mangifera indica L.	Stem, root, leaves	Solution	N/A	-	x	N/A	[148, 150]
Anacardiaceae	Rhus natalensis bernh. Ex. Krauss	Leaves	Chewed	Flavonoids	-	x	Antioxidant activity	[3, 151-153]
Anacardiaceae	Schinus molle L.	Stem	Brushing	Monoterpenes.	x	x	Antioxidant activity	[3, 154]
Ancistrocladaceae	Ancistrocladus abbreviatua	Bark	Boil crust	Naphthylisoquinoline alkaloids	-	-	N/A	[148, 155]
Annonaceae	Dennettia tripetala	Fruits, leaves, seeds, roots	Extract	Tannins, alkaloids, flavonids, terpenoids, saponins	x	x	N/A	[22]
Apiaceae	Ammi visnaga	Fruit	Raw, decoction, direct application, rinse	Tannins, coumarins, flavonoids, phenolic acids	x	x	Antioxidant activity	[156, 157]
Apiaceae	Coriandrum sativum L.	Fruit	Raw, direct application	Polyphenols: flavonoids	x	x	Antioxidant activity	[156, 158]
Apiaceae	Foeniculum vulgare mill.	Roots	Decoction	Flavonoids, phenolic compounds.	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[3, 137, 138]
Apiaceae	Oenanthe palustris (chiov.) C. Norman	Leaves	Chewed	N/A	-	-	N/A	[3]
Apocynaceae	Carissa edulis (forssk.) Vahl	Root, leaves	Pound, boil and press on tooth	Lignans, sesquiterpenes, phenols	-	x	Antioxidant activity	[159, 160]
Apocynaceae	Nerium oleander	Leaves, root	Raw, direct application	Triterpene, flavonoids	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[156, 161, 162]
Apocynaceae	Carissa spinarum l.	Bark	Chew or hold on teeth for 5-10 min.	Coumarin, lignans	-	-	Antioxidant activity	[163, 164]
Apocynaceae	Calotropis procera (ait.) Dryand.	Bark	Pounded	Triterpenoids	x	x	Antioxidant activity	[3, 165]
Aquifoliaceae	Ilex mitis (l.) Radlk.	Twigs	N/A	N/A	-	-	N/A	[3]
Araliaceae	Sche?iera abyssinian (hochst. Ex a. Rich.) Harms	Bark	Chewed	Saponins	-	-	N/A	[3]
Arecaceae	Cocos nucifera L.	Root	Powder and whole root	Phenols, tannins, flavonoids, triterpenes, steroids, alkaloid	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[148, 166-168]
Asclepiadaceae	Gomphocarpus purpurascens a. Rich.	Root	Mix with honey and chew	N/A	-	-	N/A	[169, 170]
Asparagaceae	Asparagus africanus lam.	Root	Drink	Saponins, flavonoids, tannins.	x	x	N/A	[3, 171]
Asteraceae	Echinops kebericho, mesfin	Root	Pounded dry root is mixed with coffee	N/A	x	x	N/A	[172, 173]
Asteraceae	Erlangea tomentosa	Leaves	Crush and press on the tooth	Alkaloids, saponins, coumarins, tannins	-	-	N/A	[159]
Asteraceae	Chamaemelum nobile l	Flowers	Decoction, mouthwash	Flavonoids	-	x	Antioxidant activity	[156, 174]
Asteraceae	Artemisia absinthium L.	Leaves	Decoction, mouthwash	Phenolic compounds	-	x	Antioxidant activity	[156, 175]
Asteraceae	Atractylis gummifera	Root	Raw, direct application	Polyphenols, flavonoids, tannins	-	-	Antioxidant activity	[156, 176]
Asteraceae	Spilanthes africana	Flowers	All parts	Alkaloids, saponins and glycosides	x	x	N/A	[148, 177]
Asteraceae	Echinaceae purpurea	Leaves, stem	Paste	N/A	-	x	Antioxidant activity	[148]
Asteraceae	Ageratum conyzoides	Whole plant	Dust	Alkaloids, flavonoids, terpenoids	x	x	N/A	[148, 178]

Asteraceae	Dichrocephala integrifolia	Whole plant	Paste	Alkaloids, glycoside, flavanoids, phytosterols, saponins, tannins, carotenoids	_	x	N/A	[148, 179]
Asteraceae	Acmella caulirhiza del.	Flowers	Chewed, topical application	Lipophilic alkylamides, spilanthol	x	-	N/A	[3, 152]
Asteraceae	Acmella oleracea	Flowers	Chewed	Spilanthol, sequesterpenes.	x	x	GABA mechanism, antioxidant activity	[51, 51, 51, 180]
Asteraceae	Artemisia abyssinica sch.bip. Ex a. Rich.	Stem	Chewed	Alkaloids, saponins, flavonoids and tannins.	x	x	Antioxidant activity	[3, 181]
Asteraceae	Artemisia afra jack. Ex wild.	Leaves	Chewed	N/A	-	-	N/A	[3]
Asteraceae	Echinops kebericho mes?n	Roots	Powdering	Flavonoids	x	x	Antioxidant activity	[3, 182]
Asteraceae	Echinops macrochaetus fresen.	Roots	Hold in mouth	N/A	-	-	N/A	[3]
Asteraceae	Galinsoga parvi?ora cav.	Flowers	Rubbing	Polyphenols and flavonoids, phenolic acids	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[3, 183, 184]
Asteraceae	Inula conferti?ora a. Rich.	Leaves	Chewed	N/A	-	-	N/A	[3]
Asteraceae	Kleinia squarrosa cufod.	Stem	Brushing	N/A	-	-	N/A	[3]
Asteraceae	Laggera intermedia c. B. Clarke	Leaves	Crushed	N/A	-	-	N/A	[3]
Asteraceae	Parthenium hysterophorus L.	Roots	Chewed	N/A	-	-	N/A	[3]
Asteraceae	Vernonia auriculifera hiern	Roots	Chewed	Tannins, flavonoids, terpenoids, saponins	-	-	N/A	[3, 185]
Balanitaceae	Balanites aegyptiaca (l.) Del.	Bark	Chewed	Saponins	-	x	Antioxidant activity, anti-inflamatory mechanism (COX and LOX)	[3, 186, 187]
Bignoniaceae.	Stereospermum kunthianum cham	Stem	Chewed	Flavonoids and phenolic acids	x	x	Antioxidant activity	[3, 188]
Boraginaceae	Ehretia cymosa thonn.	Bark, leaves	Chew, grind, boil, squeeze	Phenols, flavonoids, tannins, alkaloids, terpenes	-	-	Antioxidant activity	[140, 189]
Boraginaceae	Cordia africana lam.	Bark	Chewed	Flavonoids and phenolic compounds	-	x	Antioxidant activity	[3, 190]
Boraginaceae	Cynoglossum coeruleum hochst. Ex a. Dc	Leaves	Hold in mouth	N/A	-	-	N/A	[3]
Brassicaceae	Lepidium sativum L.	Seeds	Chewed	Flavonoids, saponosides, tannins, alkaloids, stereol and polyterpene.	-	x	Antioxidant activity	[3, 191]
Burseraceae	Commiphora hodai Sprague	Roots	Inhaling	N/A	-	-	N/A	[3]
Capparaceae	Boscia salicifilia oliv.	Leaves	Chew	Alkaloids, flavonoids, sesquiterpenes and their glycosides.	-	-	Antioxidant activity	[169, 192]
Capparaceae	Capparis tomentosa lam.	Roots	Chewed	Alkaloids, saponin glycosides, alkaloids, phytosterols, terpenoids, tannins, sterol, polyphenols, flavonoids	x	x	Antioxidant activity	[3, 193]
Capparaceae	Capparis fascicularis dc.	Roots	Chewed	N/A	-	-	N/A	[3]
Capparidaceae	Cadaba rotundifolia forssk.	Leaves	Chewed	Alkaloids, terpenoids and flavonoids	-	-	Antioxidant activity	[3, 194]
Capparidaceae	Crateva adansonii dc.	Leaves	Heating	Tannins, triterpenoids	-	-	Antioxidant activity	[3, 195]
Caricaceae	Carica papaya	Leaves	Solution	Alkaloids, saponins, glycosides, tannins	-	x	N/A	[148, 150, 196]
Caryophyllaceae	Drymaria cordata	Leaves	N/A	Alkaloid, glycosides, saponins, tannins	x	x	N/A	[3, 197]
Celastraceae	Catha edulis (vahl) endl	Leaves	Eat, boil, chew, mix with water.	N/A	-	-	N/A	[140]
Chenopodiaceae	Chenopodium opulifolium	Leaves	Drink	Flavonoids, saponins, terpenes, sterols, alkaloids	-	-	Antioxidant activity	[3, 159, 198]
Chenopodiaceae	Chenopodium ambrosioides	Whole plant, seeds	Paste	N/A	-	-	Antioxidant activity	[148, 199]
Clusiaceae	Clusia lanceolata cambess.	Leaves	N/A	N/A	-	-	N/A	[3]
Clusiaceae	Garcinia livingstonei t. Anderson	Stem	Chewed	Benzophenone derivatives, biflavonoids	-	-	Antioxidant activity	[3, 200, 201]
Colchicaceae	Gloriosa superba L.	Leaves	Crushed	Polyphenols, sterols and resinous substances	-	-	Antioxidant activity	[3, 202]
Combretaceae	Anogeissus leiocarpus (dc.)	Bark	Filling with powder	Flavonoids, terpenes, saponins	-	-	Antioxidant activity	[144, 203]
Asteraceae	African Aspilia	Whole plant	Paste	Terpenoids, sterols	-	x	N/A	[148, 204]
Asteraceae	Vernonia amygdalina	Leaves	Solution, chewed	Flavonoids, saponins, alkaloids, tannins, phenolics, terpenes	-	x	Antioxidant activity	[148, 205]
Asteraceae	Arnica montana	Leaves	Solution	Flavonoids, carotenoids, diterpenes, alkaloids, coumarins, lignans	-	x	Antioxidant activity	[148, 206]
Convolvulaceae	Ipomoea batatas	Leaves	Paste	Polyphenol	_	x	N/A	[148]
Crassulaceae	Kalanchoe laciniata (l.) Dc	Roots	Chewed	Flavonoids, carotenoids	x	x	Antioxidant activity	[3, 207]
Cucurbitaceae	Cucumis ficifolius	Roots	Chewed	N/A	-	-	N/A	[169]
Cucurbitaceae	Momordica foetida schumach.	Roots	Chewed	Ucurbitan triterpenes	-	-	Antioxidant activity	[3, 208]
Cupressaceae	Cupressus bethanis	Seed, bark	Solution / rinse	N/A	-	-	N/A	[148]
Cupressaceae	Cupressus lusitanica mill.	Leaves	Decoction	Ascorbic acid, tocopherols	-	-	Antioxidant activity	[3, 209]
Cupressaceae	Juniperus procera hochst. Ex endl.	Bark	Hold	N/A	x	x	Antioxidant activity	[3, 210]

Dracaenaceae	Dracaena fragrans L.	Bark	Chewed	Flavonoids, alkaloids, carotenoids, saponins	-	-	N/A	[159, 211]
Dracaenaceae	Dracaena diesteliana	Root	Solution	N/A	-	-	N/A	[148]
Ebenaceae	Euclea racemosa	Whole plant	Chewed	Flavonoids, glycosides, phenols, saponins, steroids, tannins and triterpenes	-	-	Antioxidant activity	[3, 169]
Ebenaceae	Euclea divinorum hiern	Roots	Drink	Alkaloids, flavonoids, tannins, saponins	x	x	Antioxidant activity	[3, 212]
Euphorbiaceae	Jatropha gossypifolia	Whole plant	Decoction	Alkaloids, terpenes, flavonoids, lignans, coumarins, phenolics	-	x	Antioxidant activity	[108]
Euphorbiaceae	Jatropha curcas	Sap	Topical	Alkaloids, terpenes, flavonoids, lignans, coumarins, phenolics	-	x	Antioxidant activity, anti- inflammatory mechanism (COX-LOX)	[108, 109]
Euphorbiaceae	Ricinus communis	Leaves	Solution	steroids, saponins, alkaloids, flavonoids and glycosides	x	x	Antioxidant activity	[148, 213]
Euphorbiaceae	Alchornea cordifolia	Stem, bark	Boiled	Alkaloids, terpenes, steroids, phenolic acid, saponins	-	-	N/A	[148, 214]
Euphorbiaceae	Ricinodendron heudelotii	Seeds	Paste	Tannins, flavonoids	-	x	Antioxidant activity	[148, 215]
Euphorbiaceae	Clutia abyssinica joub. & spach.	Leaves	Hold in mouth	Flavonoids, alkaloids, terpenoids and saponins	-	x	Anti- inflammatory mechanism (COX-LOX)	[163, 216]
Euphorbiaceae	Phyllanthus sepialis mull. Arg	Roots	Chewed	N/A	-	-	N/A	[3]
Euphorbiaceae	Acalypha sp.	Leaves	Boil	Tannins, flavonoids, phenolics, saponins, alkaloids, terpenoids, coumarins, anthocyanins and anthraquinones.	x	x	Antioxidant activity	[148, 217]
Fabaceae	Calpurnia aurea (aiton) benth.	Leaves, root	Chewing, rubbing, powdering, grinding	N/A	-	-	N/A	[140]
Fabaceae	Acacia albida delile	Stem	Chewing, blow drying	Triterpenoids, tannins, sterols	-	x	Antioxidant activity	[140, 218]
Fabaceae	Albizia gummiffera (j. F. Gmel.) Ca Sm.	Leaves	Crushed, rubbed	N/A	-	-	N/A	[163]
Fabaceae	Acacia nilotica	Stem, bark	Decoction	Alkaloids, flavonoid phenols, tannins, terpenes	-	-	Antioxidant activity	[3, 219-221]
Fabaceae	Abyssinian inlet a. Rich.	Bark	Chewed	Tannins, saponins and flavonoids	-	-	N/A	[222]
Fabaceae	Erythrina brucei schweinf.	Bark	Chewed	Isoflavones	-	-	N/A	[3, 223]
Fabaceae	Indigofera spicata forssk.	Roots	Chewed	N/A	-	-	N/A	[3]
Flacourtiaceae	Dovyalis abyssinica (a. Rich.) Warb.	Seeds	Chewed	N/A	-	-	N/A	[3]
Flacourtiaceae	Monsonia parvifolia schinz	Leaves	Heated	N/A	-	-	N/A	[3]
Geraniaceae	Geranium sp.	Leaves	Rubbing	Terpenes	-	x	Antioxidant activity	[3, 224]
Clusiaceae	Garcinia kola	Bark and seeds	Rinse, paste	Flavonoids, phenol, alkaloids, saponin, tannin	-	X	Antioxidant activity	[148, 225]
Lamiaceae	Coleus blumei	Leaves	Paste	Rosmarinic acid	-	X	Antioxidant activity	[148, 226]
Lamiaceae	Thymus schimperi ronniger	Whole plant	Chew	N/A	-	-	N/A	[169]
Lamiaceae	Clerodendrum myricoides (hochst.)	Roots, seeds	Crushed	Alkaloid, phenols, anthraquinones, terpenoids, and flavonoids.	-	-	N/A	[3, 227]
Lamiaceae	Isodon ramosissimus (hook.f.)	Roots, leaves	Chewed	N/A	-	-	N/A	[3]
Lamiaceae	Mentha pulegium L.	Leaves	Chewed, infusion	-	-	-	TRP mechanism	[3, 18, 156]
Lamiaceae	Ocimum urticifolium roth	Leaves	Chewed	Tannins, glycosides, saponins, flavonoids, steroids, terpenoids, phenols	-	-	N/A	[3, 228]
Lamiaceae	Oymus schimperi ronniger	Whole plant	Chewed		-	-	N/A	[3]
Lauraceae	Persea americana	Seeds, stem	Decoction / hot solution	Flavonoids, saponins, tannins, steroids, alkaloids, terpenoids.	-	X	Antioxidant activity	[106, 148, 229]
Fabaceae	Acacia oerfota (forssk.) Schweinf.,	Root	Paste	Alkaloids, terpenes, flavonoids	-	-	N/A	[144]
Fabaceae	Acacia senegal (l.) Willd.,	Leaves, thorns	Filling with powder and bowling	Flavonoids, alkaloids, terpenoids, steroids	-	-	Antioxidant activity	[144]
Fabaceae	Cassia arereh delile	Root	Filling with powder	Flavonoids, phenols, terpenoids, saponins, tannins	-	-	Antioxidant activity	[144, 230]
Loranthaceae	Plicosepalus robustus wiens & polhill	Leaves	Pulverized	N/A	-	-	N/A	[3]
Loranthaceae	Tapinanthus globiferus (a. Rich.) Tiegh.	Leaves	Rub	N/A	x	-	Antioxidant activity	[3, 231]
Malvaceae	Cola nitida	Bark and fruit	Solution and paste	Alkaloids, tannin, saponin, flavonoids	-	X	Antioxidant activity	[148, 232]
Malvaceae	Pavonia urens cav.	Root	Decoction	N/A	-	-	N/A	[3]
Malvaceae	sida tenuicarpa vollesen	Root	Brushed	N/A	-	-	N/A	[3]
Malvaceae	Sida ovata forssk.	Leaves, root	Liquid form	N/A	-	-	N/A	[140]
Malvaceae	Azadirachta indica A.	Leaves root, bark	Grinding, chewing, boiling, liquid form	Alkaloids, flavonoids, triterpenes, steroids, phenolic compounds.	-	X	Antioxidant activity	[140, 233-235]
Meliaceae	Melia azedarach L.	Leaves	Chewed	Alkaloids, terpenoids, flavonoids	-	-	Antioxidant activity	[3, 236]

Menispermaceae	Stephania abyssinica	Root	Brushed	N/A	-	-	N/A	[3]
Lamiaceae	Marrubium vulgare L	Whole plant	Decoction, mouthwash	Phenolic compounds	x	X	Antioxidant activity, anti-inflammatory mechanisms (COX-LOX)	[156, 237, 238]
Lamiaceae	Origanum majorana	Whole plant	Mouthwash	Terpenoids, flavonoids, phenolic acids.	x	X	Antioxidant activity	[156, 239]
Moraceae	Ficus palmata forssk.	Root	Chewed	Phenolic compounds, flavonoid	-	-	Antioxidant activity	[3, 240]
Moraceae	Ficus sur forssk.	Bark	Chewed	Tannins, saponins, steroids, tannins	-	-	N/A	[3, 241]
Moraceae	Ficus vasta forssk.	Bark	Eating, chewing	Phenolic compounds, flavonoids	-	-	Antioxidant activity	[140, 242]
Moringaceae	Moringa oleifera	Root	Decoction	Alkaloids, protein, quinine, saponins, flavonoids, tannin, steroids, glycosides	x	X	Antioxidant activity	[148, 243]
Myristicaceae	Pycnanthus angolensis	Stem, bark, leaves	Decoction / mouthwash	N/A	-	-	N/A	[148]
Myrtaceae	Eucalyptus globulus Labill.	Leaves	Infusion mixed with lemon, inhalation	Flavonoids	-	X	Antioxidant activity	[6, 122, 156]
Myrtaceae	Myrtus communis l	Leaves	Decoction, mouthwash	Phenolic compounds, flavonoids	-	-	Antioxidant activity	[156, 244]
Myrtaceae	Syzygium aromaticum L.	Flowers	Chewed	Phenolic compounds	-	X	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[6, 132, 156, 245]
Myrtaceae	Eucalyptus saligna	Leaves	Solution, paste	Flavonoids, derived from phenylpropene	-	-	N/A	[148]
Myrtaceae	Psidium guajava L.	Leaves	Hot rinse, chewed	Flavonids, triterpenes, tannins	x	X	Antioxidant activity	[93,148,219,246]
Myrtaceae	Eucalyptus sp	Roots	Rub	N/A	-	X	Antioxidant activity	[3, 247]
Myrtaceae	Eucalyptus camaldulensis	Leaves	Rubbing, hold on teeth, filling with powder	N/A	x	X	Antioxidant activity	[140, 144, 248]
Nitrariaceae	Peganum harmala L.	Seeds	Decoction, mouthwash	Flavonoids, alkaloids, saponins, tannins, glycosides, terpenoids and steroids	x	-	N/A	[156, 249-251]
Olacaceae	Ximenia americana L.	Bark	Pulverized	Flavonoids, polyphenols	-	-	Antioxidant activity	[3, 252]
Oleaceae	Olea europaea l.	Leaves	Chewed	Phenolic compounds	-	X	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[130, 135, 169]
Oleaceae	Jasminum abyssinicum hochst	Roots	Chewed	Alkaloids, flavonoids, terpenes, phenol	-	-	Antioxidant activity	[3, 253]
Oleaceae	Jasminum grandiflorum L.	Leaves, stem	Crushed	Flavonoids, alkaloids, glycosides	-	-	Antioxidant activity	[3, 254]
Oliniaceae	Olinia rochetiana a. Juss.	Leaves, bark	N/A	N/A	-	-	N/A	[3]
Opiliaceae	Ziziphus mauritiana lam	Stem	Boiled	Flavonoids glycoside, phenol, lignin, saponins, sterols and tannins	-	X	Antioxidant activity	[3, 255]
Orobanchaceae	Orobanche ramosa L.	Roots	Chewed	N/A	-	-	N/A	[3]
Oxalidaceae	Oxalis corniculata L.	Leaves	Chewed	Flavonoids, alkaloids, tannins, phenols	-	X	Antioxidant activity	[3, 256]
Oxalidaceae	Oxalis radicosa A. Rich.	Leaves, stem	Chewed	N/A	-	-	N/A	[3, 152]
Phytolaccaceae	Phytolacca dodecandra L'her	Stem	Chewed	Triterpenoids, saponins, alkaloid, phenolics, steroids, terpenoids	x	X	N/A	[3, 257, 258]
Plumbaginaceae	Plumbago zeylanica L.	Roots, bark	Crushed root, direct application	Alkaloids, glycosides, steroids, triterpenoids, tannins, phenolic compounds, flavanoids, saponins, coumarins	-	X	N/A	[152, 259, 260]
Polygalaceae	Securidaca longepedunculata fresen.	Leaves	Chewed	Flavonoids, tannins, triterpenoids	x	X	N/A	[3, 261]
Polygonaceae	Rumex abyssinicus jacq	Roots	Crushed, drink	Phenolic compounds, tannins, saponins, flavonoids, terpenoids, steroids, alkaloids,	x	X	N/A	[3, 169, 262]
Polygonaceae	Rumex nepalensis spreng.	Roots	Chewed	Flavonoids, terpenoids, alkaloids, saponins, tannins	-	X	Antioxidant activity	[3, 263]
Polypodiaceae	Drynaria volkensii Heiron	Roots	Chewed, heat	N/A	-	-	N/A	[3, 163]
Proteaceae	Faurea speciosa welw	Roots, leaves	Chewed, Topical application	N/A	-	-	N/A	[3, 152]
Ranunculaceae	Clematis longicauda steud.	Leaves	Crushed	Tannins, saponins, flavonoids, and steroids	-	-	N/A	[3, 264]
Ranunculaceae	Clematis simensis fresen.	Bark, seed, roots	Chewed	Triterpenoids, saponins, alkaloids, polyphenol	-	X	N/A	[3, 265]
Ranunculaceae	Ranunculus multifidus forssk.	Roots	Chewed	N/A	-	-	N/A	[3]
Ranunculaceae	Thalictrum rhynchocarpum dill	Roots	Chewed	N/A	-	-	N/A	[3]
Rosaceae	Prunus africana (hook.f.)	Bark	Chewed	Phenolic, flavonoid	-	-	Antioxidant activity	[3, 266]
Rosaceae	Prunus persica (l.) Batsch	Bark	Chewed	Phenolic compounds, carotenoids	-	X	N/A	[3, 267]
Rubiaceae	Galium boreo- aethiopicum	Roots	Chewed	N/A	-	-	N/A	[169]
Rubiaceae	Gardenia ternifolia schumach.	Roots	Chewed	Saponins, sterols, triterpenes, tannins, flavonoids	-	-	Antioxidant activity	[3]
Rubiaceae	Pavetta gardeniifolia hochst.	Roots	Crushed	N/A	-	-	N/A	[3]
Rubiaceae	Pentas lanceolata (forssk.)	Roots	Chewed	Saponins, alkaloids	-	-	N/A	[3, 152, 268]
Rutaceae	Clausena anisata (willd.)	Roots, stem,	Chewed seeds, leaves	Phenolic, alkaloid, flavonoid, saponins, tannin	-	-	Antioxidant activity	[3, 269]

Rutaceae	Ruta chalepensis L	Leaves	Chewed	Alkaloids, flavonoids, phenols, saponins.	x	X	N/A	[3, 136]
Rutaceae	Vepris dainellii (pichi-serm.) Kokwaro	Bark	Chewed	N/A	-	-	N/A	[3]
Rutaceae	Zanthoxylum chalybeum engl.	Bark	Hold	Alkaloids, phenolic	x	-	N/A	[3, 270]
Salvadoraceae	Salvadora persica L.	Stem	Brushed	Saponins, alkaloids	x	-	N/A	[3, 271]
Sapindaceae	Dodonaea angustifolia	Roots, leaves	Brushed	Di and triterpenes, saponins, flavonoids, phenolic compound.	x	X	Antioxidant activity	[3, 272, 273]
Scrophulariaceae	Verbascum sinaiticum benth.	Roots	Chewed	Alkaloids, phenolic compounds, anthraquinones, flavonoids, saponins, tannins, steroids, terpenes.	-	-	Antioxidant activity	[169, 274]
Simaroubaceae	Brucea antidysenterica J.F.Mill.	Roots, bark	Chewed	Alkaloids, flavonoids, glycosides, phenols, quinones, saponins, steroids, tannins, terpenoids	-	X	N/A	[3, 275]
Solanaceae	Solanum americanum mill.	Leaves, fruits	Grind, boiled, chewed	Alkaloids, flavonoids, tannins, saponins	-	-	N/A	[140]
Solanaceae	Datura stramonium L.	Fruits, leaves, stem, seeds	Grind, rub, liquid form, boiled, squeezed	Alkaloids, tannins, flavonoids, phenols	x	X	Antioxidant activity	[152, 276, 277]
Solanaceae	Nicotiana tabacum L.	Leaves	Boiled, chewed	Flavonoids, alkaloids, tannins, phenolic compounds, terpenoids	-	-	N/A	[140, 278]
Solanaceae	Solanum hastifollium hochst.	Roots	Chewed	N/A	-	-	N/A	[169]
Solanaceae	Solanum incanum l.	Fruits, roots	Chewed	Alkaloids, flavonoids, saponins, steroids	-	-	Antioxidant activity	[3, 279]
Solanaceae	Solanum marginatum l. F.	Roots	Chewed	Alkaloids, saponins, flavonoids, glycosides, terpenoids, steroid	-	-	N/A	[3, 280]
Solanaceae	Capsicum frutescens L.	Fruits	Paste	Alkaloids, tannins, saponins, flavonoids, carotenoids, steroids	x	X	N/A	[103, 148]
Tiliaceae	Grewia bicolor juss	Stem	Brushed	Alkaloids, triterpenes	-	-	N/A	[3, 281]
Tiliaceae	Grewia ferruginea hochst.	Roots	Shredded	N/A	-	-	N/A	[3]
Verbenaceae	Premna schimperi engl.	Leaves, root, stem	Grind, chewed, rub, boiled	Flavonoids, diterpenoids, triterpenes, sterols, alkaloids	-	X	Antioxidant activity	[140, 282]
Verbenaceae	Stachytarpheta angustifolia	Leaves	Decoction	Phenolic, tannin compounds	-	X	Antioxidant activity	[148, 283]
Verbenaceae	Premna oligotricha	Leaves	Chewed	Flavonoids, alkaloids, triterpenoids, resins, tannins, saponins and steroids,	-	-	N/A	[3, 169, 284]
Verbenaceae	Premna resinosa (hochst.)	Roots	Chewed	Alkaloids, phenols, terpenids, flavonoids	-	-	Antioxidant activity	[3, 285]
Vitaceae	Cyphostemma junceum (webb)	Whole plant	Chewed	N/A	-	-	N/A	[169]
Vitaceae	Cissus quadrangularis L..	Roots	Chewed	Sterols, tannins, alkaloids	-	-	Antioxidant activity	[3, 286]
Xanthorrhoeaceae	Aloe vera L.	Leaves	Chewed	Phenolic compounds, alkaloids	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[287-290]
Zingiberaceae	Aframomum corrorima	Seeds, rhizome	Chewed	Flavonoids, phenolics, terpenoids	-	-	Antioxidant activity	[3, 291]
Zingiberaceae	Zingiber officinale roscoe	Rhizome	Chewed	Flavonoids, alkaloids, saponins, steroids, terpenoids, tannin.	x	X	Antioxidant activity, Anti-inflammatory mechanism (COX and LOX)	[3, 60, 70, 292]

Table 4. Asia

Family	Scientific name	Used part	Preparation	Phytochemicals	Analgesic effect	Anti-inflammatory effect	Mechanism of action	Ref.
Acanthaceae	Barleria Cristata	Leaves, roots	Chewed, infusion	Triterpenoids, flavonoids, phenolic compounds	-	x	Antioxidant activity	[293]
Acanthaceae	Hygrophila auriculata	Roots, leaves	N/A	N/A	-	-	N/A	[294]
Actinidiaceae	Saurauia tristyla DC.	Roots	Decoction	Phenolic compounds, flavonoids, alkaloids, steroids, saponins	-	-	N/A	[295, 296]
Amaryllidaceae	Allium cepa L.	Bulb	Raw, cooked	Phenolic acids, flavonoids, anthocyanins	X	x	Antioxidant activity, Anti-inflammatory mechanism (COX and LOX)	[6, 59, 297, 298]
Amaranthaceae	Beta vulgaris L	Leaves	Juice	N/A	-	-	Antioxidant activity	[298, 299]
Amaranthaceae	Achyranthes aspera	Leaves, roots	Decoction	Saponins, alkaloids	X	x	Antioxidant activity	[14, 219, 294]
Anacardiaceae	Mangifera indica L.	Bark	Powdered inner bark, keep in mouth	N/A	-	-	N/A	[219]
Apocynaceae	Wrightia tinctoria	Leaves	Chewed	Flavonoids, glycoflavonoids, phenolic acids	-	x	Antioxidant activity	[300]
Apocynaceae	Plumeria rubra L	Stem, bark	N/A	N/A	-	-	N/A	[294]
Araliaceae	Panax ginseng	Leaves, seeds	Extract	Flavonoids, terpenes	-	x	GABA mechanism	[110]
Aristolochiaceae	Asarum longerhizomatosum C.	Whole plant	Ground, decoction	Flavonoids	-	x	N/A	[296, 301]
Aristolochiaceae	Asarum caudigerum	Whole plant	Direct application	N/A	-	-	N/A	[302]
Asclepiadaceae	Pergularia daemia	Latex	Direct application	Alkaloids, saponins, tannins, flavonoids, terpenoids, phenols	-	x	Antioxidant activity	[219, 303]
Asteraceae	Achillea biebersteinii	Leaves	N/A	N/A	-	-	N/A	[250, 298, 304]
Asteraceae	Bidens biternate	Roots	Paste	Glycosides, flavonoids, alkaloids, tannins, steroids, terpenoids, coumarins	-	-	N/A	[14, 305]
Asteraceae	Parthenium hysterophorus L.	Flowers	Chewed	Phenols, flavonoids	-	-	N/A	[3, 14, 306]
Asteraceae	Achillea biebersteinii	Flowers, leaves	N/A	Terpenes, flavonoids, phenolic acids	-	x	Antioxidant activity	[250, 304]
Asteraceae	Acmella oleracea	Flowers	Chewed	Spilanthol, sequesterpenes.	X	x	GABA mechanism, antioxidant activity	[51, 51, 180]
Berberidaceae	Berberis wuliangshanensis	Roots	N/A	N/A	-	-	N/A	[307]
Biebersteiniaceae	Biebersteinia multifida	Leaves, stem	Extract	Alkaloids	X	x	N/A	[298, 308]
Bignoniaceae	Incarvillea sinensis Lam.	Roots (fresh or dried)	Gargle	Alkaloids	-	-	N/A	[309, 310]
Boraginaceae	Cynoglossum lanceolatum	Fruits, leaves, seeds	Chewed	Alkaloids	X	x	Antioxidant activity	[14, 311, 312]
Caesalpiniaceae	Caesalpinia coriaria	Fruits	Powder	Tannins	-	-	Antioxidant activity	[219, 313]
Capparidaceae	Capparis spinosa	Stem, fruits	N/A	Alkaloids, flavonoids, steroids, terpenoids, tocopherol, phenolic compounds	X	x	Antioxidant activity	[250, 298, 314, 315]
Caryophyllaceae	Dianthus crinitus	Seeds	N/A	Flavonoids	-	x	Antioxidant activity	[298]
Caryophyllaceae	Dianthus orientalis	Seed, leaves, . flowers, fruits	Extract	Flavonoids, phenols	-	-	Antioxidant activity	[250, 298]
Cannaceae	Canna indica L	Roots	Direct aplication	N/A	-	-	N/A	[294]
Cleomaceae	Cleome gynandra, L.	Leaves	Extract	Polyphenols, oleic acid, linoleic acid	X	-	Antioxidant activity	[219, 316]
Convolvulaceae	Merremia chryseides	Whole plant	Decoction	N/A	-	-	N/A	[219]
Ebenaceae	Diospyros lotus	Branch, roots	Rub	Phenolic compounds	X	x	Antioxidant activity	[14, 317]
Elaeagnaceae	Elaeagnus umbellate	Branch	Rub	Alkaloids, steroids, terpenoids, saponins	-	-	Antioxidant activity	[14, 318]
Eriocaulaceae	Eriocaulon buergerianum	Flowers	Decoction	Flavonoids, phenolic compounds	-	x	N/A	[302, 319]
Euphorbiaceae	Jatropha gossypifolia	Whole plant	Decoction	alkaloids, terpenes, flavonoids, phenolics	-	x	Antioxidant activity	[108]
Euphorbiaceae	Jatropha curcas	Sap	Topical	alkaloids, terpenes, flavonoids, phenolics	-	x	Antioxidant activity, anti-inflammatory mechanism (COX-LOX)	[108, 109, 294]
Fabaceae	Acacia nilótica	Bark	Decoction	Alkaloids, flavonoid phenols, tannins, terpenes	-	-	Antioxidant activity	[219-221]
Fabaceae	Lespedeza juncea	Whole plant	Decoction	Flavonoids, alkaloids	-	-	Antioxidant activity	[14, 320]
Fabaceae	Senna tora (L.)	Leaves, Stem, Fruit, Root, Seed	N/A	N/A	-	-	N/A	[294]
Geraniaceae	Erodium cicutarium	Aerial parts	Boiled	Polyphenols	-	-	Antioxidant activity	[298, 321]
Ginkgoaceae	Ginkgo biloba	Leaves, seeds	Extract	flavonoids, terpenes	-	x	N/A	[110, 322]
Hypericaceae	Hypericum perforatum	Flowers	N/A	Flavonoids	-	x	N/A	[298, 323]
Iridaceae	Iris dichotoma Pall.	Roots, bark	Chop and chew	Phenolic compound, flavonoids or isoflavones	-	x	N/A	[310, 324]
Lamiaceae	Leucas aspera, (Willd.)	Leaves	Extract	Triterpenoids, diterpenoids, phenolic compounds, alkaloids	-	-	Antioxidant activity	[219, 325]
Lamiaceae	Teucrium polium L	Aerial parts	Extract	Flavonoids, terpenoids	-	x	Antioxidant activity	[298, 326]
Lamiaceae	Stachys pilifera	Leaves	Extract	Flavonoids, diterpenes, saponins, terpenoids	-	x	Antioxidant activity	[298, 327]
Lamiaceae	Micromeria biflora	Roots	Paste	N/A	-	-	N/A	[14]

Lamiaceae	Plectranthus	Bud, flowers	Chewed	Monoterpenoids, sesquiterpenoids, diterpenoids, phenolics	-	x	N/A	[14, 328]
Lauraceae	Litsea cubeba (Lour.) Pers.	Fruits	Decoction	Flavonoids, Terpenoids, Alkaloids	-	x	Antioxidant activity	[296, 329]
Liliaceae	Allium condensatum Turcz.	Aerial parts	Smell after calcination	N/A	-	-	N/A	[310]
Liliaceae	Fritillaria imperialis L.	Fruits	N/A	Alkaloids, terpenoids, saponins	x	x	Antioxidant activity	[298, 330]
Liliaceae	Allium tuberosum Rottl. ex	Whole plant	Ground, decoction	Alkaloids, flavonoids, terpenoids, tannins, saponins	-	x	Antioxidant activity	[296, 331]
Loganiaceae	Strychnos nux-vomica L.	Seeds	Chewed	Phenolic compounds	x	x	N/A	[302, 332]
Meliaceae	Azadirachta indica A.	Bark, leaves, branches	Powdered inner bark keep in mouth, extract	Alkaloids, flavonoids, triterpenoids, phenolic compounds	-	x	Antioxidant activity	[219, 233, 235]
Menispermaceae	Cyclea hypoglauca (Schauer)	Roots	Infusion	N/A	-	-	N/A	[296]
Moraceae	Streblus asper, Lour.	Bark	Powdered inner bark keep in mouth	N/A	-	-	N/A	[219]
Myrtaceae	Syzygium aromaticum L.	Flowers	Decoction, powder and hydrodistillate	Monoterpenes, sesquiterpenes, phenolics, hydrocarbon compounds.	x	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[132, 288, 333]
Myrtaceae	Psidium guajava L.	Leaves, bark	Chewed	Flavonoids, triterpenes, tannins	x	x	Antioxidant activity	[93, 219, 246]
Fabaceae	Mimosa pudica L.	Roots	Boiled	N/A	-	-	N/A	[294]
Malpighiaceae	Hiptage benghalensis	Stem	N/A	N/A	-	-	N/A	[294]
Nyctaginaceae	Mirabilis jalapa Linn.	Whole plant	N/A	Alkaloids, tannins, flavonoids, glycosides, phenols, steroids, triterpenoids, saponins	-	X	Antioxidant activity	[307, 334]
Oleaceae	Olea ferruginea (Sol.)	Fruits, leaves, seeds and bark	Decoction	Phenolic compounds	-	-	N/A	[335, 335, 336]
Oxalidaceae	Oxalis corniculate L.	Flowers	Chewed	Flavonoids, phytosterols, phenolic compounds, tannins	-	-	N/A	[14, 337]
Fabaceae	Astragalus verus Oliv.	Resin	N/A	N/A	-	-	N/A	[298]
Fabaceae	Clitoria ternatea L.	Roots	Paste	N/A	-	-	N/A	[294]
Fabaceae	Pongamia pinnata L.	Seeds	Oil	N/A	-	-	N/A	[294]
Pinaceae	Pinus roxburghii Sarg.	Aerial parts	Extract, juice	Flavonoids	x	X	Antioxidant activity	[335, 338]
Plantaginaceae	Plantago lanceolata L.	Leaves	Grind and keep in mouth	Phenols, flavonoids	-	X	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[127, 335, 339]
Polypodiaceae	Drynaria roosii Nakaike	Rhizome	Cooked with water, sliced, dried, medicinal liquor	Flavonoids	-	-	N/A	[302]
Poaceae	Cynodon dactylon (L.	Roots, leaves	N/A	N/A	-	-	N/A	[294]
Poaceae	Desmostachya bipinnata	Roots	N/A	N/A	-	-	N/A	[294]
Poaceae	Vetiveria zizanoides (L.)	Roots	N/A	N/A	-	-	N/A	[294]
Rhamnaceae	Rhamnus persica	Fruits, leaves	Decoction, infusion, powder	Monoterpenes, sesquiterpenes, aldehydes, phenols	-	-	Antioxidant activity	[298]
Rosaceae	Sanguisorba minor	Stem, aerial parts, roots	N/A	Flavonoids, phenols, triterpenoids	X	x	Antioxidant activity	[298, 340, 341]
Rosaceae	Prunus pérsica	Branch	Chewed	N/A	-	-	N/A	[14]
Rosaceae	Rubus parvifolius L.	Whole plant	Ground, decoction	Phenolic compounds	-	x	Antioxidant activity	[296, 342]
Rosaceae	Geum japonicum Thunb.	Whole plant	Decoction	Triterpenoids, sterols, tannins	-	x	N/A	[302, 343]
Rosaceae	Amygdalus davidiana	Bark, leaves	N/A	N/A	-	-	N/A	[307]
Rosaceae	Prunus humilis Bunge	Roots (fresh or dried)	Chop and chew, decoction	Flavonoids and phenolic compounds	-	-	Antioxidant activity	[310, 344]
Rubiaceae	Gailonia Aucheri	Leaves, flowers	N/A	N/A	-	-	N/A	[298]
Rutaceae	Zanthoxylum nitidum	Stem, branches, leaves, roots	Decoction	Alkaloids, coumarins, lignans, flavonoids, terpenes, steroids, alkylamides	x	x	Antioxidant activity	[345]
Rutaceae	Zanthoxylum bungeanum	Stem, leaves, seeds, roots, bark	Liquid, powder	Alkaloids, flavonoids, terpenoids	x	x	Antioxidant activity	[307, 346]
Rutaceae	Zanthoxylum alatum	Branch	Rub, dust	Linalol	-	x	Antioxidant activity	[14, 347]
Rutaceae	Murraya exotica L.	Roots, leaves	Ground, decoction	Alkaloids, tannins, alkalis	-	x	Antioxidant activity	[296, 348]
Solanaceae	Solanum melongena L.	Roots, stem	Direct application	Flavonoids, tropane, glycoalkaloids	x	x	Antioxidant activity	[302, 349]
Solanaceae	Solanum verbascifolium L.	Whole plant	Decoction	Flavonoids	-	-	N/A	[302, 350]
Solanaceae	Solanum nigrum, L.	Leaves	Extract	N/A	-	-	Antioxidant activity	[219, 351]
Solanaceae	Solanum surattense.	Seeds	Steam from the seeds keep in the mouth	Alkaloids	-	-	N/A	[219, 352]
Solanaceae	Hyoscyamus niger L.	Leaves, seeds	Infusion, gargle	Alkaloids: atropine, tropane and scopolamine.	x	x	Antioxidant activity	[123, 298, 353]
Solanaceae	Lycopersicum esculentum	Fruits, leaves	N/A	Flavonoids, phenols	-	-	Antioxidant activity	[298, 354]

		and flowers						
Solanaceae	Hyoscyamus muticus	Seeds, roots	N/A	Alkaloids	-	-	N/A	[298]
Thymelaeaceae	Daphne mucronata	Leaves, stem	N/A	Coumarins, flavonoids, triterpenoids	-	-	N/A	[298, 355]
Verbenaceae	Vitex negundo, L.	Leaves	Chewed	Flavonoids	x	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[219, 356]
Vitaceae	Cayratia albifolia C. L. Li	Root, leaves	Chewed	N/A	-	-	N/A	[302]
Xanthorrhoeaceae	Aloe vera L.	Leaves	Decoction	Lignin, anthraquinones, saponins	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[287, 288, 290]
Zygophyllaceae	Tribulus terrestris, L.	Fruit	Powder, massage	Alkaloids, tannins, saponins	x	-	N/A	[219, 357]
Zygophyllaceae	Peganum harmala L.	Seeds, fruit	Incense	Flavonoids, alkaloids, saponins, tannins, glycosides, terpenoids and steroids	x	-	Antioxidant activity	[249-251, 298]
Zygophyllaceae	Fagonia olivieri	Roots, fruits, stem, flowers	N/A	Flavonoids, alkaloids, tannins, saponins, terpenoids	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[358-360]
Asteraceae	Emilia sonchifolia (L.)	Flowers	Paste	Alkaloids	x	x	N/A	[93, 361]
Asteraceae	Galinsoga parviflora Cav.	Leaves	Decoction	Polyphenols and flavonoids, phenolic acids .	-	x	Antioxidant activity, anti-inflammatory mechanism (COX and LOX)	[93, 183]
Asteraceae	Xanthium strumarium L	Leaves, roots	Juice	Sesquiterpenic lactones, glycosides, phenols, polyesterols	x	x	Antioxidant activity	[93, 362]
Fabaceae	Mimosa pudica	Seeds	Powder	Alkaloids, flavonoids, glycosides, sterols, terpenoids, tannins and fatty acids.	x	-	Antioxidant activity	[93, 363]
Myricaceae	Myrica adenophora	Bark	Decoction	Flavonoids, triterpenoids, tannins, monoterpenoids, and benzenoids	x	x	Antioxidant activity	[93, 364]
Plantaginaceae	Plantago major L	Flowers	Paste	Polysaccharides, ?avonoids, glycosides, terpenoids, alkaloids, organic acids.	x	x	Antioxidant activity	[93, 341]
Rubiaceae	Spermacoce neohispida Govaerts	Flowers	Paste	N/A	-	-	N/A	[93]
Rutaceae	Zanthoxylum oxyphyllum	Leaves, fruits	Juice	N/A	-	-	N/A	[93]
Sapindaceae	Sapindus mukorossi Gaert	Seeds	Powder	Saponins	-	-	N/A	[93, 365]
Solanaceae	Nicotiana plumbaginifolia Viv	Leaves	Paste	Alkaloids, saponin, tannin, flavonoids, phenolic compounds, steroids, terpenoids and carbohydrates.	-	-	N/A	[93, 366]
Solanaceae	Solanum aculeatissimum Jacq	Leaves, Fruits	Decoction	Steroidal saponins	-	-	N/A	[93, 294, 367]
Solanaceae	Solanum virginianum Dunal	Leaves, seeds	N/A	N/A	-	-	N/A	[294]
Urticaceae	Urtica parviflora Roxb	Fruits	Boiled juice	Alkaloids, polysaccharides, . saponins, flavonoids, phenolic compounds, glycosides and tannins	-	-	Antioxidant activity	[93, 368]
Arecaceae	Borassus flabellifer	Roots	Boiled, gargling	N/A	-	-	N/A	[294]
Verbenaceae	Vitex negundo L.	Leaves, bark	N/A	N/A	-	-	N/A	[294]

Table 5. Oceania

Family	Scientific name	Used part	Preparation	Phytochemicals	Analgesic effect	Anti-inflammatory effect	Mechanism of action	Ref.
Euphorbiaceae	Petalostigma pubescens	Fruits, bark	Hold in the mouth	Saponins, phenolic compounds, flavonoids, triterpenoids, tannins and alkaloids	-	-	Antioxidant activity	[90, 369]
Euphorbiaceae	Petalostigma quadriloculare	Fruits, bark	N/A	Saponins, phenolic compounds, flavonoids, triterpenoids, tannins and alkaloids	-	-	Antioxidant activity	[90, 369]
Myoporaceae	Eremophilia fraseri	Leaves	N/A	Diterpenes, triterpenoids, phenylpropanoids, lignans, flavonoids	-	x	Antioxidant activity	[90, 370]
Myrtaceae	Melaleuca cajuputi	Bark, leaves	Extract	Flavonoids, phenolic compounds	-	-	Antioxidant activity	[90, 371]
Rhamnaceae	Ventilago viminalis	Bark, roots	N/A	N/A	-	-	N/A	[90]
Rutaceae	Geijera parviflora	Leaves	N/A	Alkaloids, flavonoids	-	x	N/A	[90, 372]
Rutaceae	Melicope vitoflora	Bark	N/A	N/A	-	-	N/A	[90]
Sapindaceae	Dodonaea viscosa	Roots, leaves	N/A	Alkaloids, flavonoids, steroids, phenolics, saponins, tannins	x	x	Antioxidant activity	[90, 373]
Tiliaceae	Grewia retusifolia	Fruit, roots, leaves	N/A	N/A	-	-	N/A	[90]
Asteraceae	Acmella grandiflora	Roots, flowers	Crushed	Spilanthol, acmellonate, tannins, flavonoids, and phenolic compounds	x	X	Antioxidant activity, GABA mechanism	[90, 374]

method to increase its action.

The parts used may vary with the medicinal plant; however, we found that the most commonly used plant parts were leaves and roots, followed by the bark, stem, and seeds (Fig. 1). Preferentially using the leaves instead of roots can also prevent detrimental effects on the plants.

The most common phytochemicals involved in the mechanism of action of medicinal plants for toothache treatment are polyphenols, more specifically, flavonoids and terpenes, which are the most abundant secondary metabolites and antioxidants in the human diet[3, 5–7]. Flavonoids are the most ubiquitous group of all plant phenolics, which could explain the implicit antioxidant capacity of all medicinal plants[84]. Furthermore, flavonoids can modulate the function of ionotropic GABA receptors, suggesting that these phytochemicals can exert different mechanisms of action to relieve pain[20].

Polyphenols are strong antioxidants that neutralize free radicals by donating an electron or a hydrogen atom[61], thus exerting antioxidant effects in plants and organisms that consume them. However, polyphenols decrease the concentrations of ROS and RNS far from the site of the primary response because the local concentrations of these radicals around the inflammatory site are substantially high (> 1 mM). Therefore, polyphenols are highly unlikely to be effective where these free radicals are produced but could be quantitatively more effective as antioxidants in the surrounding unaffected tissues[85].

Substances such as capsaicin, allicin, camphor, and menthol cause a state of activation and desensitization in the TRP receptor pathway through which pain may be reduced[18, 43]. Of these phytochemicals, only allicin was analyzed in the studies included in this review. Moreover, allicin and spilanthol, compounds present in *A. caulirhiza,* have various biological and pharmacological effects, which may cause analgesia[3, 52]. Further studies should be performed to better understand the roles of these phytochemicals.

The mechanisms of action of phytochemicals in toothache relief are only partly understood. This review shows that these mechanisms involve antioxidant activity, action on TRP receptors, GABA mechanism, and COX/LOX inhibitory activity. The tables in this review outline

163 medicinal plants with antioxidant mechanisms of action, 20 with an anti-inflammatory mechanism (COX/LOX), four with GABA mechanism, and two with TRP mechanism. Some plants have two reported mechanisms of action. However, in general, there is insufficient literature addressing each mechanism responsible for toothache relief.

Several reports cite the use of various plants for toothache treatment; however, in many of these reports, the mechanism of action underlying pain relief is not specified, as indicated in the tables in this review. Moreover, in several studies, the phytochemicals potentially responsible for the analgesic effect were not reported. Accordingly, future studies should focus on identifying the exact mechanisms that contribute to dental analgesia and the phytochemicals involved. Additionally, the "common names" of medicinal plants were not included in this research, considering the extensive information involved in the preparation of this manuscript.

As mentioned above, we found only one study comparing the pharmacological properties of medicinal plants with those of conventional pharmaceutical drugs[81]. However, 30 plants with dual anti-inflammatory mechanisms (COX/LOX) were identified, as outlined in the tables for each continent. This information could be useful in future comparative studies of conventional or dual NSAIDs.

Although dual inhibition of microsomal PGE2 synthetase (mPGES-1) and 5-LOX has not been described as a mechanism of action in the reports included in this review, several plants (some of which are indicated in our tables) contain acylphloroglucinols, phenolic compounds, and non-phenolic acidic structures that exhibit such dual action[86]. mPGES-1 is an inducible enzyme at inflammatory sites that preferentially receives its substrate from co-induced COX-2 and is responsible for the excessive formation of PGE2 during acute and chronic inflammation [87, 88.; thus, its inhibition could be a promising strategy for toothache treatment with medicinal plants. Furthermore, natural mPGES-1 inhibitors have advantages over NSAIDs since they are non-synthetic and safer because they do not inhibit COX-derived homeostatic eicosanoids[86].

However, in several *in vitro* and *in vivo* studies (utilizing indices such as IC_{50}), the vast majority of medicinal plant extracts have been tested only against one biological target (COX or LOX), which is insufficient to validate their anti-inflammatory and analgesic properties and hinders direct comparisons between plants and conventional or dual-action NSAIDs[72]. Therefore, further studies should be conducted to address this gap in research and gather more relevant information.

Multiple experimental studies of COX-1/COX-2 inhibition have used IC_{50} (the concentration at which an NSAID produces 50% inhibition of both COX enzymes) to rank the relative inhibitory activity of NSAIDs on these enzymes, and consequently, establish their selectivity over COX, correlating this *in vitro* inhibition with clinical efficacy and toxicity levels[89]. However, IC_{50} values do not indicate the mechanism of enzyme inhibition and vary with substrate concentration. Furthermore, these values are not directly comparable unless identical experimental conditions are used, and they must be analyzed carefully when inhibition is time-dependent[89]. These drawbacks also (91) hinder direct comparison between medicinal plants and NSAIDs.

Only two studies on plant combinations were found for this review. The study on phytotherapeutic Lenidase®[81]. was already described above. The other reported on the use of seven popular medicinal plant mixtures for toothache in Europe (Catalonia), including several species[76]. whose use was not found in other continents.

Although medicinal plants are distributed throughout the world[90], biodiversity could affect how intensely such plants are used for toothache, and thus the discovery of new drugs[91]. The 17 most megadiverse countries in the world are Brazil, Colombia, Mexico, Peru, Ecuador, Venezuela, the United States of America, Indonesia, Australia, Madagascar, China, the Philippines, India, New Guinea, Malaysia, South Africa, and the Democratic Republic of Congo; most of these are in the American continent[49]. However, in this present review, most of the information on medicinal plants was gathered from Asia (Table 4) and Africa (Table 5), possibly because herbal medicines remain a key component of healthcare systems in the developing cultures of these continents[90]. Oceania has only two of the 17 megadiverse countries, which may explain the scarcity of plants in this continent (Table 5). Nevertheless, in some regions, much of the traditional knowledge about medicinal plants is only spread verbally and, thus, remains unexplored and unreported[93].

In terms of plants used in different continents, *A. sativum* was found in America (Table 1), Europe (Table 2), and Africa (Table 3); *A. cepa* and *Syzygium aromaticum* were found in Europe, Africa, and Asia; and *Acmella oleracea, Jatropha curcas*, and *Jatropha gossypiifolia* were all found in America (Table 1), Africa (Table 3), and Asia (Table 4). Conversely, some species are found only in one continent, such as *Thymus schimperi* Ronniger in Africa, perhaps because this species is a rare plant highly localized in and endemic to Ethiopia[94].

Among the families of medicinal plants used worldwide, Asteraceae was the most common, followed by Solanaceae, Fabaceae, Lamiaceae, Euphorbiaceae, Rutaceae, and Myrtaceae (Fig. 2). The first three of these families have been widely reported as those most commonly used to treat inflammation and various types of pain[44, 44, 76].

Notably, the present review discusses several medicinal plants for toothache treatment, which have been globally classified by continents, unlike all the referenced studies, which were approached separately. Moreover, the five tables provide details about the parts used, preparation, phytochemicals, analgesic/anti-inflammatory effect, and mechanisms of action, contrary to most studies that do not include such details. Additionally, this review analyzes all the mechanisms of action of the medicinal plants that have been ascribed until now for toothache treatment, unlike many studies that only cite these mechanisms. Furthermore, we have included a section comparing medicinal plants and pharmaceutical drugs, unlike all the referenced studies that do not provide such a comparison. Finally, this review discusses the use of medicinal plants for the treatment of dental pain, while most articles deal with this topic on a general basis.

Future perspectives

Although phytotherapy has a long history, natural medicines are considered a hidden source of drugs because many medicinal plants have not been studied in depth[79]. Accordingly, further studies should be conducted to better understand the role and benefits of phytotherapeutic drugs[81]. for toothache treatment, particularly when combined based on the multi-objective therapeutic principle of phytotherapy[79, 95]. This principle would be analogous to the multimodal analgesic approach used for NSAIDs[96–98].

Aromatherapy also has non-pharmacological therapeutic potential for reducing toothache by combining highly complex mixtures of essential oils to produce a therapeutic effect[95]. Therefore, further research should be conducted in this field of alternative medicine.

Although polyphenols in organic food extracts (extractable polyphenols) have already been analyzed, significant amounts of potentially bioactive polyphenols that remain in the residues (non-extractable polyphenols) have been overlooked. Additionally, significant amounts of non-extractable polyphenols are found in foods and vegetables[61, 99]. Therefore, these compounds should be considered for future studies.

A promising therapeutic option for the administration of flavonoids that may increase their bioavailability is to develop protective systems, such as microcapsules, nanoparticles, and nano-formulations, which improve water solubility, dissolution, absorption, and thermal stability. Accordingly, in the near future, such systems should be developed and administered for pain management[62].

Finally, human clinical trials are essential to confirm the effectiveness of traditional phytotherapy for toothache and to investigate the pharmacodynamic and pharmacokinetic interactions between medicinal plants and other synthetic drugs. Similarly, predictive (*in silico*) models, phytochemical analyses, and ethnopharmacological studies could be milestones for drug discovery in traditional medicinal plants for toothache treatment, because many of them lack information or have not been studied.

CONCLUSION

This is the first review to compile a large volume of data on the global use of medicinal plants for the treatment of toothache. A total of 21 species of medicinal plants were found in America (Table 1), 29 in Europe (Table 2), 192 in Africa (Table 3), 112 in Asia (Table 4), and 10 in Oceania (Table 5). Asia and Africa are the continents where the most research has been done on this topic. Asteraceae was the most commonly found plant family in this review, followed by Solanaceae, Fabaceae, Lamiaceae, Euphorbiaceae, Rutaceae, and Myrtaceae.

In total, 364 medicinal plants used for toothache treatment were identified, of which 139 have not yet been scientifically studied, highlighting opportunities for ethnopharmacological research on toothache treatments. The most common species were *A. sativum, A. cepa, A. oleracea, J. curcas, J. gossypiifolia,* and *S. aromaticum.* These families and species were more commonly found in Africa and Asia, corroborating our previously reported findings. As determined in this review, the most commonly used plant parts were the leaves and roots, followed by the bark, stems, and seeds.

We identified four mechanisms of action of medicinal plants implied in toothache treatment, namely, the antioxidant effect, effects mediated through TRP receptors, GABA mechanism, and the anti-inflammatory mechanism (COX/LOX). Flavonoids, terpenes, polyphenols, and alkaloids are the phytochemicals most commonly associated with toothache treatment. Many of the plants analyzed in this review have the potential to be used as agents for toothache treatment. Therefore, future studies must prioritize the analysis of their pharmacodynamic and pharmacokinetic interactions.

Finally, to more precisely clarify the usefulness of medicinal plants as a valid option for toothache treatment, comparative studies between medicinal plants and commonly used pharmaceutical drugs should be conducted. In addition, studies published in Spanish should be included in future reviews since we only analyzed studies published in English, and this may have limited our ability to gather additional information.

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Ethical Statement

Ethical approval was not required for this review article.

Conflicts of Interest

The authors declare no conflicts of interest.

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