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Mediterranean Blue Flowers with a Scent of Cannabis

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Abstract

Background

The aromatic herb Plectranthus neochilus, known for its cannabis-like scent and widespread use in folk medicine, has become the focus of a study on the essential oils derived from its flowers and leaves. GC-MS analysis revealed a unique composition: the flower oil is predominantly composed of 2-methyl-1-butene, with a concentration exceeding 87%.

Results

While this finding is unusual, it is known that 2-methyl-1-butene can result from the thermal decompositionof-1, 1-dimethylcyclopropane. Additionally, from a microbiological perspective, it may also be produced through the bacterial reduction of isoprene by a combination of Comamonas sp. and Acetobacterium wieringae. This intriguing phenomenon warrants further investigation, though an initial discussion is provided in this study. Analysis of the leaf oil revealed that α-thujene and α-pinene are the primary constituents, together making up more than 75% of the composition.

Conclusion

A detailed study of the Plectranthus genus suggests that this species produces volatile metabolites containing cyclopropane and cyclobutane rings. It is hypothesized that these compounds could be the key biologically active substances in this species—or even within the broader Plectranthus genus. Additionally, the biological activity of the main identified compounds in this aromatic plant is discussed.

Keywords: Plectranthus Neochilus, Volatiles, Cannabis, GC/MS, Flowers and Leaves

Background

Plectranthus neochilus—commonly known as "boldo" or "boldogambá"—is an aromatic herb widely used in folk medicine to treat liver failure and dyspepsia [1]. In South Africa, tea made from P. neochilus is traditionally used for medicinal purposes, including the treatment of digestive disorders, liver ailments, hangovers, and, to a lesser extent, respiratory infections. It is one of several "boldo" species utilized worldwide due to its year-round growth, adaptability, resilience to environmental conditions, tolerance to intense sunlight, and minimal cultivation requirements [2].This species is broadly distributed across sub-Saharan Africa [3].

Extracts from the aerial parts of P. neochilus have demonstrated strong activity against Staphylococcus epidermidis and Mycobacterium smegmatis, while its essential oil has been shown to effectively inhibit Bacillus cereus [4]. Additionally, this plant is well known for its distinct, often unpleasant skunk-like odor. Interestingly, researchers from different regions have noted variations in its scent, which appear to be linked to the specific composition of its monoterpenes, sesquiterpenes, and diterpenes [5]. Several studies have highlighted the bioactivity of P. neochilus extracts, reporting cytotoxic effects against head and neck carcinoma cell lines, as well as antioxidant, anti-hyperlipidemic, and antimicrobial properties [6-10].

Intrigued by the unusual cannabis-like aroma emitted by the flowers of P. neochilus growing in Israel, we decided to investigate the composition of its essential oils derived from both leaves and flowers.

Materials and Methodology

Plant Material

Flowers and leaves of Plectranthus neochilus were used for analyses. The plant material was collected in the center of the city Tel Aviv in April 2019, where is planted as decoration.

Sample Preparation

A quantity of 10 mg of plant material was used for HS.

Instrument

GC/MS [Agilent 7890B GC, Agilent 5977B MSD, PAL 3 (RSI 85)]

Column

Agilent Technologies, Inc., Santa Clara, CA, USA, HP-5MS UI, 30 m × 250 μm, film 0.25 μm.

Standards

Commercially available standards for α-pinene, camphene, β-pinene, myrcene, Δ^3-carene, α-terpinene, p-cymene, limonene, 1,8-cineole, α-ocimene, trans-β-ocimene, γ-terpinene, terpinolene, linalool, isopulegol, geraniol, β-caryophyllene, α-humulene, cis-nerolidol, trans-nerolidol, caryophyllene oxide, guaiol, and α-bisabolol were obtained from Restek (Bellefonte, PA, USA).

Experimental Conditions for Head Space Analysis

The column temperature was initially 35 °C for 5 min, followed by temperature ramping from 35 to 150 °C at 5 °C/min, then to 250 °C at 15 °C/min (inlet: 250 °C; detector: 280 °C; split ratio 5:1;); gas: Helium (flow rate: 1 mL/min). Incubation time: 6 min; Incubation temperature: 80 °C.Analytical method validation—selectivity, specificity, accuracy, precision, linearity, range, limit of detection, limit of quantification, ruggedness, and robustness were performed. They are beyond the scope of this manuscript and will be published elsewhere.

Identification

The content compounds were identified by comparison to standards, retention times, retention indices, and the spectral matching of libraries NIST/EPA/NIH Mass Spectral Library 2017, Wiley Registry of Mass Spectral Data 11th Edition, FFNSC3, ©2015, and Adams Essential Oils Library.

Results

The essential oils extracted from the flowers and leaves of Plectranthus neochilus have been minimally studied, particularly using modern chromatography-mass spectrometry techniques. While the essential oil from the leaves has been previously analyzed—albeit on outdated gas-liquid chromatography equipment—there is no prior research on the composition of the flower oil, making it a subject of great interest [11-13].

Plant Flowers Analysis

A total of 16 volatile components were detected in the essential oil of Plectranthus neochilus flowers, with most identified compounds present in concentrations of less than 1%. However, GC-MS analysis of the flower oil yielded an unexpected result: two main compounds accounted for 95.34% of the composition. Of this, 87.35% was 2-methyl-1-butene, while 7.99% was cis-1,2-dimethylcyclopropane (see Figure. 1 and Table 1).

This unusual composition required further investigation, and an explanation was found. More than 50 years ago, Flowers and Frey studied the thermal behavior of 1,1-dimethylcyclopropane, discovering that it undergoes gas-phase thermal isomerization to form 3-methyl-1-butene, 2-methyl-2-butene, and 2-methyl-1-butene [14,15]. Decades later, Baldwin and Shukla16 demonstrated that this transformation also occurs at 420°C during gas-liquid chromatography (see Figure. 2). Based on these findings, we can infer that the original compound present in the essential oil was likely

1,1-dimethylcyclopropane, making up 87.35% of the composition.

This discovery represents a rare case where a plant's essential oil consists of over 95% terpenes containing a cyclopropane ring. As shown in the chromatogram (Figure. 1), the dominant peak is a single peak for 2-methyl-1-butene, comprising 87.35%—an uncommon occurrence in plant analysis. Notably, 2-methyl-1-butene has an odor described as sweet, wine-like, penetrating, musty, disagreeable, and suffocating. The unique combination of mono-, sesquiterpenes, and diterpenes in the essential oils of P. neochilus flowers and leaves likely contributes to its distinctive aroma.

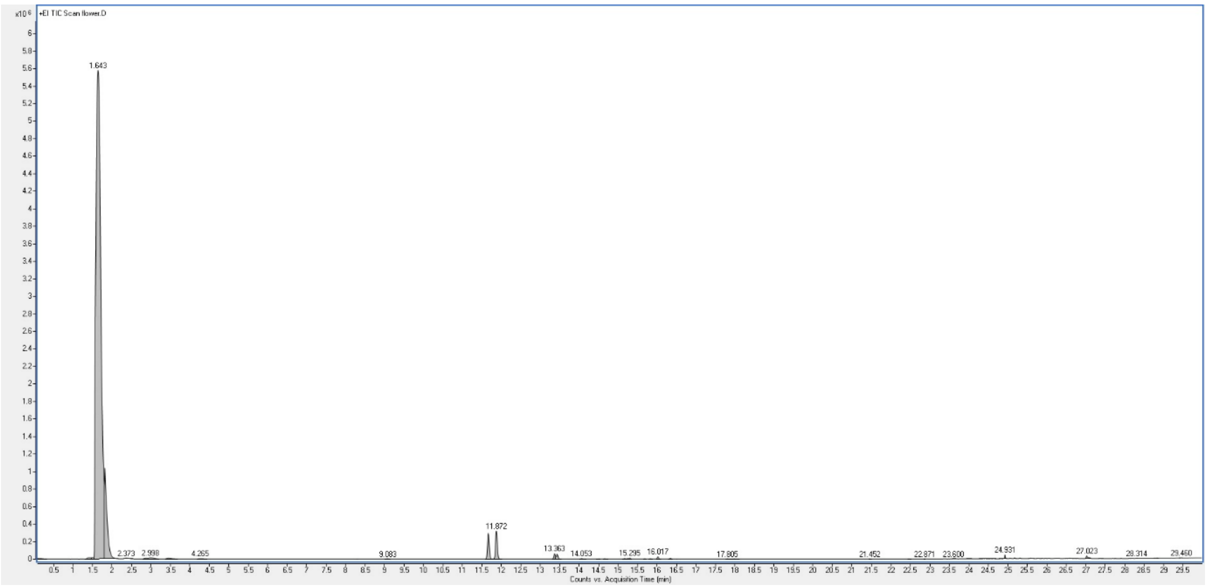

Figure 1: GC-MS Chromatogram of the Analysis of Essential Oil of P. Neochilus Flowers

Peak	RT	%	Compound	RI
1	1.643	87.35	2-methyl-1-butene	488
2	1.820	7.99	cis-1,2-dimethyl-cyclopropane	516
3	2.373	0.10	2-methyl-3-buten-2-ol	614
4	2.870	0.07	3-methyl-butanal	652
5	2.998	0.21	2-methyl-butanal	662
6	11.664	1.58	alpha-thujene	931
7	11.872	1.77	alpha-pinene	937
8	13.363	0.29	sabinene	976
9	13.428	0.29	beta-pinene	980
10	14.654	0.01	delta-3-carene	1011
11	15.167	0.02	p-cymene	1022
12	15.295	0.04	limonene	1030
13	15.680	0.01	cis-beta-ocimene	1035
14	16.017	0.12	trans-beta-ocimene	1037
15	16.337	0.03	gamma-terpinene	1060
16	24.931	0.12	caryophyllene	1419

Table 1: P. Neochilus Plant Flowers - Relative Areas of Identified Compounds to the Main Peak (2-methyl-1-butene area = 100 %) on Chromatogram and Quantitative Content of Some Compounds from Calibration Curves of their Standards

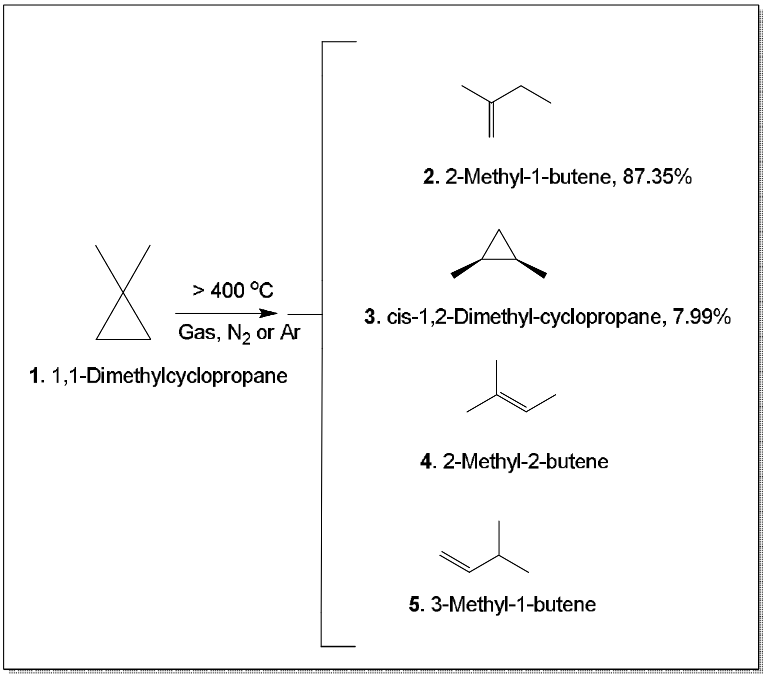

Figure 2: During gas-liquid chromatography, thermal isomerization of 1,1-dimethyl-cyclopropane (1) into several products occurs in the gas phase, the main one being 2-methyl-1-butene (2), and cis-1,2-dimethyl-cyclopropane (3). Volatile 2-Methyl-2-butene (4) and 3-Methyl-1-butene (5) were not detected, although their oxidized products, 2-methyl-butanal, and 3-methyl-butanal, were found.

Products of Bacterial Action

The high abundance of 2-methyl-1-butene (2) may have a microbiological explanation. Isoprene is the most abundant biogenic volatile organic compound in Earth's atmosphere and plays a crucial role in atmospheric chemistry. However, the microbiological processes responsible for isoprene degradation remain poorly understood. Despite this, several aerobic bacteria capable of degrading isoprene have been identified [16-20]. Numerous isoprene-degrading microorganisms have been isolated from soil and the leaves of isoprene-producing trees such as poplar and willow. These include strains from diverse genera such as Alcaligenes, Arthrobacter, Bacillus, Gordonia, Klebsiella, Leifsonia, Loktanella, Micrococcus, Methylobacterium, Mycobacterium, Nocardia, Nocardioides, Pseudomonas, Ramlibacter, Sphingopyxis, Sphingobacterium, Sphingobium, Shinella, Stappia, Pantoea, Rhodococcus, and Variovorax, indicating that a broad range of aerobic bacteria contribute to isoprene turnover [21].

Recently, an acetogenic mixed culture dominated by Acetobacterium species was reported to reduce isoprene to a mixture of three methylbutene isomers—2-methyl-1-butene (2), 2-methyl-2-butene (4), and 3-methyl-1-butene (5)—in the presence of hydrogen and bicarbonate [22,23]. physiological studies revealed that in this mixed culture, the Acetobacterium population utilized isoprene as an electron acceptor to conserve energy under anoxic conditions. However, axenic cultures of Acetobacterium species, including A. woodii DSM 1030, A. malicum DSM 4132, and A. wieringae DSM 1911, did not metabolize isoprene, suggesting that isoprene utilization is not a common trait among Acetobacterium spp [23,24].

A new strain of Acetobacterium wieringae, designated strain Y, demonstrated the ability to reduce isoprene to three methylbutene isomers: 2-methyl-1-butene (>97%), 3-methyl-1-butene (<2%), and 2-methyl-2-butene (<1%) during growth with H_2 and CO_2/HCO_3^- [25]. In the presence of isoprene, 40% less acetate was produced, suggesting that isoprene reduction plays a role in energy conservation for Acetobacterium spp. The bacteria in this enrichment culture, identified as Comamonas sp. and A. wieringae (named MAG ISORED-1 and ISORED-2, respectively), support this hypothesis [24].

In contrast, Acetobacterium wieringae DSM1911 was unable to reduce isoprene,while an enriched culture containing Acetobacterium from a wastewater treatment plant in Sydney, Australia, readily biotransformed isoprene [22,26]. Although not all Acetobacterium spp. are capable of biotransforming isoprene under anoxic conditions, strains from various geographic locations that can perform this transformation suggest that Acetobacterium strains containing reductase genes play a role in the global isoprene cycle.18 It is also possible that other microorganisms are involved in isoprene reduction in enriched cultures, such as members of the Comamonadaceae family [27,28]. Consequently, further studies are needed to explore the diversity of microorganisms capable of biotransforming isoprene under anaerobic conditions. Thus, the high concentration of 2-methyl-1-butene (>87%) in Plectranthus neochilus flowers can likely be attributed to the presence of Acetobacterium wieringae or other active Acetobacterium spp. strains, which reduce isoprene to three methylbutene isomers: 2-methyl-1-butene, 3-methyl-1-butene, and 2-methyl-2-butene. Further research is necessary to fully elucidate this phenomenon.

Plant Leaves Analysis

The essential oils extracted from the leaves of Plectranthus neochilus contained 18 volatile components, with the primary compounds being those containing cyclopropane and cyclobutane rings in their structure. GC-MS analysis of the leaf essential oil revealed that the major components were α-pinene (42.82%), α-thujene (31.9%), and β-pinene (7.29%). As shown in the chromatogram (Fig. 3), the essential oil was predominantly composed of these three compounds, with other volatile components present in minor amounts. The complete analysis of the leaf essential oil is presented in Table 2.

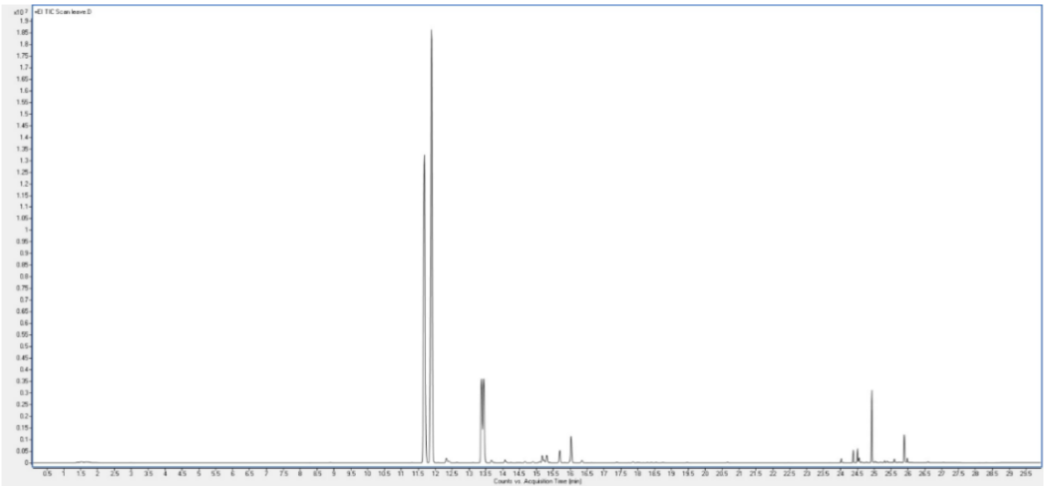

Figure 3: Chromatogram of Essential Oil from P. NeochilusLeaves

Peak	RT	%	Compound	RI
1	11.68	31.90	α-thujene	931
2	11.888	42.82	α-pinene	937
3	12.329	0.44	dehydrosabinene	947
4	13.371	6.91	sabinene	976
5	13.436	7.29	β-pinene	980
6	14.069	0.27	β-myrcene	991
7	15.167	0.59	p-cymene	1022
8	15.303	0.64	limonene	1030
9	15.688	0.90	cis-β-ocimene	1040
10	16.025	2.12	trans-β-ocimene	1050
11	16.346	0.21	γ-terpinene	1060
12	24.017	0.21	α-cubebene	1351
13	24.378	0.55	copaene	1376
14	24.506	0.61	β-bourbonene	1384
15	24.554	0.26	β-copaene	1418
16	24.931	3.04	caryophyllene	1419
17	25.885	1.29	aromadendrene	1440
18	25.981	0.01	β-cadinene	1520

Table 2: P. Neochilus Plant Leaves - Relative Areas of Identified Compounds to the Main Peak (α-pinene area = 100 %) on Chromatogram

Discussion

The essential oils of Plectranthus neochilus flowers and leaves can be hazardous, as their consumption may lead to symptoms such as nausea, vomiting, and diarrhea in humans. Cats and dogs are also at risk, exhibiting signs of gastrointestinal distress. Contact with or ingestion of the essential oil can cause headaches, dizziness, and skin irritation due to its toxicity [29,30]. It is known that the toxic effects of essential oils are primarily determined by their volatile components. These components are typically low-molecular-weight substances, often containing derivatives of sulfur, nitrogen, or phosphorus. However, light hydrocarbons with unusual structures, including cyclic fragments, can also exhibit toxicity [31-34].

We attempted to explain the unusual results observed in the analysis of volatile compounds from Plectranthus neochilus flowers through thermal isomerization in GC-MS analysis or a bacterial process, and we find the latter explanation more plausible. An age-old question that arises when people encounter a scent is: why are odors concentrated in flowers? This concentration of odors is part of a strategy that helps flowering plants reproduce and spread their species. Specific odors assist these flowers in solving a major challenge—attracting pollinators. Flowers that rely on insects, bats, and birds for pollination go a step further by producing floral scents that serve as aromatic signals, effectively "greeting" the right pollinator. Similar to perfumes, floral scents are composed of a variety of volatile chemicals that easily evaporate and disperse in the air. The combination of chemicals, their quantities, and their interactions give each flower its unique scent. These aromas can range from sweet and fruity to musky, or even foul and putrid, depending on the type of pollinator the flower is aiming to attract [35-37].

For example, blooming apple or cherry trees emit a sweet fragrance that draws bees, while the pear tree—closely related to apples and cherries—produces a musky or rotten scent, attracting flies for pollination. The corpse flower, native to the Indonesian rainforest, releases an overpowering odor of decaying flesh to attract flies and beetles for pollination [38,39].In the case of Plectranthus neochilus, the combination of terpenes isolated from its flowers resembles the smell of cannabis (see chemical composition in Table 1). Volatile compounds responsible for off-flavors and odors in P. neochilus flowers have also been detected in other plant and animal samples. For example, off-flavors in tuna oil were identified using supercritical carbon dioxide extraction. GC-MS analysis revealed key volatiles contributing to the off-flavors, including 2-methyl-2-butene (27.7%), 1,1-dimethyl-cyclopropane (2.2%), cyclopropane, 1,1-dimethyl-2-allylcyclopropane (6.2%), and octadiene [40].GC-MS analysis of canned sockeye and pink salmon also revealed the presence of 2-methyl-1-butene (2%) [41].

Volatile compounds in Romanian wines are an underexplored area, but a study found 2-methyl-1-butene (around 3%) in the wines "Tămâioasă românească" and "Busuioacă de Bohotin" from the Pietroasa region in Dealu Mare, vintage 2008 [42].

Thiol derivatives of 2-methyl-1-butene, 3-methyl-1-butene, and 2-methyl-2-butene were identified in roasted sesame seeds. Interestingly, active thiols, with sulfurous, meaty, and/or catty odors reminiscent of blackcurrant, were found in roasted sesame seeds. Among them, 2-methyl-1-propene-1-thiol, (Z)-3-methyl-1-butene-1-thiol, (E)-3-methyl-1-butene-1-thiol, (Z)-2-methyl-1-butene-1-thiol, (E)-2-methyl-1-butene-1-thiol, and 4-mercapto-3-hexanone were previously unknown as food components. Their structures were confirmed by comparing mass spectra, retention indices, and sensory properties with those of synthesized reference compounds. These relatively unstable 1-alkene-1-thiols represent a new class of food flavorings and have been suggested as key contributors to the distinctive, fleeting aroma of freshly ground roasted sesame seeds [43,44].

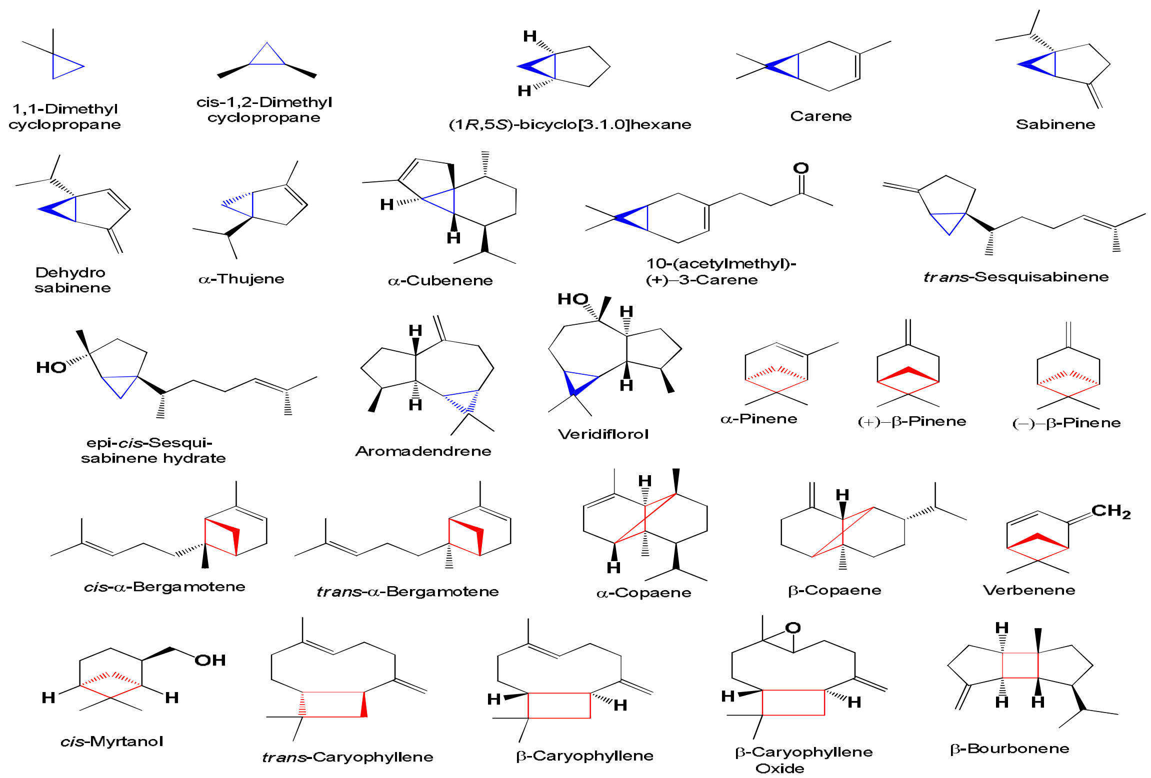

Figure 4: The most common terpenes containing cyclopropane and cyclobutane rings are produced by P. neochilus growing in various countries and on different continents. Environmental conditions, nutrition and other factors can determine the composition of the essential oil of flowers and leaves.Three methylbutenes, 2-methyl-2-butene, as well as two other isomers of this compound (2-methyl-1-butene and 3-methyl-1-butene) inhibit the germination of spores of the pathogenic Mucorale Rhizopus arrhizus NCCPF 710004, although to a lesser extent than 2-methyl-2-butene [45].

Analyzing the composition of terpenes of flowers and leaves, we conclude that P. neochilus is a powerful producer of compounds cyclopropane and cyclobutane rings. Figure 4 shows the most common terpenes containing cyclopropane and cyclobutane rings produced by P. neochilus growing in different countries and on different continents and in different climatic conditions [46,47]. Environmental conditions, mineral nutrition, and other factors can determine the composition of essential oils in flowers and leaves [48,49].

However, the most important question is who synthesizes cyclopropane and cyclobutane metabolites in the genus Plectranthus? It is known that the endophytic bacterium with probiotic properties, Rhodococcus globerulus is an endosymbiont of Plectranthus amboinicus, and colonies of endophytic bacteria such as Bacillus sp., Bacillus megaterium, Bacillus pumilus, Bacillus licheniformis, Micrococcus luteus, and Paenibacillus [50,51]. Three methylbutenes—2-methyl-2-butene, 2-methyl-1-butene, and 3-methyl-1-butene—have been shown to inhibit the germination of spores of the pathogenic Mucorale Rhizopus arrhizus NCCPF 710004, with 2-methyl-2-butene exhibiting the strongest inhibitory effect [45].

Upon analyzing the terpene composition of the flowers and leaves of Plectranthus neochilus, it is evident that this plant is a significant producer of compounds containing cyclopropane and cyclobutane rings. Figure 4 displays the most common terpenes, containing these cyclic structures, produced by P. neochilus across different countries, continents, and climatic conditions [46,47]. Environmental factors such as climate, mineral nutrition, and other variables can influence the composition of essential oils in the flowers and leaves of this species [48,49].

A key question remains: who synthesizes the cyclopropane and cyclobutane metabolites in the genus Plectranthus? It is known that the endophytic bacterium Rhodococcus globerulus, a probiotic endosymbiont of Plectranthus amboinicus, plays a role in this process [50,51]. Additionally, colonies of endophytic bacteria such as Bacillus sp., Bacillus megaterium, Bacillus pumilus, Bacillus licheniformis, Micrococcus luteus, Paenibacillus sp., Pseudomonas sp., and Acinetobacter calcoaceticus have been isolated from Plectranthus tenuiflorus [52]. Fungal endophytes like Chaetomium subglobosum, Alternaria alternata, and Fusarium oxysporum have also been found in P. amboinicus [53]. However, no reliable data have been found regarding endo-bacteria or fungal endophytes isolated from P. neochilus, leaving the question of who the true producers of the bioactive terpenes in this species are still unresolved. It is well known that both endo-bacteria and fungal endophytes make significant contributions to the biosynthesis of biologically active metabolites. This includes lichens, which consist of fungal symbionts or microflora, cyanobacteria, and plants with colonies of endo-bacteria or fungal endophytes [54-56].

Cyclopropane metabolites are quite widespread, with bacteria and fungal endophytes being the main producers [57-59]. This topic, discussed extensively in literature since the late 1990s, remains highly relevant today [60,61]. Compounds containing the cyclopropane ring are known to exhibit a broad range of biological activities, including antibacterial, antimicrobial, and anticancer effects [62,63]. Similarly, natural metabolites with cyclobutane rings form unique molecular structures, with their formation often driven by UV radiation [64,65]. Biological activity studies on compounds containing the cyclobutane group have demonstrated various effects, including anticancer properties [66-68].

The activity of the dominant compounds found in both the flowers and leaves of P. neochilus is also intriguing. The volatile 2-methyl-2-butene is the primary component in the essential oils of the flowers, as detected by GC-MS analysis. While it remains unclear whether this compound is a metabolic product of the plant or a degradation product due to GC-MS analysis conditions, previous studies by Kaur and Singh45 have shown that 2-methyl-2-butene significantly inhibits the emergence and elongation of fungal germ tubes during the germination of Rhizopus arrhizus, making it a potent antifungal compound. This highlights an interesting potential role for endogenous 2-methyl-2-butene.

The other two dominant compounds identified in the leaves were α-pinene (42%) and α-thujene (32%). α-Pinene has been used for centuries to treat respiratory tract infections and plays a key role in the fragrance and flavor industries. In vitro assays have revealed an enantioselective profile of (+)- and (−)-α-pinene, exhibiting antibacterial and insecticidal activity, respectively [69]. Further studies have suggested that α-pinene, a common volatile plant metabolite, may have anti-inflammatory effects on human chondrocytes, showing promise as a potential anti-osteoarthritic agent. Recent data indicates that α-pinene has isomer- and enantiomer-selective anti-inflammatory and anti-catabolic effects, with (+)-α-pinene being the most promising candidate for further investigation [70].

Interestingly, the oil from Cistus libanotis (or Cistus clusii) is widely used in the perfume industry and, more recently, as a raw material in food additives. The volatile fraction of fresh C. libanotis plant material, investigated using headspace solid-phase microextraction coupled with GC-MS, revealed that sabinene (25.3%) and α-thujene (23.8%) were the primary components. These compounds showed significant cytotoxic effects against DLD-1 (colorectal adenocarcinoma) and CAPAN-1 (human pancreatic ductal adenocarcinoma) cell lines, although they were less active against the healthy L929 cell line. This suggests that sabinene and α-thujene, both cyclopropane ring-containing metabolites, may exhibit cytotoxic effects, similar to the effects observed in P. neochilus [71].

Conclusion

In this study, we examined the essential oil composition of Plectranthus neochilus, an aromatic herb with a cannabis-like scent, which is widely used in folk medicine. GC-MS analysis revealed that the primary component of the flower oil is 2-methyl-1-butene, with its concentration exceeding 87%. Literature suggests that 2-methyl-1-butene could result from the thermal decomposition of 1,1-dimethylcyclopropane. However, it may also be a product of bacterial or microbial activity. This intriguing question warrants further investigation. Analysis of the leaf oil indicated that the dominant compounds are α-thujene and α-pinene, with their combined content exceeding 75%. Biological activity data for these dominant compounds are also provided.

Declarations

Ethics Approval and Consent to Participate

The study received institutional ethical committee approval and was conducted as per prescribed norms and regulations according to ICMR. Informed consent was obtained from all participants.

Consent for Publication

Informed consent was obtained from each participant or their guardian prior to surgery. The participants were provided with detailed information regarding the protocols and the use of their specimens for future research purposes.

Competing Interests

The authors declare no competing interests.

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