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The Clinical Translation of α-humulene – A Scoping Review

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Conflict of Interest: SE is the Head of Research at Curaleaf Clinic. MHS is the Chief Medical Officer at Curaleaf International.

Abstract:
α-humulene, a sesquiterpene found in essential oils of various plant species, has garnered interest due to its potential therapeutic applications. This scoping review aims to consolidate α-humulene's evidence base, informing clinical translation and guiding future research directions. A scoping review was conducted of EMBASE, MEDLINE and PubMed databases up to 14th July 2023. All studies describing original research on α-humulene extraction, pre-clinical and clinical research were included for review. Three-hundred and forty articles were analyzed. α-humulene yields ranged from negligible to 60.90% across plant species. In vitro experiments demonstrated cytotoxicity against adenocarcinomas (such as colorectal, pulmonary, breast, prostatic, lung, and ovarian), with varying responses in other cell models Mechanistic insights revealed its involvement in mitochondrial dysfunction, diminished intracellular glutathione levels, and the induction of oxidative stress. In rodent studies, oral administration of α-humulene at 50 mg/kg reduced inflammation markers in paw edema and ovalbumin-induced airway inflammation. Intraperitoneal administration of α-humulene (50-200 mg/kg) exhibited cannabimimetic properties through cannabinoid 1 and adenosine A2a receptors. α-humulene also exhibited a multitude of properties with potential scope for therapeutic utilization. However, there is a paucity of studies which have successfully translated this research into clinical populations with the associated disease. Potential barriers to clinical translation were identified, including yield variability, limited isolation studies, and challenges associated with terpene bioavailability. Consequently, rigorous pharmacokinetic studies and further mechanistic investigations are warranted to effectively uncover the potential of α-humulene.

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The Clinical Translation of α-humulene – A Scoping Review

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Abstract

α-humulene, a sesquiterpene found in essential oils of various plant species, has garnered interest due to its potential therapeutic applications. This scoping review aims to consolidate α-humulene's evidence base, informing clinical translation and guiding future research directions. A scoping review was conducted of EMBASE, MEDLINE and PubMed databases up to 14th July 2023. All studies describing original research on α-humulene extraction, pre-clinical and clinical research were included for review. Three-hundred and forty articles were analyzed. α-humulene yields ranged from negligible to 60.90% across plant species. *In vitro* experiments demonstrated cytotoxicity against adenocarcinomas (such as colorectal, pulmonary, breast, prostatic, lung, and ovarian), with varying responses in other cell models Mechanistic insights revealed its involvement in mitochondrial dysfunction, diminished intracellular glutathione levels, and the induction of oxidative stress. In rodent studies, oral administration of α-humulene at 50 mg/kg reduced inflammation markers in paw edema and ovalbumin-induced airway inflammation. Intraperitoneal administration of α-humulene (50-200 mg/kg) exhibited cannabimimetic properties through cannabinoid 1 and adenosine A2a receptors. α-humulene also exhibited a multitude of properties with potential scope for therapeutic utilization. However, there is a paucity of studies which have successfully translated this research into clinical populations with the associated disease. Potential barriers to clinical translation were identified, including yield variability, limited isolation studies, and challenges associated with terpene bioavailability. Consequently, rigorous pharmacokinetic studies and further mechanistic investigations are warranted to effectively uncover the potential of α-humulene.

Keywords: Terpenes; Anti-bacterial Agents; α-humulene; Humulus lupulus; Cannabis Indica; Cannabis Sativa; Cannabaceae

Introduction

Terpenoids are a vast and diverse group encompassing several classes of secondary metabolites from plants, each being investigated for biomedical properties [1]. Notably, they have been described as having anti-inflammatory, analgesic, antimicrobial, antioxidant, and estrogenic properties [2,3]. Sesquiterpenes are a class of terpene, to which α-humulene (also known as α-caryophyllene) and its isomer β-caryophyllene belong. These sesquiterpines share a three-isoprene unit structure, formed from the precursor farnesyl diphosphate, leading to the formation of cyclic or multi-ring compounds that contribute to their distinctive aroma [1].

α-humulene and β-caryophyllene, though structurally similiar, are differentiated by the open-ring structure present in α-humulene [4]. Historically, α-humulene was first identified as a major component in the essential oils of *Humulus lupulus* L., Cannabaceae, the common hop plant, from which it derived its name. Its structural elucidation was achieved through nuclear magnetic resonance spectroscopy. Furthermore, α-humulene has not only been sourced from *Humulus lupulus* but also from *Cannabis Indica* L., Cannabaceae, signifying its prevalence in botanical species for which there are already well-established agricultural processes [5]. The isolation and extraction of α-humulene from its botanical sources have been refined over time. Modern techniques, such as steam distillation, are employed to capture the volatile essential oils containing this sesquiterpene. Its abundance in various botanical sources makes it a subject of interest for both traditional and modern medicinal applications.

There is continual demand to identify novel compounds which possess anticancer, anti-inflammatory, and antimicrobial properties, in light of a persisting cancer burden, rising incidence of inflammatory conditions, and emergence of antimicrobial resistance [6–8]. Despite promising preclinical evidence supporting the multimodal therapeutic potential of **α-**

humulene, there are several barriers to its clinical translation. Whilst certain plant species are known to be rich sources of **α**-humulene, plant yields are often reported as being low and so far researchers have not reached a consensus on a named plant species which consistently yields high concentrations of α-humulene. At present, biosynthesis pathways are therefore being explored as an avenue to create synthetic α-humulene to overcome inherent challenges with the manufacturing of compounds which are reliant upon favorable agricultural conditions [9]. In addition, much of the research conducted to date has utilized a combination of organic compounds contained within the plant essential oil, rather than assessing the properties of α-humulene in isolation, resulting in a paucity of evidence summarising α-humulene's individual properties. It is therefore important to evaluate studies which report specifically the properties of α-humulene and identify species with acceptable yields in order to advance this scientific field.

A systematic review by Leite et al. [10] summarised the preclinical properties of sesquiterpene compounds, including α-humulene and β-caryophyllene. Whilst preclinical evidence has been promising regarding the properties of **α**-humulene, there has been minimal progress into clinical translation of this research. Hence, this review aimed to provide a synthesised evidence base for the prioritzation of future research, including optimisation of agriculture and manufacturing, alongside identification of the most promising biomedical applications.

Results

Search results

The database and manual bibliography search initially returned 544 studies (Fig. 1). Four hundred and twelve full-text articles were assessed for eligibility, with 340 articles included for qualitative synthesis. Three hundred and seven (n = 307) studies included reported the extraction yields of α-humulene (Supplementary Material A). Thirty-two studies (n = 32) [11–42] were included for evaluation of the pre-clinical properties of α-humulene. These included investigations conducted *in vitro* [11–30], *in vivo* [31–36], and combined *in vitro* and *in vivo* experiments [37–42]. Notably, no studies were found to assess the clinical properties of α-humulene.

Yield of α-humulene from extraction

Yields of α-humulene were reported from 462 different plant and animal species (Supplementary Material B). Reported yields varied from nil to 60.90%. Table 1 highlights the five species that exhibited the highest reported yields among the included studies. The most common method of α-humulene extraction was hydrodistillation in a Clevenger-Type apparatus. Concurrently, isolation was most frequently relied on gas chromatography mass spectrometry (GC-MS). Among the species analyzed, *Lantana camara* L., Verbenaceae; *Origanum majorana* L., Lamiaceae; *Cordia verbenacea* DC., Boraginaceae; *Cannabis sativa;* and *Daucus carota* L., Apiaceae were prominent contributors, with the greatest number of studies reporting α-humulene extraction data.

Specific properties of α-humulene

Antiproliferative properties

Thirteen studies evaluated the effects of α-humulene in cancer models (Table 2) [11–20,31,37,38]. Across these studies, α-humulene consistently demonstrated cytotoxic activity against tumor cells, with one exception by Loizzo et al (2008) [20] involving human amelanotic melanoma (C32) and renal cell adenocarcinoma (ACHN) at a concentration of 9.3 x 10^{-7} - 1.2 x 10^{-4}. α-humulene, sourced from *Myrica rubra* Siebold & Zucc., Myricaceae, has demonstrated substantial anti-proliferative effects on colorectal cancer cell lines *in vitro*, marked by mitochondrial membrane potential disruption and enhanced efficacy when combined with conventional anticancer drugs [11]. In hepatocellular carcinoma (HCC), α-humulene from *Eupatorium odoratum* L., Asteraceae exhibited selective inhibition of HCC cell proliferation primarily *in vitro*, associated with the suppression of protein kinase B signaling [37]. Notably, α-humulene demonstrated dose-dependent inhibition of ovarian and lymphoblast cancer cell proliferation *in vitro* and synergistic effects with doxorubicin [12]. Its preferential cytotoxicity towards tumor cells, sparing non-tumor cells, indicates potential selectivity for actively dividing cancer cells. This anti-proliferative activity has also been related to apoptosis induction and modulation of reactive oxygen species (ROS) production [37]. In an *in vivo* study on clove terpenes, α-humulene induced significant glutathione S-transferase activity in mouse liver and small intestine tissues, suggesting a role in detoxification processes [31]. Fukuoka et al. (2004) [21] showed α-humulene's antiproliferative properties in rat arterial smooth muscle cells, utilizing a cell assay that induced proliferation with heat shock protein. The study reported an IC50 value of 0.122μM, showcasing dose-dependent effects and superior potency compared to its analogue Zerumbone. Inhibitory effects were demonstrated even at a concentration of 4.89 x 10^{-6} mol/L.

Anti-inflammatory properties

Exploration into the *in-vivo* anti-inflammatory properties of α-humulene, isolated from *Cordia verbenacea* has yielded significant insights as well. Passos et al. (2007) [39] showed its potent anti-inflammatory attributes of α-humulene by demonstrating its ability to significantly inhibit carrageenan-induced paw oedema in murine models and a notable reduction in tumor necrosis factor (TNF)-α levels in response to carrageenan.. Fernandes et al. (2007) [32] conducted a similar evaluation using through oral administration of α-humulene against several experimental murine and rat models. Notably, administration of α-humulene at 50 mg/kg demonstrated a dose-dependent reduction in paw edema, indicating its efficacy in mitigating the acute phase of inflammation. Additionally, it exhibited a sustained anti-inflammatory effect by inhibiting the late phase of carrageenan-induced edema. Mechanistically, α-humulene interfered with multiple pathways involved in inflammation, including the inhibition of bradykinin, platelet-activating factor, and histamine-induced edema. Basting et al. (2019) [33] also observed a reduction in carrageenan-induced paw edema. Despite not significantly affecting neutrophil migration, α-humulene suppressed the release of TNF-α and interleukin (IL)-1β and inhibited prostaglandin E2 production.. Similar findings were observed by Medeiros et al. (2007) [34] in lipopolysaccharide-induced rat paw edema. Key observations included a reduction in pro-inflammatory cytokines, inhibition of kinin B1 receptor upregulation, and suppressing neutrophil recruitment by targeting nuclear factor-kappa B (NF-κB) activation. Notably, α-humulene's efficacy surpassed that of trans-caryophyllene.

In a murine model of airway allergic inflammation, female BALB/c mice challenged with ovalbumin experienced a significant reduction in eosinophil recruitment to bronchoalveolar lavage fluid and lung tissue when administered α-humulene preventively or therapeutically [35]. α-humulene exhibited modulation of critical asthma-related mediators, including IL-5,

C-C motif chemokine11, and leukotriene B4, along with the inhibition of P-selectin expression, a crucial factor in eosinophil migration. Additionally, α-humulene showed inhibitory effects on NF-κB and activator protein-1. Histological analysis indicated a decrease in mucus hypersecretion, suggesting a potential role in balancing T-helper cell responses.

Contrary to the widely positive findings reported regarding the anti-inflammatory activity of α-humulene, Viveiro et al. (2022) [22] investigated pterygium fibroblasts through *in vitro* exposure experiments. Third-passage pterygium fibroblasts were subjected to α-humulene concentrations (0.25, 2.5, and 25 µmol/L), and the subsequent cell viability assay revealed no significant cytotoxicity and minimal variation in inflammatory markers. This highlights the importance of considering cell-type-specific responses and experimental conditions in evaluating potential therapeutic benefits.

Antimicrobial properties

Early exploration into the *in vitro* antimicrobial potential of α-humulene was done by Pichette et al. (2006) [23] who observed antibacterial activity against *Staphylococcus aureus* at a mean inhibitory concentration (MIC) of 1.3×10^{-5} mol/L. Subsequent investigations by Azizan et al. (2017) [24] expanded on this by demonstrating dose-dependent bacteriostatic and bactericidal effects of α-humulene. Employing the broth microdilution method and α-humulene sourced from *Orthosiphon stamineus* and *Ficus deltoidei*, the study showed moderate to strong inhibition across a range of bacteria. Notably, oral Gram-negative species (*Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter Actinomycetemcomitans*) exhibited greater susceptibility compared to Gram-positive bacteria (*Enterococcus faecalis, Streptococcus mutans, Streptococcus mitis, Streptococcus salivarius*).

Mechanistically, electron microscopy revealed morphological alterations, indicating α-humulene interfered with membrane structure or cell wall of oral bacteria. This effect was ascribed to the substantial electronegativity resulting from the carbon double bond configurations in its molecular structure.

Jang et al. (2020) [25] evaluated the *in vitro* antibacterial and antibiofilm effects of α-humulene extracted from *Bacteroides fragilis*. The study determined the MIC for cell growth and biofilm formation to be 9.8 x 10^{-6} mol/L. Through qRT-PCR analysis, concentration-dependent reductions in the expression of *bmeB1* and *bmeB3* genes were observed in various *Bacteroides fragilis strains*. This indicated increased antibiofilm action given these genes are implicated in the development of the biofilm matrix and antibiotic resistance. Notably, there was a marked reduction in cellular metabolic activity at concentrations of 3.9 x 10^{-5} - 7.8 x 10^{-5} mol/L. Moreover, confocal laser scanning microscopy revealed that α-humulene not only diminished cell density and thickness but also effectively reduced protein, carbohydrate, and nucleic acid levels. Rossato et al. (2022) [26] evaluated α-humulene's antibacterial potential against *Staphylococcus aureus* and *Enterococcus faecalis* using experimental light-cured periodontal dressing formulations and the modified direct contact model. Formulations with 10% and 20% α-humulene reduced bacterial growth after 1 and 24 hours of incubation compared to the control group, indicating sustained antibacterial activity.

Xing et al. (2018) [40] focused on evaluating the antifungal properties of humulene. Findings revealed a dose-dependent impediment of *Peronophythora litchii* growth, with scanning and transmission electron microscopy uncovering discernible morphological and ultrastructural channges. *In vivo* evaluations on litchi foliage and fruits demonstrated a notable reduction in

disease severity. α-humulene exhibited weak inhibitory effects against *Peronophythora litchi* at high concentrations (8.7×10^{-4} - 4.4×10^{-3} mol/L) [40].

Antiallergic properties

The antiallergic potential of α-humulene was demonstrated by Tanaka et al. (1996) [36] , in the context of treatment for atopic conditions. Using a sensitised murine model of passive cutaneous anaphylaxis, α-humulene administration prior to antigen challenge demonstrated dose-dependent inhibition of allergic reactions at 20, 40 and 80 mg/kg, with approximately four times the potency of the reference drug tranilast. However, the observed effects were less potent than the antiallergy effects triggered by β-caryophyllene. The study suggested the bicyclic ring structure inherent in β-caryophyllene may have contributed to the enhanced antiallergy activity of the compound. Additionally, Fernandes et al. (2007) [32] demonstrated α-humulene reduced paw oedema in sensitized mice challenged with ovoalbumin, suggesting its anti-inflammatory properties in alleviating allergic responses.

Antiparasitic properties

De Oliveria et al. (2017) [27] evaluated the antischistosomal effects of α-humulene against *Schistosoma mansoni* following *in vitro* exposure. At concentrations of 1 mol/L, α-humulene exhibited notable efficacy, causing mortality rates of 60% for female worms and 80% for male worms after a 72-hour incubation period. The sesquiterpene also induced a substantial reduction in motor activity and oviposition across all concentrations, highlighting its potential as a promising antiparasitic agent. Additionally, there were significant inhibitory effects of α-humulene on the excretory system of male *Schistosoma mansoni* adult worms. However, this inhibitory activity was not observed in female worms. The mechanism underlying this was attributed to the inhibition of the expression of P-glycoprotein, a product of the multidrug

resistance 2 gene, within the excretory system of male *Schistosoma mansoni* worms. The study further employed Hoechst probe and scanning electron microscopy to assess the impact of α-humulene on the membrane integrity of *Schistosoma mansoni*. This highlighted the substantial damage caused to the tegument by α-humulene exposure.

Gastroprotective properties

Lemos et al. (2015) [41] investigated the potential gastroprotective effects of α-humulene through their study involving murine gastric ulcer models The researchers administered an oral dose of 30mg/kg of isolated α-humulene, equivalent to omeprazole dosing. This dose led to a substantial reduction of 76.20% in gastric lesions induced by 0.2 ml of an ethanol/hydrogen chloride solution (60%/0.3 M). This investigation revealed two significant mechanisms contributing to the gastroprotective effects: a reduction in gastric acid secretion and an increase in mucus production.

Larvicidal properties

The larvicidal potential of α-humulene was examined by Govindarajan et al (2016) [28] in an *in vivo* study encompassing three vector species: *Anopheles subpictus* Grassi (Culicidae)*; Aedes albopictus* Skuse (Culicidae); and *Culex tritaeniorhynchus* Giles (Culicidae). The researchers determined the lethal concentration 50 (LC50) values as 3.0×10^{-5}, 3.4×10^{-5} and 3.6×10^{-5} mol/L for the respective species. The impact on non-target species was notably less, with a significantly lower LC50 of 5.0×10^{-3} mol/L observed in *Gambusia affinis* fish. Furthermore, there were no adverse effects on fish survival or swimming activity following the administration of α-humulene concentrations approaching the calculated larvae LC90.

Hung et al. (2021) [29] also evaluated the larvicidal effects of α-humulene from the essential oil of *Lantana camara*. It showed promising larvicidal activities against important mosquito vectors, with 48-hour LC50 values of 1.9 x 10^{-4} mol/L for *Anopheles aegypti* L. (Culicidae); 1.9 x 10^{-4} mol/L for *Aedes albopictus*; and 4.3 x 10^{-4} mol/L for *Culex quinquefasciatus* Say (Culicidae). Additionally, α-humulene exhibited notable mosquito larvicidal effects with an inhibitory concentration (IC50) value of 7.9 x 10^{-4} against electric eel acetylcholinesterase. Furthermore, in-silico studies have demonstrated α-humulene exhibits significant binding energy in docking studies targeting sterol carrier protein-2, indicating its potential as an effective antilarvicidal agent [30].

Molluscicidal properties

In the context of molluscs acting as intermediate hosts for several helminths, α-humulene's potential molluscicidal properties have been subjected to scrutiny [29]. Notably, its LC50 values at 24 hours have been reported as 9.3 x 10^{-5} mol/L, 9.3 x 10^{-5} mol/L, and 9.1 x 10^{-5} mol/L for *Pomacea canaliculate (*Lam.), Ampullariidae; *Gyraulus convexiusculus* (Hutton), Planorbidae; and *Tarebia granifera* (Lam.), Thiaridae, respectively.

Cannabimimetic properties

The cannabimimetic properties of α-humulene were demonstrated by LaVigne et al. (2021) [42] through *in vivo* and *in vitro* experiments. Using various behavioral assays in mice, , α-humulene manifested notable antinociceptive effects. The study identified specific receptor targets influenced by α-humulene, revealing interactions with cannabinoid type 1 (CB1) and types 2 (CB2) receptors, as well as adenosine receptor A2a, through *in vitro* experiments. Furthermore, *in vivo* experiments demonstrated a synergistic interaction between α-humulene and the synthetic cannabinoid agonist WIN55,212-2, leading to enhanced antinociceptive

effects. There were selective effects of α-humulene on various behaviors associated with the tetrad, emphasising its complex interplay with multiple receptor systems. Notably, the *in vitro* studies showed the CB1-dependent nature of α-humulene activation, requiring relatively high concentrations for receptor activation, a phenomenon reversible by the CB1 antagonist rimonabant.

Discussion

The scoping review undertaken in this study unveils the landscape of α-humulene's pharmacological potential, revealing a diverse spectrum of documented properties across various studies. These encompass anti-inflammatory, antimicrobial, antiproliferative, antiallergic, gastroprotective, and even cannabimimetic effects. α-humulene interacts with diverse biological pathways, suggesting its potential for addressing various health conditions.

The review further emphasises the pivotal role played by specific species that yield substantial amounts of α-humulene, carrying profound implications for pharmaceutical applications. Noteworthy among these is *Aframomum melegueta*, a West African spice renowned for its historical medicinal uses and significant α-humulene content, rendering it an enticing candidate for therapeutic extraction [43]. Likewise, several *Leptospermum* species, known for their potent antimicrobial properties, exhibit notable levels of α-humulene [44]. Additionally, *Humulus lupulus*, commonly known as hops, has a high α-humulene content. Given its well-documented applications and extensively studied properties, hops offer a versatile avenue for the development of α-humulene-based therapeutics [45]. Another plant of significance is *Cannabis sativa*, in which α-humulene is already utilized in full-spectrum

cannabis-based medicinal products. The cannabimimetic effects of α-humulene may give rise to potential additive or synergistic effects when administered alongside cannabinoids and other active pharmaceutical ingredients, broadly referred to as 'the entourage effect' [46]. Collectively, these species enrich the available sources of α-humulene, highlighting its prevalence across a diverse range of botanicals. These species hold promise as potential sources for pharmaceutical extraction due to their abundant α-humulene content. By harnessing extracts derived from these species, either in combination with other compounds or as standalone treatments, further exploration of potential solutions for various health conditions becomes viable.

The translation of promising preclinical findings to clinical practice encounters barriers. Variability in α-humulene yield across different botanical sources poses logistical challenges for large-scale extraction [47]. The limited exploration of isolated α-humulene outside of whole essential oils highlights the importance of comprehensive investigations into isolated properties [48]. Addressing this inconsistency requires the identification of further plant species with high α-humulene yields or increased investigation of biosynthesis pathways for synthetic production.

The potential of α-humulene as an anticancer agent is particularly promising. Studies have established wide-ranging effects on various cancer cell lines, revealing nuanced interactions with distinct tumor types. This is coherent with preclinical studies on other terpenes, which similarly find anticancer potential [49]. The mechanism of action of α-humulene appears multifactorial, including increasing the production of reactive oxidative species and induction of apoptosis [16,37]. Moreover, α-humulene was associated with glutathione depletion, which makes cancer cells more sensitive to stress caused by reactive oxidative species [16]. α-humulene was associated with an increase in GST activity, which is also seen with other

terpenes [50]. This feature, however, is typically associated with improved cancer cell survival and resistance to certain chemotherapeutics, due to the associated efflux of anticancer agents from the cell [51]. Putra et al investigated α-humulene's interaction with the overexpressed HER-2 protein using docking methods and shed light on its potential as an anti-breast cancer agent. The in silico molecular docking simulations reveal a binding energy of -7.50 kcal/mol, affirming its efficacy against breast cancer [52]. As such its effects within human studies are eagerly awaited, especially as preclinical studies showing that α-humulene may have synergistic effects with doxorubicin and other chemotherapeutics [13]. This is particularly important as present studies indicate that α-humulene would not be a suitable chemotherapeutic agent in isolation and would otherwise be best used alongside traditional chemotherapeutics [53]. Its lower toxicity profile also supports this as a potential future use, provided efficacy can be determined [54]. Further mechanistic studies, including investigations into synergistic interactions with established chemotherapeutics, are ultimately necessary to fully leverage α-humulene's potential in cancer biology [55].

Beyond its cancer-related properties, α-humulene is as a compelling anti-inflammatory agent. Its modulation of the NF-κB pathway and subsequent suppression of key inflammatory mediators demonstrates its potential in various inflammatory conditions [56]. Insights gained from murine models of asthma highlight its immunomodulatory potential, positioning α-humulene as a contender for treating inflammatory and atopic conditions [35]. Additionally, its analgesic potential and observed gastroprotective effects hold significance [57]. In contrast to traditional non-steroidal anti-inflammatory drugs, notorious for causing peptic ulcer disease and adverse renal effects, α-humulene offers a potentially safer alternative for managing inflammation-associated conditions [58].

The pharmacodynamic profile of α-humulene indicates its capability of addressing various aspects of health and disease. Its interactions with different molecular pathways suggest complex biochemical dialogues within cells and tissues. This complexity is particularly relevant for multifactorial conditions like cancer and chronic inflammatory diseases, where several dysregulated pathways contribute to aetiology and pathogenesis [59,60]. By targeting these pathways, α-humulene introduces a novel therapeutic approach distinct from the traditional "one-target-one-drug" paradigm [61,62].

The antimicrobial properties of α-humulene enrich its pharmacological profile, spanning antibacterial, antiparasitic, and antifungal effects. Its efficacy in restraining biofilm formation and curtailing gene expression associated with biofilm matrix development and antibiotic resistance is particularly relevant given the growing appreciation for the role of biofilm in antibiotic resistance [63,64]. This enhances the potential to address antibiotic-resistant infections, a pressing global health concern [65].

The paucity of clinical studies involving α-humulene necessitates thorough evaluation in the clinical setting to validate its efficacy, safety, and optimal dosage regimens in human subjects before widespread use [66]. In addition, it is crucial to emphasise the necessity of pharmacokinetic studies, particularly for terpenes like α-humulene. Due to their lipophilic nature, terpenes often exhibit poor water solubility and are susceptible to rapid metabolism and elimination, leading to low oral bioavailability [2,67]. Therefore, rigorous pharmacokinetic studies in animals and humans are essential to optimise dosing strategies to understand α-humulene’s therapeutic potential [68]. Strategies to enhance α-humulene’s bioavailability, such as formulations that improve solubility and stability, could significantly enhance its clinical utility [69]. There is one pilot study currently underway seeking to

explore the effects of α-humulene on stress when combined with forest bathing, for which the results will be eagerly awaited [70].

Acknowledging the limitations of this scoping review is vital. The heterogeneity of study methodologies, including variations in cell lines, experimental conditions, and assessment methods, poses a challenge in directly comparing the results. This heterogeneity limits the ability to perform quantitative meta-analyses and emphasises the need for cautious interpretation. Variations in study design, quality, sample size, and reporting practices could impact the overall strength of evidence. The limited number of *in vivo* studies and the absence of clinical trials restrict the ability to directly extrapolate findings to human populations directly to provide clinical validation [71]. Preclinical studies often involve isolated cells or animal models which may not fully replicate human physiological responses [72]. Furthermore, it's important to acknowledge the limitations associated with the compilation of α-humulene yield data from various locations, with a focus solely on the highest reported yields. This approach might not account for potential variations in cultivation practices, environmental factors, and genetic influences that can significantly affect yield outcomes. Relying solely on the highest reported yields could lead to an incomplete understanding of the compound's availability and potentially skew the representation of humulene yields. Moreover, studies often failed to specify whether the α-humulene yield was from the whole plant, flower, or another plant component. This lack of clarity restricts the interpretation, as there can be substantial variation in terpene content across various flower structures [73].

Overall, this systematic review provides valuable insights into α-humulene's potential therapeutic properties. However, addressing limitations through standardised methodologies,

clinical trials, and consistent reporting practices is crucial for an accurate understanding of its multifaceted effects and clinical applications. The future of α-humulene's clinical translation hinges on collaborative efforts, pharmacokinetic evaluations, rigorous clinical trials, innovative formulation strategies, and partnerships across disciplines. Through these efforts, α-humulene's clinical translation can be accelerated in light of its many promising therapeutic properties.

Materials and Methods

A scoping review, utilizing methods outlined by Arksey & O'Malley and Levac et al. [74,75], was conducted of the current literature on α-humulene.

Research question

This scoping review focused on identifying and clarifying key research aspects and characteristics of available literature with regards to α-humulene. Given its potential therapeutic effects in the clinical setting, this review evaluated the evidence base for α-humulene in terms of its extraction and properties that may be translated for medicinal purposes. This review also aimed to identify any specific gaps in the evidence base that may inform the work of future researchers in this area of sesquiterpene research.

Data sources and search strategy

A broad search was conducted of MEDLINE, PubMed, and EMBASE databases in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [76]. A search was conducted from 1946 to July 14, 2023, utilizing the search terms 'humulene,' 'alpha-humulene,' and 'alpha-caryophyllene' with the Boolean operator 'OR' (Table S1, S1a-c). The literature search was conducted by three independent

researchers. For discrepancies identified, a senior author was planned to review these if necessary. Additional relevant articles were included through manual search of bibliographies of included studies. Articles were screened in relation to the topic area and included if deemed to meet the inclusion criteria. The precise search strategies performed can be found in Supplementary Material C.

Study selection criteria

Inclusion criteria consisted of original articles related to α-humulene including extraction, pre-clinical and clinical research. Studies were excluded if they did not constitute original primary research or the outcomes of α-humulene were not reported in isolation to other essential oils extracted from plant species.

Data extraction and presentation

Data extraction was performed independently by three authors. If outcomes were not reported within the published article, but described within the methodology, corresponding authors were contacted for additional information. Concentrations are presented as percentage yield or micromolar concentrations (μM) with the standard deviation (S.D.), standard error (S.E.) or range if reported.

Supporting information

Supplementary material A: References for studies of extraction yields for different species

Supplementary material B: Reported yields of α-humulene

Supplementary material C: Search strategy

Contributors Statement

Data collection: N. Dalavaye, M. Nicholas, M. Pillai; Design of the study: N. Dalavaye, M. Nicholas, M. Pillai, S. Erridge, M.H.Sodergren; Statistical analysis: N. Dalavaye, M. Nicholas, M. Pillai, S. Erridge; analysis and interpretation of the data: N. Dalavaye, M. Nicholas, M. Pillai, S. Erridge, M.H.Sodergren; drafting the manuscript: N. Dalavaye, M. Nicholas, M. Pillai, S. Erridge; critical revision of the manuscript: N. Dalavaye, M. Nicholas, M. Pillai, S. Erridge, M.H.Sodergren

Conflicts of interest

SE is the Head of Research at Curaleaf Clinic. MHS is the Chief Medical Officer at Curaleaf International.

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Legends for Figures

Fig.1 PRISMA flow chart showing the process of inclusion and exclusion of patients for analysis in this scoping review.

Table 1: Summarising the species with the top five highest reported yields of α-humulene

Species	Chemovar	Extraction	Isolation	Yield	Reference
Aframomum melegueta [alligator pepper]	Nigeria	Hydrodistillation for 3h	Fractionation	60.90%	Ajaiyeoba E et al 1999 [77]
Leptospermum sp. [Mt Maroon A.R. Bean 6665]	Australia	Hydrodistillation with incubation	GC-MS	44.00-51.00%	Brophy J et al 2000 [78]
Humulus lupulus. [Chinook variety]	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	31.50 - 34.62%	Duarte et al 2023 [79]
Camponotus japonicus [insect]	Japan	Macerated in 10mL of pentane	GC-MS	35.80%	Sakurai K et al 2020 [80]
Zingiber nimmonii	India	Hydrodistillation	GC-MS	19.60%	Govindarajan et al

		using a Clevenger-type apparatus for 8h			2016 [81]

GC-MS – gas chromatography – mass spectrometry

Table 2: Summary of studies investigating the anticancer properties of isolated α-humulene

Model	Concentration/ Dose	Results	Reference
In vitro colorectal adenocarcinoma epithelial cells [CaCo-2 and SW-620]	5 x 10^{-5}, 1 x 10^{-4} and 1.5x 10^{-4} M	α-humulene exhibited antiproliferative activity in combination with oxaliplatin and 5-fluorouracil at 100 and 150 µmol/L due to decreased mitochondrial membrane potential.	Ambroz et al 2019 [11]
In vitro hepatocellular carcinoma cells [huh7, SMMC-7721, HepG2 and Hep3B] and in vivo HepG2-bearing nude mice	*In vitro*: 6.1 x 10^{-6} – 2.4 x 10^{-4} M *In vivo*: 10 and 20 mg/kg	In vitro, α-humulene inhibited proliferation of all hepatocellular carcinoma cell lines at 15 µmol/L, inducing cytotoxicity via intrinsic apoptotic pathways. Similar findings were reported *in vivo* at 10 mg/kg.	Chen et al 2019 [37]
In vitro ovarian cancer cells [A2780 and SKOV3 and lymphoblasts CCRF/CEM and CEM/ADR]	20, 40, 100 and 200 µM	α-humulene showed antiproliferative activity against certain ovarian cancer cell lines [A2780 at 40 µM, SKOV3 at 200 µM] and lymphoblast cell lines [CCRF/CEM at 200 µM, no effect on CEM/ADR at 200 µM].	Ambroz et al 2017 [12]
In vitro colon adenocarcinoma	0 - 2.4 x 10^{-4} M	α-humulene demonstrated antiproliferative	Ambroz et al

Model	Concentration/ Dose	Results	Reference
[CaCo-2] and non-cancer cells [rat hepatocytes]		activity against cancer cells at 4.9 x 10^{-5} mol/L, with an IC50 of 24.4±2.4. Additionally, α-humulene potentiated doxorubicin's anticancer properties in cancer cells, while showing no effect on non-cancer cell viability	2015 [13]
In vitro mice melanoma, human hepatocellular carcinoma, chronic human myelocytic leukaemia and human promyelocytic leukaemia	9.3 x 10^{-7} - 1.2 x 10^{-4} M	No significant anticancer activity of α-humulene was identified for any concentration tested.	Costa et al 2015 [38]
In vitro: colon human cancer [HT-29], human hepatocellular carcinoma [J5] and human pulmonary adenocarcinoma [A549]	0 – 9.8 x 10^{-4} M	α-humulene exhibited significant cytotoxicity against all cell lines, with IC50 values of 5.2 x 10^{-5}, 1.8 x 10^{-4} and 1.3 x 10^{-4} mol/L for HT-29, J5 and A549 respectively.	Su et al 2015 [14]
In vitro: human colorectal adenocarcinoma [HCT-116], human breast cancer [MCF-7] and murine macrophages [RAW264.7]	7.6 x 10^{-6} - 4.9 x 10^{-4} M	α-humulene demonstrated cytotoxic potential by inhibiting cancer cell growth, with IC50 values of 3.1 x 10^{-4}, 4.2 x 10^{-4} and 1.9 x 10^{-4} mol/L for HCT-116 MCF-7 and RAW264.7 cell lines respectively.	Hadri et al 2010 [15]
Murine small bowel mucosa and liver	9.8 x 10^{-5} M	α-humulene showed potential inhibitory action against carcinogenesis by increasing Glutathione S-transferase [GST] activity. The enzyme activity increased by 99% in the liver and 152% in the small bowel.	Zheng et al 1992 [31]
Cell lines of human breast adenocarcinoma [MCF-7], prostatic adenocarcinoma [PC-3], lung carcinoma [A-549],	2.4 x 10^{-4} and 9.8 x 10^{-4} M	α-humulene caused dose-dependent glutathione depletion of 38% and 71% at 50 and 200 μM respectively, along with increased production of reactive oxygen	Legault et al 2003 [16]

Model	Concentration/ Dose	Results	Reference
colon adenocarcinoma and fibroblasts [DLD-1 e L-929]		species by 163% and 278% after 1 and 4 hours. Normal human fibroblasts showed lower cytotoxic effects.	
Cell lines of human breast adenocarcinoma [MCF-7], colon adenocarcinoma [DLD-1: ATCC # CCL-221], murine fibroblasts [L-929 ATCC # CCL-1]	$7.8 \times 10^{-5} – 3.1 \times 10^{-4}$ M	α-humulene showed cytotoxicity at 1.6×10^{-4} and 3.1×10^{-4} mol/L. Cell growth inhibition by α-humulene was significantly increased from 50 ± 6% alone to 75 ± 6% by co-administration of non-cytotoxic levels [10 µg/mL] of caryophyllene, potentially due to altered membrane permeability.	Legault et al 2010 [17]
Cell lines of human breast adenocarcinoma [MCF-7 and MDA-MB-468], human malignant melanoma: [UACC-257]	Concentration not reported	α-humulene from Eugenia zuchowskiae inhibited all cell lines, with similar cytotoxicity against MCF-7 line as doxorubicin [LC50 of 1.1×10^{-4} and 1.4×10^{-4} mol/L respectively].	Cole et al 2007 [18]
Cell lines of human cervical carcinoma [HeLa], human colon adenocarcinoma [HT-29], monkey kidney [Vero]	$9.8 \times 10^{-7} – 9.8 \times 10^{-4}$ M	α-humulene demonstrated cytotoxicity against all cell lines. Tumor cell lines were more sensitive to cytotoxic activity than non-tumor Vero cells and murine macrophages.	Silva et al 2008 [19]
Cell lines of human amelanotic melanoma [C32], renal cell adenocarcinoma [ACHN]	up to 4.9×10^{-4} M	α-humulene did not demonstrate cytotoxicity with IC50 > 4.9×10^{-4} mol/L against both C32 and ACHN lines. However, β-caryophyllene showed cytotoxic activity against both.	Loizzo et al 2008 [20]

IC50 - half maximal inhibitory concentration; LC50 - half maximal lethal concentration

Additional file 1
Search strategies and results

Table S1: Summary of Databases Searched

Table	Vendor/ Interface	Database	Date searched	Database update	Searcher(s)
1a	Ovid	MEDLINE	14/07/2023	1946 to July 13 2023	N. Dalavaye; M. Nicholas; M. Pillai
1b	National Library of Medicine	PubMed	14/07/2023	13/07/2023	N. Dalavaye; M. Nicholas; M. Pillai
1c	Ovid	EMBASE	14/07/2023	1947 to July 13 2023	N. Dalavaye; M. Nicholas; M. Pillai

Table S1a: Ovid MEDLINE search strategy

Provider/Interface	Ovid
Database	MEDLINE
Date searched	14/07/2023
Database update	1946 to July 13 2023
Search developer(s)	S. Erridge
Limit to English	No
Date Range	1946-2023

1	Humulene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
2	Alpha-Humulene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
3	Alpha-Caryophyllene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
4	1 or 2 or 3

S1b: PubMed search strategy

Provider/Interface	National Library of Medicine
Database	PubMed
Date searched	14/07/2023
Database update	13/07/2023
Search developer(s)	S. Erridge
Limit to English	No
Date Range	-13/07/2023

1	Humulene
2	Alpha-Humulene
3	Alpha-Caryophyllene
4	1 OR 2 OR 3

S1c: Ovid EMBASE search strategy

Provider/Interface	Ovid
Database	EMBASE
Date searched	14/07/2023
Database update	1947 to July 13 2023
Search developer(s)	S. Erridge
Limit to English	No
Date Range	1947-2023

1	Humulene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
2	Alpha-Humulene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
3	Alpha-Caryophyllene.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
4	1 or 2 or 3

Supplementary Material A

Included studies reporting extraction yields of α-humulene

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Supplementary Table 2: Overview of extraction of α-humulene by included studies

Organism	Chemovar	Extraction	Isolation	Yield	Reference
Acalypha plicata Müll-Arg.	Venezuela	Hydrodistillation in a Clevenger-type apparatus for 5 h	GC-MS	1.20%	10.1002/ffj.1679
Achillea lingulata	Serbia	Hydrodistillation in a Clevenger-type apparatus for 2.5 h	GC-MS	0.48%	10.1002/ffj.1778
Achillea Umbellata	Greece	Hydrodistillation in a Clevenger-type apparatus for 2.5 h	GC-MS	0.04%	10.1002/ffj.1778
Acinos arvensis (Lam.) Dandy	Serbia	Hydrodistillation for 2.5 h using a Clevenger-type apparatus	GC-MS	0.70%	10.1002/ffj.1409
Acritopappus confertus	Brazil	Hydrodistillation using a Clevenger-type apparatus modified by Gottlieb for 3 hours	GC-MS	1.30%	10.1002/ffj.1483
Acroptilon repens (L.) DC. (Russian knapweed)	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.00%	10.1002/ffj.1568
Aethionema sancakense	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS	19.8%	10.3390/ molecules27186129
Aframomum corrorima	Ethiopia	Steam distillation	GC-MS	0.1% (Seeds) 1.1% (Husks)	10.1002/ffj.1634
Aframomum exscapum (Sims) hepper	Guadelope	Hydrodistillation using a Clevenger-type apparatus for 10 h	GC-MS	0.1% (Fruit pulp), 0.4% (Stems), nil (Leaves), nil (Seeds)	10.1002/ffj.1741
Aframomum giganteum	Gabon	Hydrodistillation	GC-MS	0.2% (Leaves) 0.6% (Rhizomes)	10.1002/ffj.1403
Aframomum melegueta	France	Commercial (hexane:ethyl acetate extract), supercritical fluid extraction product (Carbon dioxide extract)	GC-MS	10.5% [Commercial], 7.2% [supercritical fluid extraction product]	10.1002/ffj.1554
Aframomum melegueta (Roscoe) K. Schum. (alligator pepper)	Nigeria	Hydrodistillation for 3h	Fractionation	60.90%	10.1002/%28SICI%291099-1026%28199903/04%2914:2%3C109::AID-FFJ775%3E3.0.CO;2-M
Ageratum fastigiatum	Brazil	Hydrodistillation according to Method I of the Brazilian Pharmacopeia, 5th Edition (2010) for 4 h	GC-MS	3.52%	10.1016/ j.bjp.2015.03.002
Alpinia zerumbet	Japan	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.0 g/L (leaves)	10.1002/ffj.2047
	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.29%	10.1590/1983-084X/ 15_054

Anemia tomentosavar.anthriscifolia	Argentina	Hydrodistillation in a Clevenger-type apparatus	GC-MS	0.20%	10.1002/ffj.1341 Juliani
Annona leptopetala	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	1.32%	10.1016/ j.bjp.2018.06.009
Anthemis triumfetti (Asteraceae)	NR	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.60%	10.1002/ffj.1592
Artabotrys jollyanus	Cote d'Ivoire	Hydrodistillation in a Clevenger type apparatus	GC-MS	3.00%	10.1016/ j.bjp.2017.04.001 Goore
Artemisia scoparia Waldst. & Kit	India	Hydrodistillation according to the method recommended by the British Pharmacopoeia, 1988.	GC-MS	0.30%	10.1002/ffj.1278
Artemisia scoparia Waldst. et Kit	Turkey	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	0.70%	10.1002/ffj.1426
Artemisia spicigera C. Koch	Turkey	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	nil	10.1002/ffj.1426
Atlantia Sessiflorawere	Vietnam	Hydrodistillation using a Clevenger apparatus for 3.5 hours	GC-MS	8.02+0.05%	10.3855/JIDC.12469
Baccharis trimera Less	Brazil	Commercial	GC-FID	3.10%	10.4314/tjpr.v14i11.19
Baeckea frutescens	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	5.80%	10.1016/ j.jchromb.2006.11.042
Baeckea frutescens L	Malaysia	Hydrodistillation for 8 hours. Separated and dried over anhydrous magnesium sulphate	GC-MS	10.6% (Coastal sample)	10.1002/%28SICI%291099-1026%281998070%2913:4%3C245::AID-FFJ736%3E3.0.CO;2-J
Blumea lacera	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3.7% (Flower), 3.5% (Leaf), 1.5% (Stem)	10.3390/ molecules27227961
Blumea sinuata	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	4.3%	10.3390/ molecules27227961
Boesenbergia stenophylla R. M. Sm	Malaysia	Hydrodistillation using a Clevenger-type apparatus for 8 h	GC-MS	5.3% (Leaf), 2.8% (Rhizone)	10.1002/ffj.1227
Bubonium graveolens	Algeria	Hydrodistillation using a Clevenger-type apparatus for 6 h	GC-MS	2.1% (Leaves), 1.9% (Flower)	10.1002/ffj.1794
Buddleja tucumanensis	Bolivia	Hydrodistillation with a Clevenger-type apparatus	GC-MS	1.10%	10.1002/ffj.1526 Lorenzo
Bupleurum gibraltarium	Spain	Hydrodistillation using a Clevenger-type apparatus for 8 h	GC-MS	0.40%	10.1021/jf040219n
C. japonicus (an insect, collected form the twigs of Podocarpus nagi)	Japan	Macerated in 10ml of pentane	GC-MS	35.80%	https://dx.doi.org/ 10.1080/09168451.2020.1763156
C. obtusa var. formosana	Taiwan	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.30%	10.1002/ffj.1685

Calamintha sylvatica Bromf. Subs. Sylvatica	Serbia	Hydrodistillation for 3 h using a Clevenger-type apparatus	GC-MS	0.2% (Pre-blossom) 0.6% (Full blossom) 0.8% (Post-blossom)	10.1002/ffj.995
Calendula officinalis L.	Bosnia	Hydrodistillation	GC-MS, GC-FID	1.9% (Leaves) 1.3% (Flowers)	10.1002/ffj.3661
Callicarpa americana	Mississippi	Hydrodistillation using a Clevenger-type apparatus	GC-MS	10.00%	10.1016/ j.jchromb.2006.11.045
Callitris intratropica	Nigeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.40%	10.1002/ffj.1214
Calocedrus formosana	Taiwan	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.40%	10.1002/ffj.1685
Calycorectes australis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	1%	10.1002/ffj.1640
Calycorectes psidiiflorus	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	1%	10.1002/ffj.1640
Cannabis Sativa L	Argentina (Cepas Argentinas Terapéuticas)	Headspace extraction with NaCL at 90oC.	GC-FID	0.0059-0.0071 mg/g	https://doi.org/ 10.1016/ j.chroma.2022.463669
	France	Commercial	GC-MS	8.71%	10.1002/ffj.993
	Poland (Henola variety; fiber type)	Ethanolic extract filtered through a Millipore filter	GC-FID	0.206-0.534 mg/g (fast GC-FID); 0.138-0.531 mg/g (conventional GC-FID)	10.1002/ jssc.201900822
	United states (Culver cultivar)	Steam distillation	GC-MS	7.365% (30 mins distillation of dioecious, densely seeded system); 7.336% (240 mins of distillation of dioecious, densely seeded system); 2.59% (30 mins distillation of open, all-female, clonal transplant system); 4.23% (240 mins of distillation of open, all-female, clonal transplant system)	https://doi.org/ 10.1021/ acs.jafc.1c06912?urlappend=%3Fref%3DPDF&jav=VoR&rel=cite-as
	United states	Non-stop steam distillation	GC-MS	9.1% (chopped autoflower type hemp t&H)	https://dx.doi.org/ 10.1038/s41598-021-99335-4
Capparis spinosa var. aegyptia (Lam.) Boiss	Egypt	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	4.24%	10.1016/ j.bjp.2016.04.001
Carum copticum	Iran	Extracted with equal volumes redistilled dichloromethane	GC-MS	2.01%	10.1002/ffj.1129 Lockwood
Cedrela fissilis	Brazil	Hydrodistillation in a Clevenger-type apparatus for 4 h	GC-MS	4.9% (Leaf) 1.2% (Stem bark)	10.1002/ffj.1347

Cedrelopsis grevei H. Baillon	Madagascar	Commercial	GC-MS	0.8-5.4%	10.1002/ffj.1263
Centaurea calcitrapa L. (C.c.)	Italy	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.40%	10.1002/ffj.1585
	Poland	Solid phase microextraction	GC-MS	9.77%	10.3390/ molecules27041371
Centaurea huber-morathii Wagenitz	Turkey	Plant material was placed in a Eppendorf Microdistiller sample vial together with water. n-Hexane (0.3 ml) was added to the collecting vial to trap volatile compounds.	GC-MS	0.30%	10.1002/ffj.1620
Centaurea sphaerocephala L. ssp. sphaerocephala (C.s.)	Italy	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.70%	10.1002/ffj.1585
Centella asiatica (L.) Urban (Family: Apiaceae)	South Africa	Leaf powder soaked in 1 L of methanol with continuous stirring for 72 h	GC-MS	1.25%	10.1016/ j.biopha.2018.02.115
Ceroplastes rubens (an insect, collected form the twigs of Podocarpus nagi)	Japan	Macerated into 10ml oof pentane	GC-MS	3.90%	https://dx.doi.org/ 10.1080/09168451.2020.1763156
Chaerophyllum aksekiense	Turkey	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	5.50%	10.1002/(SICI)1099-1026(200001/02)15:1<43::AID-FFJ864>3.0.CO;2-%23
Chaetomium globosum	N/A	Dried ethyl acetate extract of the liquid culture filtrate	GC-MS	1.60%	10.1016/ j.biopha.2017.10.120
Chamaecyparis formosensis	Taiwan	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	2%	10.1002/ffj.1685
Chamomilla recutita L. Rausch	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	NR	10.1002/ffj.1035
Chloroxylon swietenia DC.	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.46% (leaves)	10.1007/s00436-007-0485-z
Cinnamomum camphora	Mauritius	NR	GC-MS	1.00%	10.1002/ cbdv.202000921
Cinnamomum jensenianum	China	Plant material soaked in distilled water, extracted with volatile oil extractor	GC-MS	0.26%	10.4314/tjpr.v17i9.23
Cinnamomum rhyncophyllum Miq.	Malaysia	Hydrodistillation using a Clevenger-type apparatus for 8 h	GC-MS	1.1% (Leaf), 0.1% (Bark), nil (Wood)	10.1002/ffj.1301
Cinnamomum tamala Nees et Eberm.	India	Hydrodistillation method recommended by the British Pharmacopoeia,	GC-MS	0.20%	10.1002/ffj.1236
Cirsium japonicum DC	Japan	Hydrodistillation in a Likens – Nickerson-type apparatus	GC-MS	0.60% (Rhizomes)	10.1002/ffj.1135
Citrus	France	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.1-0.2%	10.1002/ffj.1658
Citrus aurantium L.	West Indies	Rasping fresh bitter orange peels + cold pressing	GC-MS, GC-FID	0.01%	10.1002/ffj.2087
Citrus limon (L.)	Algeria	Hydrodistillation using a Clevenger-type apparatus for 3	GC-FID	0.04%	10.1002/ffj.1829

		h			
Citrus medical. Cv. Diamante	Italy	Syringe aspiration	GC-MS, GC-FID	0.06% (Peel) 0.04% (Rind)	10.1002/ jssc.200800404
Clinopodium nepeta L	Turkey	Homogenised plant item was extracted with 250 ml extraction solvent (methanol) for 24 hours	GC-MS	0.10%	10.1002/ffj.3636
Clusia lanceolata	Brazil	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	8.42% (galled leaves), 8.941% (non-galled leaves)	10.1016/ j.bjp.2014.11.005
Conium maculatum L.	Iran	Hydrodistillation using a Clevenger-type apparatus for 3 h.	GC-MS	1.40%	10.1002/ffj.1722
Conyza sumatrensis	Côte d'Ivoire	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	1-1.4% (leaves), 1.9-2.4% (flower), 0.2% (roots)	10.1002/ffj.1743
Copaifera duckei oleoresin	Brazil	Commercial	GC-MS, GC-FID	2%	10.1016/ j.bjp.2018.09.004
Copaifera langsdorffii Desf., Fabaceae,	Brazil	Macerated for 72 h with 70% aqueous ethanol. Filtered and concentrated under reduced pressure	GC-MS	Major component	10.1016/ j.bjp.2015.05.005
Copaifera multijuga	Brazil	Distilled 4 h in distillation column and a serpentine condenser	GC-MS	10.20%	https://dx.doi.org/ 10.1590/S0102-695X2013005000038
Cordia verbenacea	Turkey	Steam distillation for 1.5 to 2 h	GC-MS, GC-FID	1.23%	10.1016/ j.biopha.2019.108693
	Brazil	NR	HPLC	2.90%	10.1016/ j.bjp.2019.01.009
	Brazil	Supercritical fluid extraction; Soxhlet extraction for 6h	GC-MS	2.10% (SFE) 1.10% (Soxhlet)	10.1016/ j.biortech.2009.07.061
Croton ericoides	Rio, Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.10%	10.1007/s00436-012-2918-6
Croton isabelli	Rio, Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.30%	10.1007/s00436-012-2918-6
Croton pallidulus	Rio, Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.20%	10.1007/s00436-012-2918-6
Croton sellowii Baill (shrub)	NR	Maceration with acetone. Solvent removed under vacum	GC-MS, GC-FID	0.8% (leaves)	10.1002/ffj.1298
Croton zambesicus	Benin	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS, GC-FID	1.60%	10.1002/ffj.1558
	Cameroon	Hydrodistillation using a Clevenger-type apparatus for 12 h	GC-MS	2.2% (Leaves), 2% (Rootbark), 2.3% (Stembark)	10.1002/ffj.1081
Cunninghamia lanceolata var. konishii	Taiwan	Hydrodistillation using a Clevenger-	GC-MS, GC-FID	0.50%	10.1002/ffj.1685

		type apparatus			
Cupressus sempervirens ssp. Pyramidalis L.	NR	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.4% (Leaves) Trace (Cones)	10.1111/j.1365-2184.2008.00561.x
Cupriavidus necator	Germany	20% n-dodecane	GC-MS	2-10mg/L	https://doi.org/10.3390%2Fmolecules27248684
Curcuma angustifolia	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.30%	10.1002/ffj.1680
Curcuma longa L	India	Hydrodistillation using a Clevenger-type apparatus for 4.5 h	GC-MS	0.1 - 0.3%	10.1002/ffj.1780
Cyperus fuscus L	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.60%	10.4314/tjpr.v17i8.24
Daucus carota L	Israel	Solid-phase microextraction device extraction	GC-MS	124.47 ng/g	https://dx.doi.org/10.1021/acs.jafc.5b00546
	Denmark	Dynamic headspace sampling with nitrogen	GC-MS	Cultivars (Brasilia -1200 , Duke -740 , Fancy- 1610, and Cortez -2540) ng/50g	10.1021/jf010213n
	Denmark	Dynamic headspace sampling	GC-MS	294ng/g (Refrigerated (1 °C)) 64ng/g (Frozen (-24°C))	10.1021/jf030212q
Daucus reboudii Coss.	Algeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.10%	10.1002/ffj.1636
Dianthus caryophyllus	Greece	Steam distillation for 4 h in a modified Clevenger distillation apparatus	GC-MS	1.90%	10.1007/s00436-012-3097-1
Dipteryx alata Vogel, Fabaceae	Brazil	Manual hydraulic pressing and mechanical continuous pressing	GC-MS	0.08% (Hydraulic pressing) Nil (Continuous screw pressing)	10.1016/j.bjp.2015.07.019
Dorema ammoniacum	NR	Steam-distillation method via Clevenger apparatus	GC-MS	4.25%	https://doi.org/10.1155%2F2022%2F9725244
Dorema aucheri Boiss., Seseli	Iran	Hydrodistillation using a Clevenger-type apparatus for 3 h.	GC-MS	0.20%	10.1002/ffj.1722
Doronicum corsicum	France	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.40%	10.1002/ffj.1824
Dryobalanops aromatica	Malaysia	Fractional distillation in the presence of double distilled water for 2 h.	GC-MS	16.31%	10.4314/tjpr.v15i6.23
Echinacea Angustifolia	Iran	Hydrodistillation for 3 h, using a Clevenger-type apparatus.	GC-MS	2.80%	10.1002/ffj.1657
Echinacea Pallida	Iran	Hydrodistillation for 3 h, using a Clevenger-type apparatus.	GC-MS	1.50%	10.1002/ffj.1657

Echinacea Purpurea	Iran	Hydrodistillation for 3 h, using a Clevenger-type apparatus.	GC-MS	1.50%	10.1002/ffj.1657
Elettariopsis elan C.K. Lim	Malaysia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.1% (leaves), 0.2% (rhizomes), 0.2% roots	10.1002/ffj.1654
Emilia sonchifolia	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.8%	10.3390/ molecules27227961
Eriocephalus africanus L.var. Africanus	Spain	Hydrodistillation for 3 h in a Clevenger-type apparatus	GC-MS	0.09±0.09% (Burjassot) 0.03±0.04% (Sagunto) 0.03±0.02% (Valencia)	10.1002/ffj.1821
Eryngium yuccifolium Michaux	Germany	Hydrodistillation using n-pentane as a solvent for 6 h	GC-MS	0.60%	10.1002/ffj.1631
Erythrina corallodendron L.	China	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.57%	10.1097/ MD.0000000000017009
Eucalyptus (E.) dunnii	Brazil	Headspace solid-phase microextraction	CG- ion-trap MS	NR (predicted 1-10%)	10.1021/jf026047g
Eucalyptus Citriodora	Brazil	Headspace solid-phase microextraction	CG- ion-trap MS	nil	10.1021/jf026047g
	India	Hydrodistillation for 3 h using a Clevenger-type apparatus	GC-MS	0.6g/100g	10.1002/ffj.3296
Eucalyptus saligna	Brazil	Headspace solid-phase microextraction	CG- ion-trap MS	nil	10.1021/jf026047g
Eugenia caryophyllata	South Korea	NR	GC-MS, GC-FID	0.8% (bud oil) 3.4% (leaf oil)	10.1021/jf034225f
	China	Solvent free microwave extraction and hydrodistillation	GC-MS	3.09% (Hydrodistillation) 5.06% (Solvent free microwave extraction)	10.1002/ jssc.201000148
Eugenia caryophyllus	Germany	NR	GC-MS	2.10%	10.1021/jf060608c
Euphorbia convolvuloides	Ivory coast	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.7% (aerial plant parts)	https://dx.doi.org/ 10.1002/ffj.3624
Euphorbia acanthothamnos	Greece	Dichloromethane extract	GC-MS	nil	10.1002/ffj.1148
Euphorbia apios	Greece	Dichloromethane extract	GC-MS	0.60%	10.1002/ffj.1148
Euphorbia characias	Greece	Dichloromethane extract	GC-MS	nil	10.1002/ffj.1148
Euphorbia dendroides	Greece	Dichloromethane extract	GC-MS	1.10%	10.1002/ffj.1148
Euphorbia helioscopia	Greece	Dichloromethane extract	GC-MS	0.40%	10.1002/ffj.1148
Euphorbia heterophylla	Ivory coast	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.5% (aerial plant parts)	https://dx.doi.org/ 10.1002/ffj.3624
Euphorbia hirta	Ivory coast	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.4% (aerial plant parts)	https://dx.doi.org/ 10.1002/ffj.3624

Euphorbia rigida	Greece	Dichloromethane extract	GC-MS	0.70%	10.1002/ffj.1148
Ferulago campestris (Apiaceae)	Italy	Hydrodistillation in a Clevenger-type apparatus for 4 h	GC-MS GC-FID	1.6 ±0.14% (Flowers) 5.1 ±0.52% (Leaves)	10.1002/ffj.1941
Ferulago campestris (Besser) Grecescu	Italy	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS, GC-FID	0.6-0.7%	10.1002/ffj.2010
Foeniculum vulgare Mill (Fennel)	China	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.07%	https://dx.doi.org/10.1016/j.jchromb.2017.07.053
Galeopsis pubescens	Italy	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS, GC-FID	0.80%	10.1002/ffj.1307
Galeopsis tetrahit	Italy	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS, GC-FID	0.30%	10.1002/ffj.1307
Garcinia atroviridis Griff. Ex T. Anders (Clusiaceae)	Malaysia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	10.70%	10.1016/j.jchromb.2006.11.043
Garcinia huillensis Welw. ex. Oliv.	Zimbabwe	Hydrodistillation using a Clevenger-type apparatus for 1.5 h	GC-MS	10.1-23%	10.1002/ffj.1420
Geniosporum rotundifolium Briq	Tanzania	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.53%	10.4314/tjpr.v15i1.15
Gnaphlium affine	China	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3.22%	https://dx.doi.org/10.1016/j.fct.2011.03.014
Grammosciadium macrodon Boiss	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1%	10.4314/tjpr.v15i2.26
Grammosciadium platycarpum	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Nil	10.4314/tjpr.v15i2.26
Guatteria juruensis	Brazil	Hydrodistillation for 4 h, using a Clevenger-type apparatus	GC-MS	Nil	10.1002/ffj.1500
Guatteria Microcalyx,	Brazil	Hydrodistillation for 4 h, using a Clevenger-type apparatus	GC-MS	0.10%	10.1002/ffj.1500
Guatteria Poeppigiana	Brazil	Hydrodistillation for 4 h, using a Clevenger-type apparatus	GC-MS	Trace	10.1002/ffj.1500
Gundelia. tournefortii (EOGT)	Zarka, Jordan	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	2.10%	10.4314/tjpr.v15i10.17
Gynura bicolor DC (Asteraceae - plants and shoots	Japan	solvent-assisted flavour evaporation (SAFE) of solvent extracts	GC-MS	9.6% (plants), 11.6% (regenerates), 5.6% (cultured shoots)	10.1002/ffj.1938
Gynura bicolor DC (Asteraceae)- roots	Japan	Roots immersed in freshly distilled diethyl ether	GC-MS	8.1% (Field grown roots), 12.3% (cultured)	10.1002/ffj.2016
Haumaniastrum villosum (Bene) AJ Paton (Lamiaceae)	Tanzania	Hydrodistillation using a Clevenger-type apparatus	GC-MS	5.63%	10.4314/tjpr.v15i1.15
Hedyosmum angustifolium	Bolivia	A Clevenger-type glass hydrodistillation apparatus	GC-MS	0.20%	10.1002/ffj.1146
Helichrysum faradifani Sc. Ell.	Madagascar	Commercial	GC-MS	1.40%	10.1002/ffj.1531
Helichrysum kraussii Sch. Bip	South Africa	Steam distillation	GC-MS	9.80%	10.1002/ffj.1152

		using a Clevenger-type apparatus for 3 h			
Helichrysum rugulosum Less	South Africa	Steam distillation using a Clevenger-type apparatus for 3 h	GC-MS	Nil	10.1002/ffj.1152
Heterothalamus alienus (Spreng.) Kuntze	Argentina	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	1.6-2.1%	10.1002/ffj.1747
Hexachlamys edulis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	8.00%	10.1002/ffj.1385
Hexachlamys hamiltonii	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	2.50%	10.1002/ffj.1385
Hexachlamys humilis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	2.70%	10.1002/ffj.1385
Hexachlamys itatiaiensis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	5.80%	10.1002/ffj.1385
Homalomena sagittifolia Jungh.	Malaysia	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	3.9% (leaves), 0.2% (rhizomes)	10.1002/ffj.1714
Hortia oreadica	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.59%	10.1016/ j.bjp.2015.08.008
Hoslundia opposita Vahl	Zimbabwe	Hydrodistillation using a Clevenger-type apparatus for 1.5 - 2 h	GC-MS	0.2-7.6%	10.1002/ffj.1402
	Ivory coast	Hydrodistillation using a Clevenger-type apparatus	GC-MS	5.70%	10.1002/ffj.1715
Humulus lupulus L.	Brazil (Chinook variety)	Hydrodistillation using a Clevenger-type apparatus	GC-MS	31.50% (90 mins distillation); 32.63% (180 mins distillation); 34.62% (300 mins distillation)	https://doi.org/ 10.1007/s00284-023-03359-0
	Germany	Supercritical fluid carbon dioxide extraction	GC-MS	6.72%	10.1021/jf402496t
	Japan	Stir bar−sorptive extraction (SBSE) method	GC-MS	0.73%	10.1021/jf050072f
	Poland (Marynka and Magnum varieties)	Headspace extraction at 40oC for 20 mins	GC-MS	0.0032-0.0169mg/L	https://doi.org/ 10.3390%2Fmolecules27227910
	Portugal	Headspace solid-phase microextraction	GC-MS	16.6 ± 0.8%	10.1002/ jssc.201200244
Hymenocrater incanus Bunge	Iran	Hydrodistillation using a Clevenger-type apparatus for 3.5 h,	GC-MS	0.60%	10.1002/ffj.983
Hypericum brasiliense	Brazil	Hydrodistillation for 3 h	GC-MS	12.74%	10.1002/ffj.1319
Hypericum olympicum L	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.50%	10.1002/ffj.1521
Hypericum perforatum L.	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	Trace	10.1002/ffj.1521
Hypericum tetrapterum Fries	Greece	Hydrodistillation using a Clevenger-	GC-MS, GC-FID	Trace	10.1002/ffj.1521

		type apparatus			
Hyptis carpinifolia.	Brazil	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	0.2-0.9%	10.1016/ j.bjp.2016.05.011
Hyptis pectinata	Brazil	Hydrodistillation for 140 mins in Clevenger style apparatus	GC-MS	Room temperature storage 2.79% to 2.21% at 1 year. Freezer 2.79% to 2.43% at 1 year.	10.1590/1983-084X/ 15_177
Hyptis suaveolens (Lamiaceae)	Italy	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	0.90%	10.1007/s00436-011-2730-8
Illicium verum	Greece	Steam distillation for 4 h in a modified Clevenger distillation apparatus	GC-MS	Nil	10.1007/s00436-012-3097-1
Inula graveolens	France	Commercial	GC-MS	0.20%	10.1002/ffj.1304
Isolona campanulata Engler & Diels	Côte-d'Ivoire	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS, GC-FID	10.40%	10.1002/ffj.1555
Isolona dewevrei	Cote d'Ivoire	Hydrodistillation for 3h clevenger type apparatus	GC-MS	1.20%	Https://dx.doi.org/ 10.1002/ffj.3612 Kambire
J. drupacea Labill.	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.80%	10.1007/s00436-011-2706-8
J. foetidissima Willd.	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Nil	10.1007/s00436-011-2706-8
J. oxycedrus L. ssp. macrocarpa	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Nil	10.1007/s00436-011-2706-8
J. oxycedrus L. ssp. oxycedrus	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.44%	10.1007/s00436-011-2706-8
J. phoenicea L	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.01%	10.1007/s00436-011-2706-8
Juglans regia L	Czech Republic	Solvent extraction with a shaker	GC-MS	≈ 9%	10.1002/ jssc.200700371
	Algeria	Microwave-assisted hydrodistillation for 1 h, Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS, GC-FID	15.64% (Microwave-assisted hydrodistillation for 1 h), 8.08% (Hydrodistillation using a Clevenger-type apparatus for 3 h)	10.1002/ hlca.201200359
Juniperus communis	Croatia and Bosnia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.40% (Fruit)	Https://dx.doi.org/ 10.1002/ffj.3602
Juniperus communis var. saxatilis	Belgrade	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3.08%	10.1016/ j.fct.2017.12.044

Juniperus communisl. Ssp. Nana	Italy	Supercritical CO2 extractions and hydrodistillation: performed in a circulatory Clevenger-type apparatus for 5 h	GC-MS	Leaves: 0.8-2.7%; Berries: 1.5-2.0%; Wood: 2.8-4.9%	10.1002/ffj.1549
Juniperus deltoides	Croatia and Bosnia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.90% (Leaf)	Https://dx.doi.org/10.1002/ffj.3602
Juniperus drupacea	Greece	Steam distillation using a Clevenger apparatus for 3 h	GC-MS	0.99%	10.1007/s00436-016-4959-8
Juniperus macrocarpa	Croatia and Bosnia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.30% (Leaf)	Https://dx.doi.org/10.1002/ffj.3602
Juniperus oxycedrus,	Croatia and Bosnia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.3% (Leaf)	Https://dx.doi.org/10.1002/ffj.3602
Juniperus oxycedrusssp.oxycedrus	France	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	0.8-1.2% (Berry oil), 0.2% (Leaf oil)	10.1002/ffj.1579
Juniperus phoenica	Greece	Steam distillation using a Clevenger apparatus for 3 h	GC-MS	1.15%	10.1007/s00436-016-4959-9
Juniperus- J. communis L. ssp. hemisphaerica	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.44%	10.1007/s00436-011-2706-8
Kielmeyera rugosa	Brazil	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	3 - 5%	10.1002/ffj.1751
Lantana camara L.	Congo	Hydrodistillation using a Clevenger-type apparatus	GC-MS	10.6% (leaves)	10.1002/ffj.1553
	Nigeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS	19.5% (leaves)	10.1002/ffj.1206
	India	Hydrodistillation in a conventional Clevenger-type apparatus for 4 h.	GC-MS	2.4% (Fruit); 0.7% (stem); 2.7% (leaves); 2.7% (flowers)	10.1002/ffj.1197
	Iran	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	6-10.8%	10.1002/ffj.1048
	NR	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	5.2% (Pink flowers) 2.6% (yellow flowers)	10.1002/ffj.1239
	Brazil	Hydrodistillation using n-pentane and a Chrompak distillation apparatus	GC-MS	1.2-10.7% (leaves and thin branches), 9.5% (flowers)	10.1002/(SICI)1099-1026(199907/08)14:4<208::AID-FFJ811>3.0.CO;2-F
	South China	Hydrodistillation using a Clevenger-type apparatus	GC-MS	9.31%	10.1002/ffj.1292
	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.3-6.9%	https://doi.org/10.1002/cbdv.202100145
Lantana salvifolia Jacq. (Verbenaceae)	Congo	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.5% (leaves)	10.1002/ffj.1553
Lavandula angustifolia	Italy	Commercial	GC-MS, GC-FID	0.41%	10.1080/13693780400004810

Lavandula angustifolia x hybrida cultivars	Italy	Hydrodistillation with a Clevenger apparatus for 2h	GC-MS	0.06% (L. Angustifolia) Hybrida cultivars: 0.25% (Ordinario) Nil (Alardii) 0.11% (Abrialis) 0.13% (R.C) 0.07% (Super Z)	10.1002/ffj.3145
Lepechinia conferta	Venezuela	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.70%	10.1002/ffj.1550
Lepidium sativum	Greece	Steam distillation for 4 h in a modified Clevenger distillation apparatus	GC-MS	Nil	10.1007/s00436-012-3097-1
Leptospermum amboinense	Australia	Hydrodistillation with cohobation	GC-MS	0.4 - 0.9%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum brachyandrum (F. Muell.) Druce	Australia	Steam distillation with cohobation	GC-MS	9-18%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum emarginatum	Australia	Hydrodistillation with cohobation	GC-MS	0.10%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum grandiflorum	Australia	Hydrodistillation with cohobation	GC-MS	0.6 - 0.8%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum liversidgei	Australia	Hydrodistillation with cohobation	GC-MS	0.40%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum luehmannii F. M. Bailey	Australia	Steam distillation with cohobation	GC-MS	3-5%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum madidum A. R. Bean subsp. madidum	Australia	Steam distillation with cohobation	GC-MS	4-11%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum madidum ssp.sativum	Australia	Hydrodistillation with incubation	GC-MS	2.30%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum morrisonii	Australia	Hydrodistillation with incubation	GC-MS	0.60%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum oreophilum	Australia	Hydrodistillation with incubation	GC-MS	1 - 2%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum pallidum A. R. Bean	Australia	Steam distillation with cohobation	GC-MS	0.30%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum petersonii	Australia	Hydrodistillation with cohobation	GC-MS	0.40%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum polygalifolium ssp. 'wallum'	Australia	Hydrodistillation with incubation	GC-MS	7-11%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp. howese	Australia	Hydrodistillation with incubation	GC-MS	0.20%	10.1002/1099-1026(200007/08)15:4<

					271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp. montanum	Australia	Hydrodistillation with incubation	GC-MS	1.00%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp. polygalifolium	Australia	Hydrodistillation with incubation	GC-MS	0.10%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp. Transmontanum	Australia	Hydrodistillation with incubation	GC-MS	1.20%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp. tropicum	Australia	Hydrodistillation with incubation	GC-MS	nil	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum polygalifolium ssp.cismontanum	Australia	Hydrodistillation with incubation	GC-MS	0.8-9%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum purpurascens Joy Thomps	Australia	Steam distillation with cohobation	GC-MS	0.30%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum rotundifolium	Australia	Hydrodistillation with cohobation	GC-MS	0.20%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Leptospermum sp. (Mt Maroon A.R. Bean 6665)	Australia	Hydrodistillation with incubation	GC-MS	44-51%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum speciosum Schauer	Australia	Steam distillation with cohobation	GC-MS	0.10%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum variabile	Australia	Hydrodistillation with incubation	GC-MS	11-22%	10.1002/1099-1026(200007/08)15:4<271::AID-FFJ910>3.0.CO;2-E
Leptospermum whitei Cheel	Australia	Steam distillation with cohobation	GC-MS	0.50%	10.1002/(SICI)1099-1026(199801/02)13:1<19::AID-FFJ679>3.0.CO;2-9
Leptospermum wooroonooran	Australia	Hydrodistillation with cohobation	GC-MS	11 - 20%	10.1002/1099-1026(200009/10)15:5<342::AID-FFJ924>3.0.CO;2-V
Libanotis W. D. Koch var. Armeniacum Bordz.	Iran	Hydrodistillation using a Clevenger-type apparatus for 3 h.	GC-MS	Nil	10.1002/ffj.1722
Licuala Grandis	Thailand	Dynamic headspace extraction	GC-MS	1.60%	10.1002/ffj.1797
Licuala lauterbachii	Thailand	Dynamic headspace extraction	GC-MS	Nil	10.1002/ffj.1797
Licuala Mattanensis,	Thailand	Dynamic headspace extraction	GC-MS	0.10%	10.1002/ffj.1797
Licuala spinosa	Thailand	Dynamic headspace extraction	GC-MS	Nil	10.1002/ffj.1797
Lippia adoensis	Nigeria	Hydrodistillation for 4 h	GC-MS	0.60%	10.1002/ffj.1234
Lippia alba	Guatemala	Hydrodistillation using a Clevenger-type apparatus for 1.5 h	GC-MS	1.10%	10.1002/ffj.1309

Lippia alba (Mill.) N.E. Brown (Verbenaceae)	Colombia	Microwave-assisted hydrodistillation method	Chromatog GC-MS	Nil	10.1590/S1415-47572011005000030
Lippia gracilis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 140 mins	GC-MS	0.47% (LGRA-106), 1% (LGRA-108), 0.38% (LGRA-109), 0.49% (LGRA-201)	10.1016/ j.vetpar.2012.12.046
Lippia Graveolens	NR	Water distillation in a Clevenger-type apparatus	GC-MS	1.60%	10.1007/s00436-010-1800-7
Lippia integrifolia	Argentina	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	1.3-4.5%	10.1002/ffj.1736
Lippia javanica (Burm. f.)	Tanzania	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.40%	https://dx.doi.org/ 10.1002/ffj.3625
Liquidambar orientalis Mill.	Turkey	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	0%	10.1002/ffj.1370
Liquidambar Styraciflua,	Honduras	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	1.10%	10.1002/ffj.1370
Mandarina Bavaria hops	Germany	Headspace-solidphase microextraction	GC-MS	25 ± 9%	10.1021/ acs.jafc.9b06139 Machado
Mangifera indica (mango fruit)	Colombia	Simultaneous Distillation-extraction	GC-MS	0.90%	10.1002/ffj.1812
Pinus pinaster Ait	France	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.20%	10.1002/ffj.1865
Marsh white grapefruit	Florida	Fruit extract dissolved in 0.1 ml of methylene chloride.	Capillary gas chromatography	0.03%	10.1021/jf981064k
Melaleuca alternifolia	Italy	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	Nil	10.1007/s00436-013-3651-5
Melaleuca quinquenervia (Cav.) S. T. Blake	New Caledonia	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.21%	10.1002/ffj.1649
Melodorum fruticosum flowers	Thailand	modified Likens–Nickerson apparatus	GC-MS	0.18%	10.1016/ j.fct.2010.07.002
Mentha avensis (corn mint)	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	<0.05%	10.1002/ffj.1417
Mentha suaveolens ssp. insularis	France	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.10%	10.1002/ffj.1863
Mentha x piperita L.	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Nil	10.1002/ffj.1333
Meum athamanticum (L.) Jacq.,	Germany	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.10%	10.1016/ j.jchromb.2006.11.046
Microglossa pyrifolia	Côte d'Ivoire	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	27.1–36.4% (leaves), 1.4% (buds)	10.1002/ffj.1743
Miocene amber	India	Dichloromethane: methanol by ultrasonication for 20 mins	GC-MS	NR	10.1038/s41598-017-09385-w

Monanthotaxis diclina(Sprague)	Congo (Zaire)	Steam distilled 3h	Filtered over anyhdrous sodium sulphate	0.2% (Root) 6.9% (Fruit)	10.1002/%28SICI%291099-1026%28199703%2912:2%3C95::AID-FFJ611%3E3.0.CO;2-Z
Mosla dianthera Maxim	Vietnam	Steam distillation for 1h with distilled water	GC-MS	5.09%	Https://pubmed.ncbi.nlm.nih.gov/10898640/ Kim
Mosla soochowensis	China	Steam distillation	GC-MS	4.04%	10.4314/tjpr.v16i4.23
Murraya exotica	India	Hydro-distillation using the Clevenger X77 type of apparatus for 4 h	GC-MS	0.03%	https://dx.doi.org/10.1007/s00436-015-4370-x
Murraya paniculata (L.) Jack	Nigeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS	5.10%	10.1002/ffj.1365
	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.80%	10.1002/ffj.1804
Myrciaria tenella	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.3-5.3%	10.3390/molecules27072234
Myriactis nepalensis Less.	China	Hydrodistillation using a Clevenger-type apparatus for 3.5 h	GC-MS	3.2%	10.3390/molecules27144631
Myrrhinium atropurpureum	Brazil	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	1.42%	10.1111/and.13074
Myrtus communis	Tunisia	Steam distillation	GC-MS	0.25% (Flowering stage)	10.1002/ffj.1453
	Morocco	Continuous distillation	GC-MS	0.30%	10.1002/ffj.1651
Nectandra Barbellata	Brazil	Hydrodistillation in a Clevenger apparatus for 3h	Thin layer chromatography then GCMS	3.79%	10.1016/j.bjp.2017.11.008
Nepeta crassifolia Boiss	Iran	Hydrodistillation using a Clevenger-type apparatus for 6 h	GC-MS	nil	10.1002/ffj.1199
Nepeta glomerulosa Boiss. subsp. carmanica	Iran	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	3.20%	10.1002/(SICI)1099-1026(199909/10)14:5<265::AID-FFJ822>3.0.CO;2-A
Nepeta italica L	Turkey	Homogenized plant item was extracted with 250 ml extraction solvent (methanol) for 24 hours.	GC-MS	nil	10.1002/ffj.3636
Nepeta macrosiphon Boiss.	Iran	Steam-distilled for 5 h using a Clevenger-type apparatus .	GC-MS	0.60%	10.1002/ffj.1287
Nigella arvensis L	Czech Republic	Hydrodistillation in a Clevenger-type apparatus for 3 h	GC-MS	trace	10.1002/ffj.1713
Ocimum basilicum	Saudi	Hydrodistillation	GC-MS	0.93%	10.1007/s11011-017-

	Arabia	using a Clevenger-type apparatus for 4 h			0173-3
	West Lafayette, USA	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	11.50%	10.1002/ffj.1513
	Brazil	Steam distillation for 1 h	GC-MS	Nil	10.1002/ffj.1134
Ocimum basilicum L. (sweet basil)	Germany; Mesten	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.52% German 0.67% Mesten	https://doi.org/10.1021/jf0725629
Ocimum basilicum. var. minimum	Brazil	Steam distillation for 1 h	GC-MS	nil	10.1002/ffj.1134
Ocimum basilicum. var. purpurascens Benth	Brazil	Steam distillation for 1 h	GC-MS	1.60%	10.1002/ffj.1134
Ocimum gratissimum	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.20%	10.1007/s00436-017-5662-0
Ocimum sanctum	Misisippi	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.99%	https://doi.org/10.1021/jf0725629
Ocotea elegans	Brazil	Hydrodistillation in a Clevenger apparatus for 3h	Thin layer chromatography then GCMS	Nil	10.1016/j.bjp.2017.11.008
Ocotea Indecora	Brazil	Hydrodistillation in a Clevenger apparatus for 3h	Thin layer chromatography then GCMS	Nil	10.1016/j.bjp.2017.11.008
Oplopanax horridus	Canada	Steam distillation	GC-MS	0.2% (Stem) 0.1% (Root)	10.1002/ffj.1716
Origanum compactum	Morocco	Hydrodistillation	GC-MS	0.22%	10.1016/j.mrgentox.2007.01.011
Origanum ehrenbergii Boiss	Lebanon	Cyclohexane, dichlormethane, ethyl acetate and methanol extracts	GC-MS	"low presence" (Cyclohexane extract), "low presence" (Dichloromethane extract), nil (Ethyl acetate extract), nil (Methanol extract)	10.1002/ffj.3646
Origanum glandulosum Desf	Algeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.30%	10.1002/ffj.1738
Origanum majorana	Iran	Leaves were placed in a sealed glass vial for 30 min at room temperature with a nanofiber sheet above it to collect volatiles. The nanofiber sheet was folded and inserted inside a 5 ml glass vial for solvent desorption using 2 ml of hexane for 10 min and the organic extract was concentrated by a gentle flow of nitrogen up to 0.5 ml.	GC-MS	0.17%	10.1002/jssc.201301355
	Lithuania	Hydrodistillation using a Clevenger-	GC-MS	0.2% (Hydrodistillation	10.1002/ffj.1478

		type apparatus, Simultaneous distillation–solvent extraction		using a Clevenger-type apparatus) , 0.1% (Simultaneous distillation–solvent extraction)	
	Germany	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.20%	10.1002/ffj.1077
Origanum Virens		Water distillation in a Clevenger-type apparatus	GC-MS	0.10%	10.1007/s00436-010-1800-7
Origanum vulgare	USA	Commercial	GC-MS, GC-FID	0.51%	10.1016/j.biopha.2018.10.028
Ostericum grosseserratum	China	Hydrodistillation using a Clevenger-type apparatus for 6 h	GC-MS	0.70%	10.4314/tjpr.v12i1.16
Otacanthus azureus	French Guyana	Hydrodistillation	GC-MS	10.56%	10.1111/jam.12377
Panax ginseng	Korea	Dichloromethane extract	GC-MS	5.5 - 6.4%	10.1021/jf301835v
Panax notoginseng	Korea	Dichloromethane extract	GC-MS	3.70%	10.1021/jf301835v
Panax quinquefolius	Korea	Dichloromethane extract	GC-MS	nil	10.1021/jf301835v
Pangasius (Pangasianodon hypophthalmus)	Bangladesh	dynamic headspace sampling method (terpenes in the flesh)	GC-MS	8.3 ng/g	10.1021/acs.jafc.7b00497
Parthenium hysterophorus	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.5%	10.3390/molecules27227961
Pectis elongata Kunth	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	0.10%	10.1002/ffj.1546
Pelargonium Geraniaceae	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.50%	10.1002/%28SICI%291099-1026%28200003/04%2915:2%3C105::AID-FFJ875%3E3.0.CO;2-G
Perovskia abrotanoides Karel.	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	6.40%	10.1002/ffj.1508
Perovskia atriplicifolia Benth	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	8.0% (arial plant parts)	10.1021/jf0341619
	Iran	Steam distillation	GC-MS	6.39% (flower), 9.36% (leaf), 9.55% (stem)	10.1002/ffj.988
Perovskia atriplicifolia Benth	Pakistan	Hydro-distillation in a Clevenger-type apparatus for 5 h.	GC-MS	5.70%	10.1002/%28SICI%291099-1026%28199901/02%2914:1%3C38::AID-FFJ778%3E3.0.CO;2-8
Petroselinum crispum	Mauritius	NR	GC-MS	nil	10.1002/cbdv.202000921

Phellodendron amurenserupr.	Poland	Hydrodistillation	GC-MS	0.60% (Unripe fruit) 0.40% (Ripe fruit) 0.40% (Air-dried ripe fruit) 0.40% (Leaves) 0.30% (Flowers)	10.1002/ffj.1349 Lis
Phlomis chorassanica Bunge. (Lamiaceae)	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3.3% (aerial plant parts)	10.1002/ffj.1338
Phlomis cretica	Greece	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	2.20%	10.1002/ffj.1717
Phlomis ferruginea Ten.	Italy	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	4.10%	10.1002/ffj.1740
Phlomis olivieri Benth	Iran	Steam distillation	GC-MS	2.70%	10.1002/ffj.1156
Phlomis persica Boiss	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.4% (aerial plant parts)	10.1002/ffj.1338
Phoenix dactylifera L.	Saudi Arabia	Hydrodistillation using a Clevenger-type apparatus for 4-5 h	GC-MS, GC-FID	0.40%	10.1016/ j.actatropica.2013.08.003
Pilocarpus pennatifolius Lemmaire (Rutaceae)	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.1% (leaves)	10.1002/ffj.1306
Pimpinella anisum	Greece	Steam distillation for 4 h in a modified Clevenger distillation apparatus	GC-MS	Nil	10.1007/s00436-012-3097-1 KIMBARIS
	Poland	Hydrodistillation using a Clevenger-type apparatus	GC-MS, counter-current chromatography	0.19%	10.1002/ jssc.201300407
Pinus attenuata Lemmon	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3.50%	10.1002/ffj.990
Pinus heldreichii Christ	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.00%	10.1002/ffj.990
Pinus mugo Turra	Serbia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.40%	10.1002/ffj.1390
Pinus peuce Griseb	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.90%	10.1002/ffj.990
Pinus pinaster Ait.	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	14.80%	10.1002/ffj.990
	France	Hydrodistillation using a Clevenger-type apparatus	GC-MS	2.20%	10.1002/ffj.1865
Pinus radiata D. Don	Greece	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Trace <0.05%	10.1002/ffj.990
Piper aduncum	Panama, Bolivia	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.9% (Panama), no trace (Bolivia)	10.1002/ffj.1369
	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	4.1% (leaves)	https://dx.doi.org/ 10.1590/S0102-695X2013000500005
Piper cernuum		Computer aided detection (SISTEMAT system)	13C NMR spectroscopy	1.74%	10.1016/S0003-2670(01)01204-1

Piper cubeba	India	NR	GC-MS	0.19%	10.1007/s00436-011-2695-7
Piper fridrichsthalii	Panama, Costa Rica	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.3% (Costa Rica), 1.4% (Panama)	10.1002/ffj.1181
Piper gaudichaudianum	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	16.50%	https://dx.doi.org/10.1016/j.fct.2009.06.035
	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	16.50%	10.1016/j.fct.2013.03.013
Piper nigrum		Extraction with methanol and extraction with water reflux distillation	Capillary electrochromatography	0.70%	10.1002/jssc.200600456
Piper pseudoliindenii	Costa RIca	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	7.00%	10.1002/ffj.1181
Piper regnellii		Computer aided detection (SISTEMAT system)	13C NMR spectroscopy	0.40%	10.1016/S0003-2670(01)01204-1
Pittosporum senacia subsp. senacia	Mauritius	NR	GC-MS	0.30%	10.1002/cbdv.202000921
Pittosporum tobira	Lisbon, Portugal	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.3% (leaves), 1.0% (fruit, capsules), 0.2% (flower)	10.1002/ffj.1798
Platycladus orientalis L.		Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.40%	10.1111/j.1365-2184.2008.00561.x
	China	Soaked in sodium chloride solution and distilled by electric heating	Headspace solid-phase microextraction combined with GC-MS	7.34–14.41%	https://doi.org/10.3390/molecules28052043
Plectranthus amboinicus (Lour.) Spreng	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	9.67%	https://dx.doi.org/10.1007/s00436-010-1996-6
Plectranthus barbatus	India	Hydro-distillation of in a Clevenger apparatus for 8 h	GC-MS	1.62%	10.1007/s00436-015-4809-0
Plectranthus grandis	Brazil	Steam distillation using a Clevenger apparatus for 2 h	GC-MS	2.5 – 3.8%	10.1002/ffj.1730
Plectranthus ornatus	Brazil	Steam distillation using a Clevenger apparatus for 2 h	GC-MS	2.9 – 3.3%	10.1002/ffj.1730
Plinia Cauliflora	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	nil	10.1002/ffj.1638
Plinia cordifolia	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	1.80%	10.1002/ffj.1638
Plinia Edulis	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	2.60%	10.1002/ffj.1638
Plinia Trunciflora	Brazil	Hydrodistillation using a Clevenger-type apparatus for 5 h	GC-MS, GC-FID	0.90%	10.1002/ffj.1638
Polygonum hydropiper L	Singapore	Dynamic headspace	GC-MS	1.3% (Dynamic	10.1002/ffj.1363

		sampling, simultaneous distillation and extraction and liquid–liquid extraction with dichloromethane (D		headspace sampling) 0.9% (Liquid extraction)	
Prangos asperula Boiss.		Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.30%	10.1111/j.1365-2184.2008.00561.x
Psidium acutangulum,	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	4.90%	10.1002/ffj.1219
Psidium guajava	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	1.10%	10.1002/ffj.1219
Psidium guineense	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	nil	10.1002/ffj.1219
Psidium striatulum	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	2.80%	10.1002/ffj.1219
Pterodon pubescensm	Turkey	Stainless steel tank with mechanical stirring using dichloromethane as liquid extractor	GC-MS, GC-FID	0.64%	10.1016/ j.biopha.2019.108693
Pulicaria mauritanica Coss. (Asteraceae)	Algeria	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID, C-NMR	GC-MS trace <0.05% C-NMR 0.4%	https://doi.org/ 10.1002/ffj.3223
Ravensara aromatica Sonnerat	Madagascar	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	0 - 0.1%	10.1002/ffj.1735
Rhabdosciadium microcalycinum Hand.-Mazz	Turkey	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	0.20%	10.1002/ffj.1639
Rhabdosciadium oligocarpum (Post ex Boiss.) Hedge et Lamond	Turkey	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	0.20%	10.1002/ffj.1639
Rosmarinus officinalis var. troglodytorum	Tunisia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.38%	10.1016/ j.fct.2010.08.010
Rosmarinus officinalis var. typicus	Tunisia	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.78%	
Rosmarinus officinalis	Algeria	Steam Distillation	GC-MS	0.4% (Steam Distillation), Nil (Hydrodistillation using a Clevenger-type apparatus)	10.1002/ffj.1226
	Messina, Sicily	MAHD- milestone dry dist microwave reactor.	GC-MS, GC-FID	0.78%	10.1002/ jssc.200400037
Saccharomyces cerevisiae (with engineered mevalonate pathway	Germany	Ethyl acetate extration	GC-MS	12.5-22.5mg/L	https://doi.org/ 10.1016/ j.ymben.2022.10.004
Saccocalyx satureioides Coss et Durieu	Algeria	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	0.30%	10.1002/ffj.1661
Salvia amplexicaulis	Lithuania	Simultaneous distillation/extraction	GC-MS, GC-FID	6.9 mg/kg	10.1002/ffj.3389

		in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2			
Salvia argentea L.	Serbia	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	10.70%	10.1002/ffj.989
Salvia austriaca	Lithuania	simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	1.3 mg/kg	10.1002/ffj.3389
Salvia brachyodon	Belgrade	Hydrodistillation using a Clevenger-type apparatus	GC-MS	10.80%	10.1002/ffj.1132
Salvia canariensis	Gran Canaria	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.1% (After flowering) 1.6% (Before) 0.8% (During)	Https://onlinelibrary.wiley.com/doi/10.1002/ffj.1504
Salvia chionantha Boiss	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS	4.82%	10.1016/j.jchromb.2006.11.044
Salvia dumetorum	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	1.6 mg/kg	10.1002/ffj.3389
Salvia forsskaolei	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	23.5 mg/kg	10.1002/ffj.3389
Salvia fruticosa	Israel	Steam distillation for 1 h	GC-MS	3.90%	10.1021/jf901162f
Salvia glutinosa	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	30.2 mg/kg	10.1002/ffj.3389
Salvia Glutinosa L	Serbia	Hydrodistillation	GC-MS	4.20%	10.1002/ffj.1291
Salvia guaranitica	Brazil	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	1.02-3.32%	10.1002/ffj.1817
Salvia nemorosa	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	2.3 mg/kg	10.1002/ffj.3389
Salvia Nemorosa	Serbia	Hydrodistillation	GC-MS	1.90%	10.1002/ffj.1291
Salvia officinalis	Tunisia (Sfax town)	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS, GC-FID	4.60%	10.1016/j.biopha.2018.09.108
	Tunisia	Hydrodistillation	GC-MS	8.94%	10.1021/jf901877x

	(Kelibia)	using a Clevenger-type apparatus for 3 h			
	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	2057.9 mg/kg	10.1002/ffj.3389
	Hungary	Steam distillation using a Clevenger-type apparatus for 3 h	GC-MS, GC-FID	15.1% (Salvia officinalis L), 33.24% (Salvia officinalis cv. 'Purpurascens), 23.38% (Salvia officinalis cv. 'Tricolor'), 14.55% (Salvia officinalis cv. 'Kew Gold'), 8.52% (Salvia judaica Boiss)	10.1021/jf9005092
	Tunisa	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	4.37%	10.1016/ j.fct.2009.08.005
	Serbia, Montenegro	Hydrodistillation using n-hexane	GC-MS, GC-FID	3.35-12.49%	10.1002/ffj.1065
	Portugal	Macerated in 10ml of pentane	GC-MS	7.46% (leaves), 5.23% (stem), 4.31% (flowers)	https://doi.org/ 10.1021/jf001102b
	Portugal	Hydrodistillation using a Clevenger-type apparatus	GC-MS	6.80%	https://doi.org/ 10.1021/jf020945v
Salvia officinalis × Salvia fruticosa, cv. Newe Ya'ar No. 4	Israel	Hydrodistillation using a Clevenger-type apparatus for 1.5 h	GC-MS	5.19% (Stem), 3.17% (Mature leaves), 4.96% (Young leaves), 6.59% (leaf primordia in main branch), 6.34% (leaf primordia in secondary branches), 6.34% (leaf primordia in secondary branches), 3.42% (upper shoots), 3.86% (lower shoots)	10.1021/jf9901587
Salvia pratensis	Lithuania	Simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	11.6 mg/kg	10.1002/ffj.3389
Salvia przewalskiimaxim.	Tibet	Hydrodistillation for 3 h, using a Clevenger-type apparatus	GC-MS	0.21% (Leaves) 3.64% (Flowers)	10.1002/ffj.1607
Salvia reflexa Hornem	Serbia	Hydrodistillation	GC-MS	Nil	10.1002/ffj.1291
Salvia santoliniifolia	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	7.80%	10.1002/%28SICI%291099-1026%28199903/04%2914:2%3C77::AID-FFJ726%3E3.0.CO;2-9
Salvia sclarea	Greece	Hydrodistillation	GC-MS	<0.05%	10.1021/jf020422n

		using a Clevenger-type apparatus			
	Lithuania	simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	Nil	10.1002/ffj.3389
	Uruguay	Steam distillation for 2 h at normal atmospheric pressure	GC-MS	0.40%	10.1002/ffj.1282
Salvia verticillata	Lithuania	simultaneous distillation/extraction in a Likens-Nickerson apparatus and supercritical fluid extraction with CO2	GC-MS, GC-FID	11.6 mg/kg	10.1002/ffj.3389
	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Nil	10.1002/%28SICI%291099-1026%28199903/04%2914:2%3C77::AID-FFJ726%3E3.0.CO;2-9
Sambucus ebulus	Iran	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	Nil (control), 5.41% (treated with indole-3-acetic acid), 1.85% (treated with naphthalene acetic acid)	10.4314/tjpr.v13i4.13
Santolina chamaecyparissus	India	Hydrodistillation	Triplicate distillations	0.6% (Jammu), 2.3% (Srinagar) 2.5% (Tissue culture raised foliage)	10.1002/ffj.1440
Satureja spicigera C. Koch Boiss.	Iran	Hydrodistilled using a Clevenger-type apparatus for 4 h	Dried over anhydrous sodium sulphate	0.2%.	10.1002/ffj.1642
Satureja. Macrantha C. A. Mey	Iran	Hydrodistilled using a Clevenger-type apparatus for 4 h	Dried over anhydrous sodium sulphate	0.2%.	10.1002/ffj.1642
Scaligeria tripartita	Turkey	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.2% (fruit)	10.1016/ j.jchromb.2006.11.041
Schinus mole	Sardinia	CO2 based extraction; Hydrodistilled using a Clevenger-type apparatus for 4 h	GC-MS	0.4% (CO2 based extraction) 0.2% (hydrodistilled)	10.1002/ffj.1350
Schinus polygamus (Cav.) Cabrera f. Chubutensis	Argentina	Hydrodistilled in a Clevenger-type apparatus	GC-MS	0.80%	Https:// onlinelibrary.wiley.com /doi/10.1002/ffj.1270
Scleria hirtella	Brazil	Hydrodistillation for 4 h, using a Clevenger apparatus.	GC-MS	0.10%	10.1002/ffj.1593
Senecio nutans Sch.-Bip.	Peru	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	Nil	10.1002/ffj.1204
Senecio selloi Spreng. DC.	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.6% (aerial plant parts)	10.1590/S1516-05722013000400005

Sephredium brevifolium	Skardu Baltistan, Pakistan	Hydrodistillation using a Clevenger-type apparatus	GC-MS	3%	10.1016/ j.bjp.2019.04.013
Seseli andronakii Woron.	Athens	Hydrodistillation using a Clevenger-type apparatus	GC-MS	no trace <0.1%	10.1002/ffj.1572
Seseli petraeum M. Bieb.	Athens	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.00%	10.1002/ffj.1572
Seseli tortuosum	Italy	Hydrodistillation using a Clevenger-type apparatus for 2 h	GC-MS	0.30%	10.1002/ffj.1154
Silphium perfoliatum	Poland	Steam distillation method in Deryng's apparatus	GC-MS	1.4% (Leaf oil) 0.6% (Influorescence oil) 2.9% (Rhizome oil)	10.1002/ffj.1418
Solanum tuberosum	Bonin, Japan	Hydrodistillation using a Clevenger-type apparatus	GC-MS	41.2 ng/cm2	10.1021/jf040437g
Sphaeranthus africans	Vietnam	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.4%	10.3390/ molecules27227961
Spreng (Verbenaceae)	Tanzania	Hydrodistillation using a Clevenger-type apparatus	GC-MS	1.40%	https://dx.doi.org/ 10.1002/ffj.3625
Spruce Picea orientalis (L.) Link	Belgrade	Boiled in water then mixed with petrolium benzine for distillation	GC-MS	1.02% (Wood extract), 0.18% (needle extract)	10.1002/ffj.1196
Stachys alpina ssp. Dinarica	Bosnia and Herzegovina	Hydrodistillation in a Clevenger-type apparatus	GC-MS	2.80%	10.1002/ffj.1684
Stachys sylvatica L.	Italy	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.1% (inflorescence), 0.6% (leaves)	10.1002/ffj.1308
Styrax japonicus	China	Static headspace solid-phase microextraction	GC-MS	1.57%	10.1002/ffj.3654
Syzygium aromaticum	Madagascar	Clove oil purchased	GC-MS	0.5% (Madagascar) 1.80% (Indian)	10.1080/10611860500422958
	India	NR	GC-MS	3.78%	10.1016/ j.jbiosc.2016.09.011
	Iran	NR	GC-MS	1.73%	10.1002/ffj.3595
Syzygium aromaticum (Eugenia caryophyllata)	Italy	Commercial and steam distilled clove oil	HPLC	1.10 ±0.02 g/100ml	10.1002/ jssc.200600023
Syzygium coriaceum	Mauritius	NR	GC-MS	0.70%	10.1002/ cbdv.202000921
Syzygium jambos (L.) Alston, (Myrtaceae)- rose apple	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS	7.07% (leaves)	https://dx.doi.org/ 10.1590/S0102-695X2013005000035
Syzygium samarangense	Mauritius	NR	GC-MS	0.30%	10.1002/ cbdv.202000921
Syzygium zeylanicum (Myrtaceae)	India	Hydrodistillation 8h Clevenger apparatus, dried with anhydrous naso4	GC-MS	37.80%	10.1007/s00436-016-5025-2
Taiwania cryptomerioides	Taiwan	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	0.30%	10.1002/ffj.1685
Tetrataenium lasiopetalum	Iran	Hydrodistillation using a Clevenger-	GC-MS, GC-FID	0.4% (aerial plant parts)	10.1002/ffj.1767

		type apparatus			
Teucrium Scordium	Sicily	Hydrodistillation 3h	Dried over anhydrous sodium sulphate	0.50%	Https:// www.tandfonline.com/ doi/full/ 10.1080/14786419.20 19.1709193
Teucrium fruticans	Sicily and Malta	Hydrodistillation 3h	Dried over anhydrous sodium sulphate	5.6% (Sicily) 3.3%, (Malta)	Https:// www.tandfonline.com/ doi/full/ 10.1080/14786419.20 19.1709193
Teucrium libanitis	Spain	Hydrodistillation using a Clevenger-type apparatus for 2.5 h	GC-MS	Nil	10.1002/ffj.1256
Teucrium royleanum	Pakistan	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.60%	10.1002/ffj.1774
Teucrium siculum	Sicily	Hydrodistillation 3h	Dried over anhydrous sodium sulphate	8.60%	Https:// www.tandfonline.com/ doi/full/ 10.1080/14786419.20 19.1709193
Teucrium turredanum	Spain	Hydrodistillation using a Clevenger-type apparatus for 2.5 h	GC-MS	4.7–10.1%	10.1002/ffj.1256
Thymbra Capitata	NR	Water distillation in a Clevenger-type apparatus	GC-MS	0.10%	10.1007/s00436-010-1800-7
Thymbra spicata L	Turkey	Homogenized plant item was extracted with 250 ml extraction solvent (methanol) for 24 hours.	GC-MS	nil	10.1002/ffj.3636
Thymus cilicicus	Turkey	Homogenized plant item was extracted with 250 ml extraction solvent (methanol) for 24 hours.	GC-MS	0.10%	10.1002/ffj.3636
Thymus citriodorus	Italy	Steam distillation	GC-MS	nil	10.1016/ j.resmic.2016.11.004
Thymus vulgaris	Italy	Steam distillation	GC-MS	0.10%	10.1016/ j.resmic.2016.11.004
Thymus Zygis sylvestris		Water distillation in a Clevenger-type apparatus	GC-MS	Trace	10.1007/s00436-010-1800-7
Tilapia (Oreochromis niloticus)	Bangladesh	Dynamic headspace sampling method	GC-MS	115 ng/g	10.1021/ acs.jafc.7b00497
Triumfetta rhomboideajacq.	Burkina-Faso	Hydrodistillation with a Clevenger-type apparatus for 2h	GC-MS	4.90%	10.1002/ffj.1511 Mevy
Turnera diffusa Willd. var.afrodisiaca(Ward) Urb.	Brazil	Hydrodistillation using a Clevenger-type apparatus for 4 h	GC-MS	0.20%	10.1002/ffj.1155
Turnera subulata Sm.	Brazil	Hydrodistillation using a Clevenger-type apparatus for 3 h	GC-MS	1.30%	10.1590/1983-084X/ 13_011

Unonopsis guatterioides	French Guyana	Steam distilled 3h	Filtered over anyhdrous sodium sulphate	2.5% (Root) 6.3% (Fruit)	10.1002/%28SICI%291099-1026%28199703%2912:2%3C95::AID-FFJ611%3E3.0.CO;2-Z
Valeriana officinalis	United States	3 h of hydrodistillation, using a Clevenger type distillation apparatus	GC-MS	0.68% (Select cultivar) 8.46% (Anthose cultivar)	10.1021/jf0353990
Varronia curassavica	Brazil	Hydrodistillation using a Clevenger-type apparatus	GC-MS, GC-FID	1.36% (Plant subject to 20% light-full sun), 1.24% (Plant subject to 50% light-full sun), 1.14% (Plant subject to 70% light-full sun), 1.58% (Plant subject to 100% light-full sun)	10.1016/j.bjp.2014.10.005
Vernonia brasiliana (L.) Druce	Brazil	Hydrodistillation	GC-MS	8.85%	10.1016/j.biopha.2020.111025
Washington navel–type oranges	Turkey	Peel oil extracted by simple distillation	GC-MS	0.11%	10.1002/ffj.3576
Xylopia rubescens Oliv.	Côte d'Ivoire	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.80%	10.1002/ffj.3155
Ylang-ylang	Comoro Islands	NR	GC-MS, GC-FID	20.9 mg/ml	https://dx.doi.org/10.1002/ffj.3625
	Madagascar	NR	GC-MS, GC-FID	39.9 mg/ml	https://dx.doi.org/10.1002/ffj.3625
Zanthoxylum avicennae (Lam.) DC. (Rutaceae)	China	Hydrodistillation using a modified Clevenger-type apparatus for 6 h	GC-MS	0.07%	10.4314/tjpr.v13i3.13
Zanthoxylum bungeanum	China	Molecularly imprinted solid-phase extraction	GC-MS	1.11%	10.1002/jssc.201701014
Zanthoxylum rhetsa seeds	India	Hydrodistillation using a Clevenger-type apparatus	GC-MS	Trace <0.1%	10.1002/ffj.1598
Zataria multiflora	Iran	Commercial	GC-MS	0.13%	10.1016/j.ijbiomac.2018.12.085
Zataria multiflora Boiss.	Iran	Hydrodistillation using a Clevenger-type apparatus	GC-MS	0.19%	10.1016/j.fct.2010.03.025
Zingiber nimmonii	India	Hydro-distillation in a Clevenger apparatus for 8 h	GC-MS	19.60%	10.1007/s00436-016-4920-x Govindarajan
Zingiber zerumbet	Malaysia	Root dried at 60°C for 24 h. Dried root underwent Soxhlet extraction.	HPLC	60-15,800 µg/g (Plant grown in a variety of growth regulators and elicitors)	10.3390/molecules27154744
Ziziphora clinopodioides	Turkey	Homogenized plant item was extracted with 250 ml extraction solvent	GC-MS	nil	10.1002/ffj.3636

		(methanol) for 24 hours.			

GC-FID – gas chromatography – flame ionisation detection; GC-MS – gas chromatography – mass spectrometry; HPLC – high-performance liquid chromatography; NMR – nuclear magnetic resonance; NR – not recorded