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ORIGINAL RESEARCH ARTICLE

Analysis of geothermal impact on metabolite compounds of heat-tolerant plant species using clustering and similarity cliff

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ABSTRACT

BACKGROUND AND OBJECTIVES: Geothermal zones, famous for their extreme temperatures and exceptional environmental features, offer captivating locations for exploring. These areas are also known to harbor a variety of medicinal plants, historically used for therapeutic properties. Nevertheless, there is a scarcity of information concerning the precise chemical compounds present in plants originating from geothermal regions, especially in relation to their diversity and potential medicinal uses. This study aims to fill this gap by clustering and analyzing the similarity of samples from medicinal plants in three geothermal areas in Aceh Province, Indonesia.

METHODS: The collection of medicinal plants was conducted in three geothermal regions within Aceh Province, Indonesia, specifically Ie-Brôuk, Ie-Jue, and Ie-Seu'um. Gas chromatography-mass spectroscopy were conducted to determine chemical compounds from medicinal plants. Clustering analysis and similarity cliff were assessed by employing the simplified molecular input line-entry system and fragment-based fingerprint.

FINDINGS: Fifteen different plant species from diverse families—*Apocynaceae, Asteraceae, Euphorbiaceae, Fabaceae, Lamiaceae, Moraceae, Pteridaceae, Rhamnaceae, and Verbenaceae* were found in this study. A total of 343 chemical compounds were discovered in medicinal plants from the geothermal areas through the use of gas chromatography-mass spectroscopy, indicating a significant diversity. Hexadecanoic acid, methyl ester found in each plant of samples as indiciated as core in flower plot. Clustering analysis identified 98 distinct clusters across the three geothermal areas, with a significant concentration of compounds in the fatty acid group, particularly in cluster 2. The analysis of flexophore similarity revealed 23 neighbor counts, signifying a significant abundance of fatty acids as a predominant. These findings suggest that the chemical compositions of plants in geothermal regions are influenced by the unique environmental conditions, leading to distinct chemical fingerprints for each area.

CONCLUSION: This study illustrates that medicinal plants found in geothermal regions contain a broad range of chemical compounds, showcasing a notable diversity in their chemical compositions. The comparison of three geothermal areas in Aceh Province showed that each area has unique characteristics based on the chemical properties of the plants. The findings contribute to a better understanding of the chemical diversity in geothermal regions and emphasize the possibility of uncovering new medicinal compounds. Subsequent studies should increase the sample size and investigate the functional implications of these compounds to maximize their medicinal benefits.

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INTRODUCTION

The process of transferring heat from a heat source to a designated heat sink point on the surface is accomplished through a mechanism known as earth heat transfer (Deon *et al.,* 2015; Idroes *et al.*, 2024a). The thermal activities influenced by anomalous subsurface temperatures and exposed to the earth's surface are referred to geothermal surface manifestations (Xiong *et al.*, 2022). In Indonesia, the geothermal system is characterized by the emergence of liquid at boiling temperature, and it is predominantly found in areas exhibiting vulcanism and active volcanoes along the volcanic trajectory (Hochstein and Sudarman, 2008; Idroes et al., 2024b). One of surface manifestation is presence in Seulawah Agam Mountain in Aceh Province, Indonesia. Seulawah Agam is a Pleistocene–Holocene stratovolcano with a summit height of 1810 meters (m) located in Aceh Province on the northwest tip of Sumatra (Hochstein and Sudarman, 2008). Various manifestations can be observed at the Seulawah Agam geothermal site, such as Ie-Seu'um, Ie-Brôuk, Ie-Jue, and the Van Heutz crater in the northern zone. In the southern zone, the manifestations are identified as Aleu Ie-Seu'um, Alue Ie Masam, Alue PU, and Alue Teungku (Idroes *et al*., 2019; Lala *et al*., 2024). The harsh conditions found in surface geothermal areas, also called solfataras, can provide an environment for plants that have adapted to difficult circumstances (Stout and Al-Niemi, 2002). Numerous studies have demonstrated the possibility of exploring the geothermal manifestation area, encompassing the geochemical content (Idroes, *et al*., 2019), heavy metal concentration (Abubakar *et al*., 2023; Maulydia *et al*., 2024b) and bioactivity prediction (Maulydia *et al*., 2024a, 2023a). The high biodiversity potential of Mount Seulawah Agam provides numerous benefits to the surrounding communities. The Acehnese population shows a strong inclination towards utilizing medicinal plants for complementary treatment, with a significant number of these plants serving as medicinal remedies (Fakri *et al*., 2023). Traditional medicine in the Seulawah Agam comes from 32 different plant species from 21 family (Doudi *et al*., 2021). Studies conducted in a geothermal area of Ie-Seu'um, Aceh Besar district, revealed the variety of secondary metabolites that *Vitex pinnata* L. and *Calotropis gigantea*, suggesting that this plant may have antimicrobial properties (Kemala *et al*., 2022; Nuraskin *et al*., 2020). Throughout history, numerous medicinal plants have been utilized within traditional healthcare practices (Imelda *et al*., 2023; Tallei *et al*., 2023). Currently, there is a scarcity of data regarding chemical compounds derived from medicinal plants found in geothermal regions, particularly within Aceh Province. It is remain unknown information about metabolite compounds underlie the apparent adaptation of heat-tolerant plant species found in three geothermal areas of the north zone of Seulawah Agam. The study examines the medicinal plants around three north zone sites (Ie-Seu'um, Ie-Jue, and Ie-Brôuk) that are close to geothermal manifestations. The aim of the study is to examine and assess the chemical makeup of medicinal plants located in three geothermal regions withinarea, Aceh Province, Indonesia. This study can provide reliable recommendations for the use of these compounds in addition to offering more scientific evidence in favor of the use of medicinal plants in geothermal areas and the realization of their potential as complementary therapies. This study was conducted in Aceh Province, Indonesia, in 2024.

MATERIALS AND METHODS

Sampling points and plant preparation

Three locations of the geothermal manifestations in Seulawah Agam, Aceh Besar District, Aceh Province, Indonesia—Ie-Seu'um, Ie-Jue, and Ie-Brôuk—were chosen for sampling. The location of Ie-Seu'um as mentioned in earlier study (Maulydia *et al*., 2024b). Next, is Ie-Jue, which is located at 5°32'23" north (N) - 95°37'45" east (E) and Ie-Brôuk, which is located at 5°31'048"N-95° 37'017"E (Fig. 1). The plant materials gathered consisted of branches, leaves, and flowers. Prior to extracting the compounds, these components underwent a meticulous washing process to eliminate any impurities. After washing, the materials were air-dried at room temperature until all moisture was gone. Once dried, the plant parts were ground into ground dried leaf samples. This powder was mixed with ethanol at a ratio of 1 part plant material to 10 parts solvent weight: volume (w:v) and left to soak for three days. The active compounds were able to dissolve into the ethanol through this procedure, resulting in the formation of an extract that is ethanolic in nature. Subsequently, the solution was concentrated by eliminating the solvent through the utilization of a rotary evaporator (Buchi Rotavapor®,

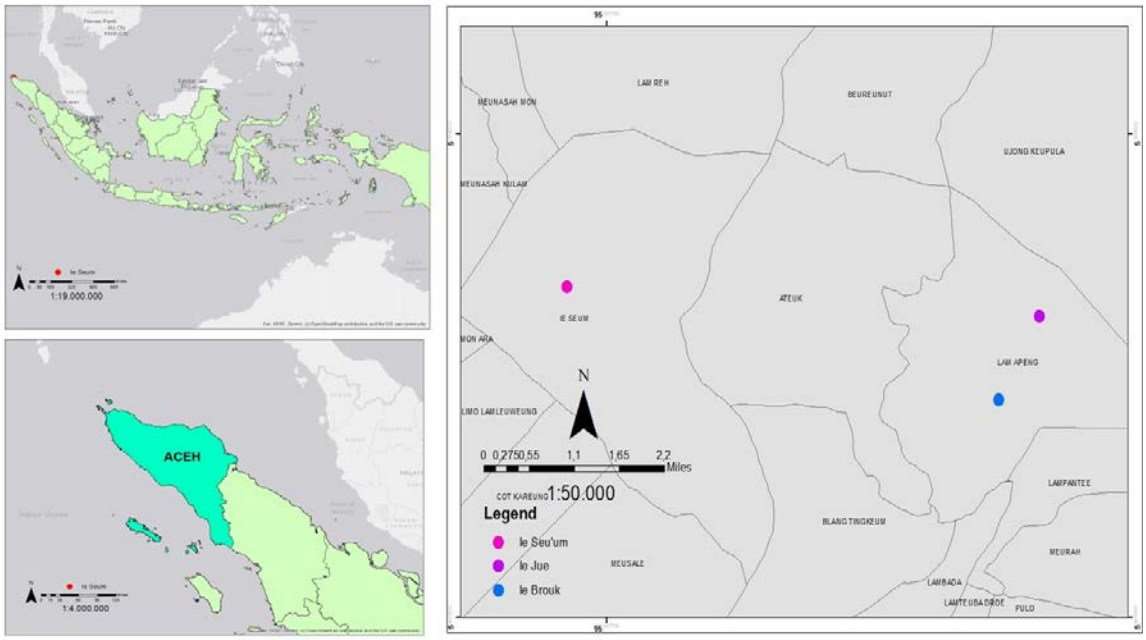


Fig. 1: Sampling point of three geothermal areas (Maulydia *et al*., 2024b)

Switzerland), which effectively evaporated the ethanol under diminished pressure. Finally, the concentrated extract was vacuum filtered to remove any remaining particulate matter, resulting in a pure, dry extract ready for further analysis or use (Rachmawati *et al*., 2022).

Gas chromatography-mass spectroscopy (GC-MS)

The ethanolic extracts of samples were analyzed using GC-MS. A TRACE 1310 GC paired with an iSQ (single quadrupole) 7000 MS, both equipped with a TraceGOLD TG-35MS column (30 m x 0.25 millimeters (mm) x 0.25 micrometers (µm)) from Thermo Fisher Scientific Inc. (United States of America), was utilized for this purpose. The injector's temperature was held steady at 250 degrees Celsius (°C), and the ion source was also maintained at 250°C. The column temperature was set to increase gradually from 60°C to 280°C, with a rate of 10°C per minute. Helium served as the carrier gas at a flow rate of 1 microliters (µL) per minute. Mass spectra acquisition was performed at an energy level of 75 electron volts (eV), scanning a range of 400 to 500 atomic mass units (AMU) (Maulydia *et al.,* 2024b).

Clustering analysis

Datawarrior was employed to perform a clustering analysis. In this section, chemical compounds will be gathered and classified into three domains and fifteen plants utilizing the simplified molecular input line-entry system (SMILES). The cluster algorithm in DataWarrior is based on a bottom-up, hierarchical approach where an observation starts in its own cluster and joins other clusters in pairs as it moves up the hierarchy (Sander *et al*., 2015). The first step involves computing the full similarity matrix triangle for all compounds by utilizing a specific descriptor known as fragment fingerprint (FragFp). The FragFP descriptor has 512 bits, each of which represents a fragment in the dictionary; these bits are set to 1 if the corresponding fragment is present in the molecule at least once, making it possible to encrypt structural information effectively (Liphardt and Sander, 2023). Subsequently, the initial cluster is formed by combining the compounds that exhibit the highest degree of similarity. The updated similarity matrix replaces the similarity values of both compounds with a new set of similarities between the cluster center and each compound. The process of calculating these new values includes averaging the initial similarity values of the two compounds. By joining the most similar compound or cluster pair and combining the corresponding similarity values into a weighted mean

Table 1: Medicinal plants in three geothermal areas

No	Species	Family	Ethnobotanical use	Sources
		Ie-Seu'um		
1	*Tridax procumbens*	*Asteraceae*	Anticancer, immunomodulatory agent	Ingole *et al.*, 2022
2	*Lantana camara*	*Verbenaceae*	Cancers, tumours	Ghisalberti, 2000
3	*Chromolaena odorata*	*Asteraceae*	Wound healing	Dhar *et al.*, 2018
4	*Acrostichum aureum*	*Pteridaceae*	Anti-inflammatory	Wu *et al.*, 2018
5	*Calotropis gigantea*	*Apocynaceae*	Toothache	Ningsih *et al.*, 2023
		Ie-Jue		
1	*Chromolena odorata*	*Asteraceae*	Anti-inflammatory	Dhar *et al.*, 2018
2	*Blumea balsamifera*	*Asteraceae*	Antitumor hepatoprotective	Pang *et al.*, 2014
3	*Ziziphus rufula*	*Rhamnaceae*	Anti-inflammatory	Alsayari and Wahab, 2021
4	*Ocimum Americanum*	*Lamiaceae*	Anti-bacterial activity	Luanda *et al.*, 2023
5	*Tephrosia noctiflora*	*Fabaceae*	Insecticide	Zhang *et al.*, 2020
		Ie-Brôuk		
1	*Chromolena odorata*	*Asteraceae*	Treat skin infections	Dhar *et al.*, 2018
2	*Streblus asper* Lour	*Moraceae*	Stomachache, cancer	Rastogi *et al.*, 2006
3	*Sumbaviopsis albicans*	*Euphorbiaceae*	Glucosidase inhibitor	Elya *et al.*, 2012
4	*Baccaurea pyriformis*	*Phylanthaceae*	Stomachache	Navia *et al.*, 2022
5	*Antidesma montanum* Blume	*Phylanthaceae*	Glucosidase inhibitor	Elya *et al.*, 2012

that is based on the number of cluster members, the process works step by step (Sander *et al*., 2015).

Similarity cliff

The similarity cliff analysis uses flexophore as a representative. Flexophore is an adaptation of the induced fit theory, which explains how ligands and proteins are recognized (Von Korff *et al*., 2008). The graph is fully connected, with every pair of pharmacophore points in the descriptor linked by a distance histogram. The primary component of the flexophore will be presented in the findings. Additionally, a similarity cliff analysis is conducted using Datawarrior.

RESULTS AND DISCUSSION

A compilation of samples influenced by the abundance of flora in the local environment and potentially utilized by the Acehnese population for traditional healing practices. Based on this study, the Ie-Seu'um, Ie-Jue, and Ie-Brôuk manifestation geothermal areas are known to contain a variety of plant family, including *Apocynaceae, Asteraceae, Euphorbiaceae, Fabaceae, Lamiaceae, Moraceae, Pteridaceae, Rhamnaceae,* and *Verbenaceae* (Table 1). There is a limited number of flowering plant species that are able to tolerate elevated temperatures, even in geothermal areas characterized by diverse physical environments (Stout and Al-Niemi, 2002). Asteraceae, which includes *Blumea balsamifera*, *Chromolaena odorata*, and *Tridax procumbens*, is the most widespread family class. The Asteraceae family is recognized as one of the most extensive families of flowering plants, with numerous species that have been extensively used in traditional medicine for their medicinal properties. In a thorough investigation of various geothermal zones in Ie-Brôuk, Ie-Jue, and Ie-Seu'um, *C. odorata* was the heat-tolerant plant that was most frequently found.

Gas chromatography-mass spectroscopy

Identification of metabolite compounds from geothermal area were done using GC-MS analysis. With remove the duplicate compounds, a total 343 compounds from Ie-Brôuk (123 compounds), Ie-Jue (140 compounds), and Ie-Seu'um (100 compounds) is used in this study. It is evident that the GC-MS analysis revealed a higher abundance of metabolite compounds in Ie-Jue compared to Ie-Brôuk and Ie-Seu'um. The Ie-Jue area exhibits characteristic surface heat manifestations, such as steaming ground or warm soil. The hot water source in the area reaches

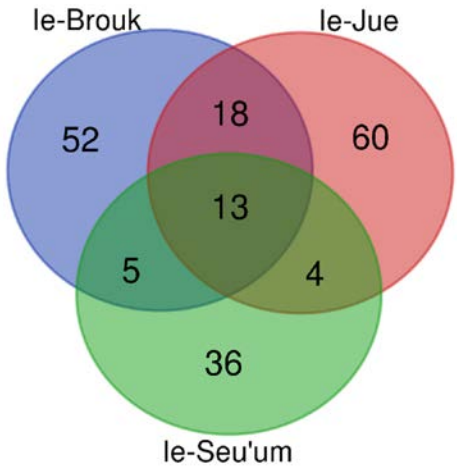


Fig. 2: Venn diagram of number metabolite compounds from three geothermal area

temperatures between 80 and 102°C, with the surrounding air measuring between 40 and 45°C, and a humidity level of 51 percent (%) (Idroes *et al.,* 2019). The ability of plant to be survive in this area is can gain attention cause having uniqe chemical compunds (Maulydia *et al.,* 2023b). Studies have shown that increased temperatures can lead to changes in the metabolism and lipid makeup of plants (Narayanan *et al.,* 2018). The area of Ie-Brôuk exhibits earth heat in the form of hot water discharge. The manifestation area is characterized by a wide array of biodiversity, encompassing various plant species ranging from small plants to towering trees. Research revealed moist soil conditions around the manifestation area, as well as a small water drain. The water temperature surrounding the Ie-Brôuk region varies from 40 to 50°C (Idroes *et al.,* 2019). Ie-Seu'um is the hottest manifestation area. It can be seen that the metabolite compounds less than Ie-Jue and Ie-Brôuk. Using venn diagram (Fig. 2), the overlapping of three geothermal area showed that 13 compounds is found in Ie-Brôuk, Ie-Jue, and Ie-Se'uum. There are *trans*-Z-α-bisabolene epoxide ($C_{15}H_{24}O$), caryophyllene oxide ($C_{15}H_{24}O$), octadecanoic acid ($C_{18}H_{36}O_2$), *cis*-Z-α-bisabolene epoxide ($C_{15}H_{24}O$), Z-(13,14-epoxy)tetradec-11-en-1-ol acetate ($C_{16}H_{28}O_3$), *n*-hexadecanoic acid ($C_{16}H_{32}O_2$), neophytadiene ($C_{20}H_{38}$), methyl 9-*cis* 11-*trans*-octadecadienoate ($C_{19}H_{34}O_2$), 2,4-ditert-butylphenol ($C_{14}H_{22}O$), 3-triflouroacetoxypentadecane ($C_{17}H_{31}F_3O_2$), 2-pentadecanone 6,10,14-trimethyl ($C_{18}H_{36}O$), phytol ($C_{20}H_{40}O$), and hexadecenoic acid, methyl ester ($C_{17}H_{32}O_2$).

The flower plot displays the quantity of individual metabolite compounds found in fifteen different plants (Fig. 3). The plot visually illustrates the distribution and abundance of metabolite compounds present in the samples. The flower plot consist each petal with *A. aureum* (AA: 16 compounds), *A. montanum* (AM: 18 compounds), *B. balsamifera* (BB: 19 compounds), *B. pyriformis* (BP: 15 compounds), *C. gigantea* (CG: 25 compounds), *C. odorata* (CO: 71 compounds), *L. camara* (LA: 21 compounds), *O. americanum* (OA: 27), *S. albicans* (SA: 22 compounds), *S. asper* Lour (SAL: 21 compounds), *T. noctiflora* (TN: 33 compounds), *T. procumbens* (TP: 27 compounds), and *Z. rufula* (ZR: 28 compounds). The number of compounds can be inferred from the color of the petal, and vice versa. *C. odorata* contains a total of 71 compounds, which is a result of the combination of three different areas. As the representative, the compounds from GC-MS analysis can be seeen in Table 2.

According to the floral diagram depicted in Fig. 3, hexadecanoic acid, methyl ester emerges as the central metabolite compound among medicinal plants in three distinct geothermal regions. Several studies showed that from GC-MS analysis, hexadecanoic acid methyl esters abundant in several plants, namely *Imperata cylindrica* (Lalthanpuii and Zarzokimi, 2019) , *Blumea balsamifera* (Maulydia *et al*., 2023b), *Pleurotus ferulae* (Yang *et al*., 2018), and many more. Hexadecanoic acid, methyl ester in *Syzygium aromaticum* proved antibacterial activity against

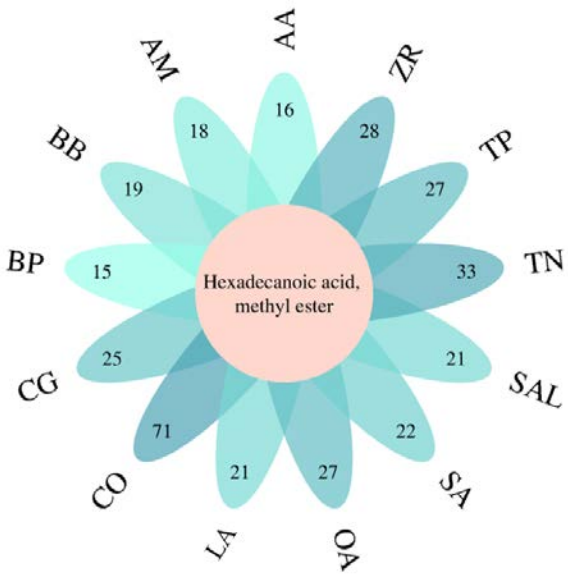


Fig. 3: Flower plot of number of compounds from each plant

Staphylococcus aureus, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (Shaaban *et al*., 2021). Numerous organisms utilize the antimicrobial characteristics of fatty acid methyl ester to protect themselves from bacteria with the membrane of the bacterial cell as primary locations of action. Furthermore, it inhibits the production of cellular energy, the function of enzymes, and ultimately the immediate destruction of bacterial cells (Shaaban *et al*., 2021).

Clustering analysis

A cheminformatics technique known as clustering can be employed to partition a vast compound collection into smaller sets of related compounds. Research on properties of medicinal plants, such as clustering analysis, is crucial, as seen in the essential oil of *Helianthus annuus* L. and the wide-ranging metabolite class (He *et al*., 2022; Lee *et al*., 2021). Based on 343 compounds from Ie-Brôuk (123 compounds), Ie-Jue (140 compounds), and Ie-Seu'um (100 compounds), 98 clusters of metabolites were discovered as represented in violin plot (Fig. 4). Each color indicated different areas with violin blue (Ie-Brôuk), red (Ie-Jue), and green (Ie-Seu'um). The median cluster count identified within cluster 33 containing the compound 4-trifluoroacetoxyhexadecane.

Clusters 1 to 10 exhibit a significant number of composite constituents in correlation with the increase in violin density. The enlarged size of this cluster showed that in cluster one there is four compounds, (1R,4aR,7R,8aR)-7-(2-hydroxypropan-2-yl)-1,4a-dimethyldecahydronaphthalen-1-ol or proximadiol ($C_{15}H_{28}O_2$), (1aR,3aS,7S,7aS,7bR)-1,1,3a,7 tetramethyldecahydro-1hcyclopropa[a]naphthalen-7-ol or 4-epi-maaliol ($C_{15}H_{26}O$), endo-borneol ($C_{10}H_{18}O$), and cedran-diol, (8S,14) ($C_{15}H_{26}O_2$). The correlation class of these compound are that they both fall within the category of bicyclic monoterpenoids. It is interesting to note that these compounds are from the same area, namely Ie-Jue and found in two plants *O. americanum* and *B. balsamifera.* Based on this result, it is know that bicyclic monoterpenoids class is present in higher soil temperature (Fig. 5). Certain plants have been documented to alter their metabolomes when exposed to geothermal heat stress. This alteration leads to an enhanced synthesis of phenolic acids and terpenes, both of which possess medicinal properties. Consequently, this metabolic shift can potentially augment the therapeutic efficacy of medicinal plants (Bartwal *et al.,* 2013). Next, with 59 compounds, cluster two was dominant. Long chain fatty acids ester, such as (E)-9-octadecenoic acid ethyl ester ($C_{20}H_{38}O_2$), butyl

Table 2: Chemical compound from each plant

Plants	Compounds name	Area (%)	SI (%)	RT (min)	Pubchem CID
	Phytol	32.72	98.48	46.89	5280435
T. procumbens	Neophytadiene	4.14	93.35	39.80	10446
	β-acorenol	0.81	98.78	29.11	14105907
	Caryophyllene	10.72	96.96	27.62	5281515
L. camara	Germacrene D	12.35	94.53	29.69	5317570
	Phytol	15.6	99.04	46.89	5280435
	Adamantane, 1-thiocyanatomethyl-	11.13	88.57	35.41	6422917
C. odorata (IS)	Neophytadiene	13.56	86.51	39.79	10446
	Phytol	21.27	93.37	46.88	5280435
	Caryophyllene	1.07	95.57	27.63	5281515
C. gigantea	n-Hexadecanoic acid	30.07	99.56	43.04	985
	Phytol	38.67	99.89	46.95	5280435
	Neophytadiene	1.66	83.51	39.81	10446
A. aureum	n-Hexadecanoic acid	27.73	98.69	42.89	985
	Phytol	18.49	98.70	46.89	5280435
O. americanum	1H-Cycloprop[e]azulen-4-ol, decahydro1,1,4,7-tetramethyl-, [1aR(1aa,4β,4aβ,7a,7aβ,7ba)]-	16.47	99.18	24.24	6432543
	Hexadecanoic acid, methyl ester	8.61	97.31	31.79	8181
	endo-borneol	5.45	96.65	13.71	6552009
	Phytol	17.34	99.88	35.39	5280435
T. noctiflora	(Z)-18-Octadec-9-enolide	10.07	98.49	35.99	6428982
	9,12,15-Octadecatrienoic acid, (Z,Z,Z)-	9.89	98.76	36.09	5280934
	Piroximadiol	41.76	99.16	29.68	165258
B. balsamifera	Hexadecanoic acid, methyl ester	8.54	97.88	31.77	8181
	1-Hexadecen-3-ol, 3,5,11,15-tetramethyl-	6.84	96.48	35.30	551282
	Hexadecanoic acid, methyl ester	16.34	99.89	31.82	8181
Z. rufula	Phytol	9.21	99.56	35.34	5280435
	n-Hexadecanoic acid	7.98	98.65	32.68	985
	Hexadecanoic acid, methyl ester	20.29	99.14	31.79	8181
C. odorata (IJ)	Phytol	11.12	98.25	35.32	5280435
	Stigmasterol	5.93	93.94	52.22	5280794
	Hexadecanoic acid, methyl ester	10.36	99.89	31.86	8181
S. albicans	cis-Vaccenic acid	5.13	99.33	35.85	5282761
	Lupeol	1.79	99.40	54.20	259846
	Hexadecanoic acid, methyl ester	17.25	99.02	31.79	8181
C. odorata (IB)	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-	10.53	98.61	35.10	5319706
	Lupeol	1.54	97.73	54.11	13849
	Phytol	24.50	98.91	35.33	5280435
S. asper	Hexadecanoic acid, methyl ester	10.45	97.08	31.79	8181
	β-Sitosterol	4.82	94.45	52.98	222284
	Hexadecanoic acid, methyl ester	21.07	99.68	31.78	8181
A. montanum	Phytol	7.68	98.69	35.31	5280435
	β-Sitosterol	4.13	96.45	52.95	222284
	Hexadecanoic acid, methyl ester	20.08	97.02	31.80	8181
B. pyriformis	Phytol	12.35	95.06	35.32	5280435
	Ethyl 13-methyl-tetradecanoate	8.15	94.87	36.76	71380066

Description: IB = Ie-Brôuk, IJ = Ie-Jue, IS = Ie-Seu'um, SI = similarity index; RT = retention time; CID = compound identifier

6,9,12-hexadecatrienoate ($C_{20}H_{34}O_2$), hexadecanoic acid, ethyl ester ($C_{18}H_{36}O_2$), hexadecanoic acid, methyl ester ($C_{17}H_{32}O_2$), and methyl 9-*cis*,11-*trans*-octadecadienoate ($C_{19}H_{34}O_2$), are known to be present in this cluster. Elevated temperatures result in an enhanced production of phospholipids (oleate, stearate, and palmitate in the endoplasmic reticulum and plasma membrane), triacylglycerol (containing

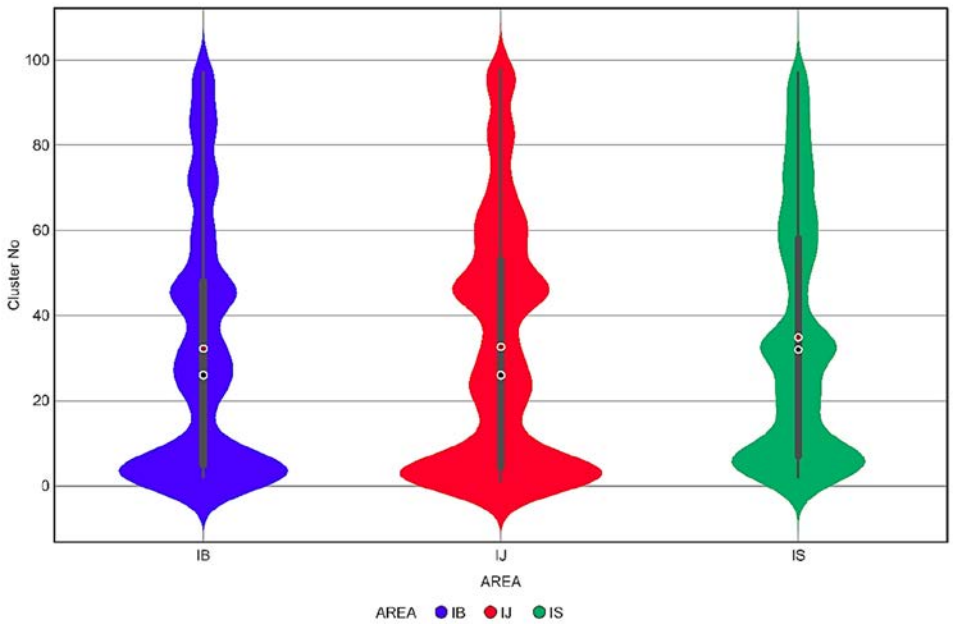


Fig. 4: Violin plot of cluster analysis

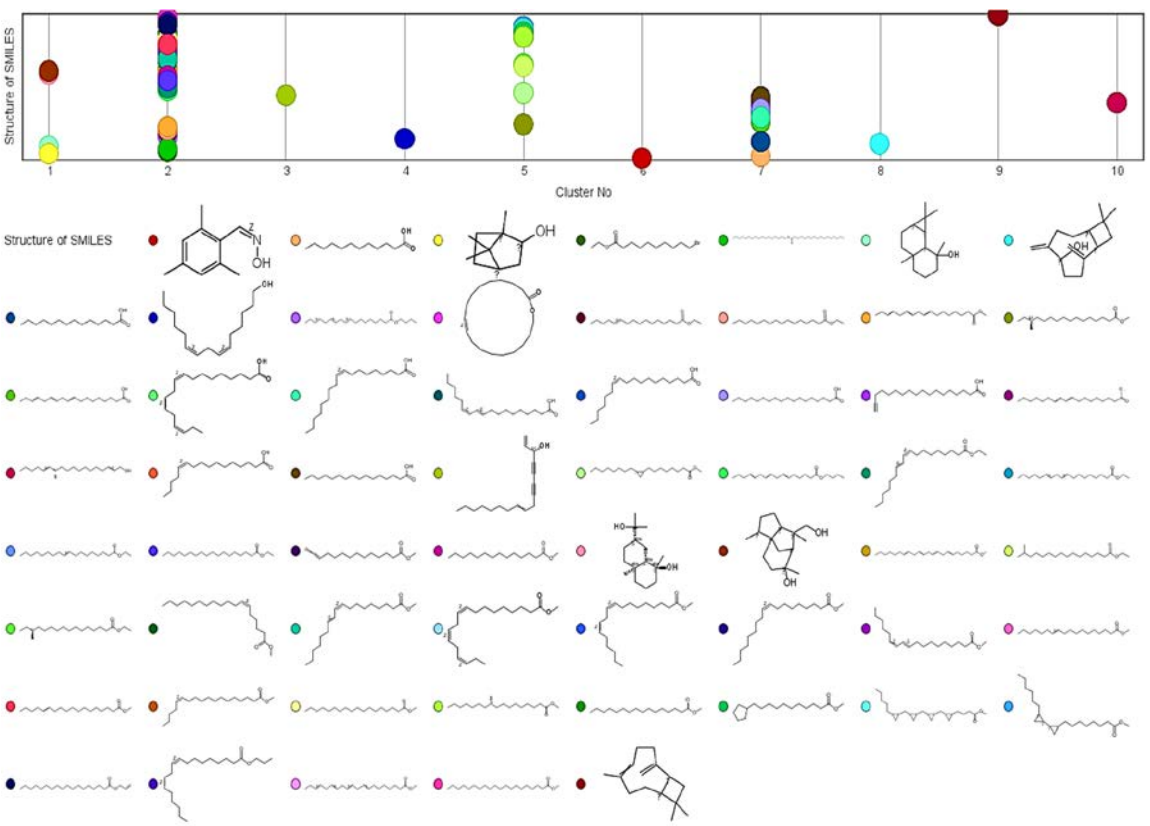


Fig. 5: Structure SMILES based on cluster

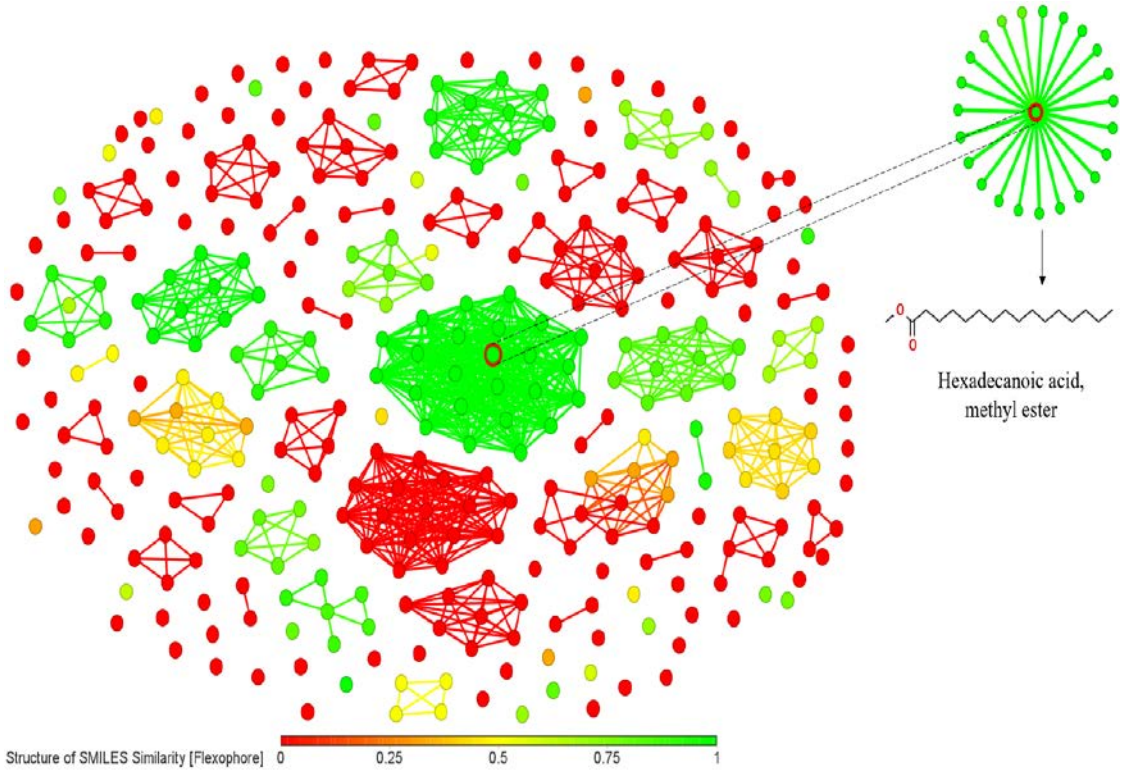


Fig. 6: Similarity cliff of hexadecanoic acid

hexadecatrienoic acid and α-linolenate as lipid droplets), and galactolipids (containing linoleate in chloroplasts) (Higashi and Saito, 2019). Overall, additional cluster data indicates that the fatty acids and their conjugates are *cis*-vaccenic acid ($C_{18}H_{34}O_2$), dodecanoic acid ($C_{12}H_{24}O_2$), and pentadeconoic acid ($C_{15}H_{28}O_3$). The following are the derivatives of lineolate acid: 9,12,15-octadecatrienoic acid, methyl ester, (Z,Z) ($C_{19}H_{32}O_2$), and 10-*trans*-methyl,12-*cis*-octadecadienoate ($C_{19}H_{34}O_2$). In plant lipids, fatty acid double bonds are predominantly *cis* oriented. Plants employ adaptive strategies to decrease the number of double bonds and, thus, the level of unsaturation in response to elevated temperatures. This keeps lipid molecules closely packed within membranes, preserving the ideal fluidity and integrity of the membranes (Narayanan *et al.*, 2018). Stigmastan derivatives, namely, stigma-3,5-diene ($C_{29}H_{48}$) and β-sitosterol ($C_{29}H_{50}O$). The ketone is the megastigmatrienone ($C_{13}H_{18}O$). Sesquiterpenoids are neophytadiene ($C_{20}H_{38}$). Diterpenos are phytol ($C_{20}H_{40}O$). Triterpenoides are lupeol ($C_{30}H_{50}O$). Organosulfonic acid is 3-(N,N dimethyllaurylammonio) propanesulfonate ($C_{17}H_{37}NO_3S$) and gamma butyrolactone is 7.9-di-tert-butyl-1-oxaspiro(4.5) deca-6.9-diene-2,8-dione ($C_{17}H_{24}O_3$) also presence in this study.

Similarity cliff

In the current study, the flexophore descriptor was utilized to examine the traditional viewpoint on the similarity compound and its group. By using Flexophore descriptors and the SMILES notation to quantify and visualize structural similarities, the network graph (Fig. 6) offers a visual representation of the similarities between a group of chemical compounds (Von Korff *et al.*, 2008). The flexophore similarity indexes of chemical compounds with the same shape, pharmacophore, and size will be elevated on a scale of 0 to 1, as indicated by different colors (Kumar *et al.*, 2021). In Fig. 6, compounds with greater resemblance are linked by colored

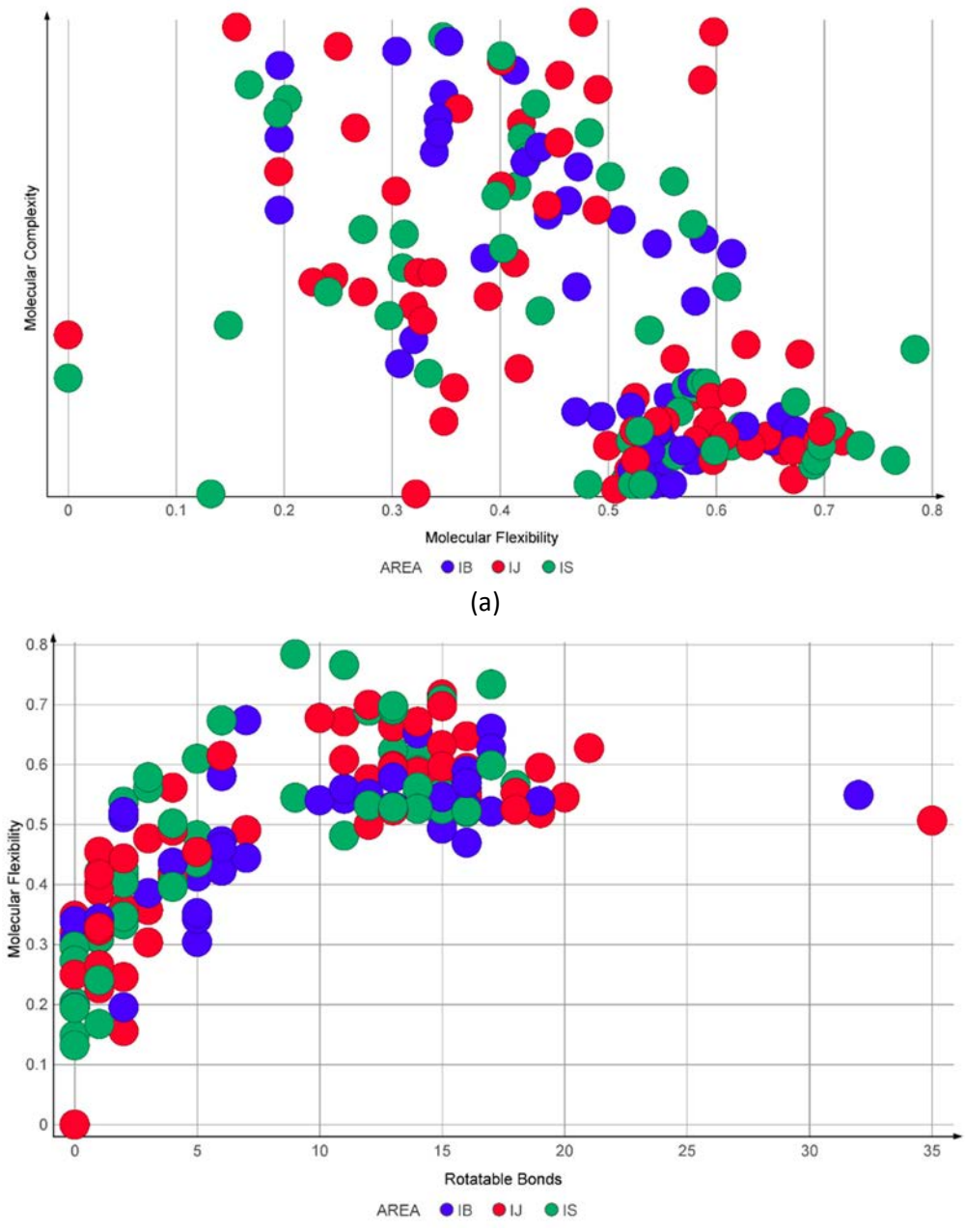


Fig. 7:(a) Comparative of molecular complexity and molecular flexibility, and (b) Molecular flexibility and rotatable bond

lines, illustrating the level of similarity in their pharmacophore structures. Many molecules with similar structures were unable to be grouped together due to the variations in their molecular distances. The flexophore with point one (green notes) is visible in the center of the circle, with a total neighbour count of 23. Fifteen different plants contain a wide range of compounds, with the majority belonging to the class of fatty acids. Fig. 3 depicts hexadecanoic acid, methyl ester, also known as methyl palmitate, belongs to

a cluster that is highly similar, indicating that it has structural relatives in the dataset. This substance falls under the category of fatty acid methyl esters (FAME) and is frequently present in nature, existing in both plants and animals. It serves various purposes and has significant effects on the human body.

To comprehend the behavior and purposes of molecules, particularly within biological and chemical systems, it is essential to have a profound understanding of fundamental concepts such as molecular flexibility and complexity. These concepts serve as the building blocks for unraveling the intricate nature of these systems and their underlying mechanisms. A comprehensive understanding of how molecules behave in different contexts relies heavily on the intricate interplay between their complexity and flexibility. The estimated values of molecular flexibility and molecular complexity for the synthesized molecules offer valuable information about their structural characteristics (Malik *et al*., 2021). Molecular flexibility is the main factors that determine bioavailability, according to Veber (2002), who also identified the function of flexibility as a filter for absorption, distribution, metabolism, and excretion (ADME) properties. This study demonstrated a connection between the flexibility of molecules and the complexity observed in metabolite compounds. Molecules with a flexibility and complexity value of less than 0.5 are thought to be low in both complexity and flexibility (Malik *et al*., 2021). It was observed that three geothermal sites possess a predominant compound characterized by a flexibility range of 0.5 to 0.7, yet with lower complexity. This observation implies that at this point, fatty acids class of compound were found to have low flexibility due to their relatively simplistic structures (Fig. 7a). The investigation of the relationship between rotatable bonds and molecular flexibility has revealed that the number of rotatable bonds has an impact on the overall flexibility of the molecule (Fig. 7b). Molecular flexibility is primarily determined by the presence of single bonds, typically carbon sp3-carbon sp3 (Caron *et al*., 2020). The flexibility of a molecule increases with the number of single bonds due to the 'free' rotation of its atoms around them which is correlated to number of rotatable bonds as figured out in this study.

CONCLUSION

This study provides a thorough examination of the wide range of chemical compounds found in medicinal plants located in three geothermal regions within Seulawah Agam Mountain, Aceh Province, Indonesia. The distinct geothermal features of Ie-Brôuk, Ie-Jue, and Ie-Seu'um have attracted attention for a study on how environmental factors can affect the chemical composition of the flora in these areas. Fifteen plant species from various families—*Apocynaceae, Asteraceae, Euphorbiaceae, Fabaceae, Lamiaceae, Moraceae, Pteridaceae, Rhamnaceae,* and *Verbenaceae*—were selected for in-depth chemical analysis using SMILES and fragmentation fingerprint. The species of plants were *Tridax procumbens, Lantana camara, Chromolaena odorata, Acrostichum aureum, Calotropis gigantea, Blumea balsamifera, Ziziphus rufula, Ocimum americanum, Tephrosia noctiflora, Streblus asper Lour, Sumbaviopsis albicans, Baccaurea pyriformis,* and *Antidesma montanum*. The study found that *Chromoloaena odorata* is the one plant that is widespread in all three areas. Gas chromatography-mass spectroscopy analysis identified a wide range of chemical compounds in medicinal plants from the geothermal áreas with total 343 compounds from Ie-Brôuk (123 compounds), Ie-Jue (140 compounds), and Ie-Seu'um (100 compounds). The results of the clustering analysis revealed 98 distinct clusters, indicating a high degree of chemical diversity among the compounds identified. Significantly, a notable proportion of these compounds were classified under the fatty acid category, specifically within cluster 2. Long chain fatty acids ester, such as (E)-9-octadecenoic acid ethyl ester, butyl 6,9,12-hexadecatrienoate, hexadecanoic acid, ethyl ester, hexadecanoic acid, methyl ester, and methyl 9-*cis*,11-*trans*-octadecadienoate, are known to be present in this cluster. Fatty acids appear to be a significant element in the chemical compositions of these plants. The flexophore similarity analysis, which assessed structural similarities among the compounds, revealed 23 neighboring counts, underscoring the abundance of fatty acids. These findings underscore the influence of unique geothermal conditions on the chemical compositions of plants. Each geothermal region displayed unique chemical signatures, which were indicative of the particular environmental conditions. Three geothermal areas have a major compound with flexibility in the range of 0.5 to 0.7 but lower complexity. This finding indicates that at this point,

fatty acids class of compound were found to have low flexibility due to their relatively simple structures. The variety of chemical compounds found in geothermal regions indicates that they could potentially provide unique medicinal compounds, which justifies the need for additional research and investigation. The high diversity and presence of bioactive compounds like fatty acids highlight the potential of these plants for pharmaceutical and therapeutic applications. Overall, this study enhances our understanding of the chemical ecology of geothermal regions and lays the groundwork for future research into the medicinal potential of plants adapted to such unique environments. The unique chemical compositions found in Ie-Brôuk, Ie-Jue, and Ie-Seu'um suggest that the surrounding environmental factors play a crucial role in influencing the chemical composition of indigenous plants, presenting exciting opportunities for uncovering novel natural compounds that could have positive impacts on health.

AUTHOR CONTRIBUTIONS

N.B. Maulydia performed the data analysis, interpreted the results, and preparing the manuscript. K. Khairan prepared figures and interpretations of the results. F. Mohd Fauzi prepared figures and interpretations of the results. T.E. Tallei participated in the interpretation of the results and manuscript preparation. R. Idroes, the corresponding author, has contributed to supervising the data analysis, interpreting the results, and preparing the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been completely observed by the authors.

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ABBREVIATIONS

%	Percent
°C	Degrees Celcius
µL	Microliters
µm	Micrometers
AA	*Acrostichum aureum*
ADME	Absorption, distribution, metabolism, and excretion
AM	*Antidesma montanum*
AMU	*Atomic mass units*
BB	*Blumea balsamifera*
$C_{10}H_{18}O$	*Endo-borneol*
$C_{13}H_{18}O$	Megastigmatrienone
$C_{14}H_{22}O$	2,4-ditert-butylphenol
$C_{15}H_{24}O$	Caryophyllene oxide

$C_{15}H_{24}O$	*cis*-Z-α-bisabolene epoxide
$C_{15}H_{26}O$	4-epi-maaliol
$C_{15}H_{26}O_2$	Cedran-diol, (8S,14)
$C_{15}H_{24}O$	*trans*-Z-α-bisabolene epoxide
$C_{15}H_{28}O_2$	Proximadiol
$C_{15}H_{28}O_3$	Pentadeconoic acid
$C_{16}H_{28}O_3$	(Z-(13,14-epoxy)tetradec-11-en-1-ol acetate
$C_{16}H_{32}O_2$	n-hexadecanoic acid
$C_{17}H_{24}O_3$	7.9-di-tert-butyl-1-oxaspiro(4.5) deca-6.9-diene-2,8-dione
$C_{17}H_{32}O_2$	Hexadecenoic acid, methyl ester
$C_{17}H_{31}F_3O_2$	3-triflouroacetoxypentadecane
$C_{17}H_{37}NO_3S$	3-(N,N dimethyllaurylammonio) propanesulfonate
$C_{18}H_{34}O_2$	*cis*-vaccenic acid
$C_{18}H_{36}O$	2-pentadecanone 6,10,14-trimethyl
$C_{18}H_{36}O_2$	Octadecanoic acid
$C_{18}H_{36}O_2$	Hexadecenoic acid, ethyl ester
$C_{19}H_{32}O_2$	9,12,15-octadecatrienoic acid, methyl ester, (Z,Z)
$C_{19}H_{34}O_2$	Methyl 9-*cis* 11-*trans*-octadecadienoate
$C_{19}H_{34}O_2$	10-*trans*-methyl,12-*cis*-octadecadienoate
$C_{20}H_{34}O_2$	Butyl 6,9,12-hexadecatrienoate
$C_{20}H_{38}$	Neophytadiene
$C_{20}H_{38}O_2$	(E)-9-octadecenoic acid ethyl ester
$C_{20}H_{40}O$	Phytol
$C_{29}H_{48}$	Stigma-3,5-diene
$C_{29}H_{50}O$	β-sitosterol
$C_{30}H_{50}O$	Lupeol

BP	*Baccaurea pyriformis*
CG	*Calotropis gigantea*
CID	Compound identifier
CO	*Chromolaena odorata*
E	East
eV	Electron volts
FAME	Fatty acid methyl ester
FragFp	Fragment fingerprint
GC-MS	Gas chromatography-mass spectroscopy
IB	Ie-Brôuk
IJ	Ie-Jue
IS	Ie-Seu'um
iSQ	Single quadrupole
LA	*Lantana camara*
m	Meters
min	Minutes
mm	Millimeters
N	North
OA	*Ocimum americanum*
PCA	Principal component analysis
RT	Retention time
SA	*Sumbaviopsis albicans*
SAL	*Streblus asper* L
SI	Similarity index
SMILES	Simplified molecular input line-entry system
TN	*Tephrosia noctiflora*
TP	*Tridax procumbens*
w:v	weight: volume
ZR	*Ziziphus rufula*

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