



Research Article

Unraveling the functional components in medicinal *Aloe* species based on UPLC-MS/MS metabolomics

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Abstract: The typical *Aloe* plant is well known for its dual role as food and medicine, possessing an array of immune-modulating, antioxidant, antimicrobial, and antitumor properties. Species of *Aloe* are widely used in cosmetics, therapeutics, and health products. Here, using the LC-QTRAP ultra-high-performance liquid chromatography platform, a total of 813 metabolites were identified in *Aloe* plants. Principal component analysis and correlation analysis were conducted on 15 typical medicinal *Aloe* species. An enrichment analysis of the metabolites found was performed using Kyoto Encyclopedia of Genes and Genomes, Human Metabolome Database, and LipidMaps databases. Based on the metabolomic data, 105 key metabolites were selected for a heatmap analysis, including 34 flavonoids, 16 quinones, 13 phenolic acids, 13 amino acids and derivatives, 6 organic acids, 5 lipids, 3 alkaloids, 2 lignans and coumarins, and 13 other metabolites. Dendrogram-based chemodiversity classification grouped these *Aloe* species into three major clusters: Group 1 whose sole member is *Aloe vera*; Group 2 consisting of *Aloe arborescens*, *Aloe kedongensis*, *Aloe secundiflora*, *Aloe greatheadii* var. *davyana*, *Aloe zebrina*, and *Aloe dewetii*; and Group 3 comprising *Aloe vera* var. *chinensis*, *Aloe marlothii*, *Aloe ferox*, *Aloe divaricata*, *Aloe rupestris*, *Aloe petricola*, *Aloe africana*, and *Aloe excelsa*. Further, the partial least squares discrimination analysis uncovered significant chemodiversity among the *Aloe* species. The enrichment analysis revealed that *Aloe* species metabolites were enriched mainly in pathways related to aminoacyl-tRNA biosynthesis, phenylalanine, tyrosine, and tryptophan biosynthesis, valine, leucine, and isoleucine biosynthesis, phenylalanine metabolism, the citrate cycle, glyoxylate and dicarboxylate metabolism, and valine, leucine, and isoleucine degradation. Altogether, these findings suggest significant potential for advancing key *Aloe* species to meet various human needs. Ultimately, this study enhances our understanding of the metabolic profiles of different *Aloe* species for their potential improved use in future applications.

Keywords: *Aloe*; metabolites; functional component; chemodiversity classification; enrichment analysis.

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1 Introduction

The *Aloe* genus is the most abundant (>500 species) in the Asphodelaceae family, native to Africa, the Arabian Peninsula, Socotra Island, Mascarene Islands, and Madagascar, but since widely introduced and cultivated in many warm areas of the world^[1,2], such as the Mediterranean, India, Australia, and South America. *Aloe* is a succulent xerophyte capable of thriving in hot, arid environments, whose crassulacean acid metabolism enables it

to conserve water during drought conditions while maintaining its normal photosynthesis^[3]. Long recognized for its cosmetic and medicinal qualities, the consumption of *Aloe* has increased substantially with rising consumer interest in its potential health benefits.

Aloe plants are extensively utilized in the food, pharmaceutical, and cosmetics industries, featuring in products being prominent in such products as lassi, ice cream, soaps, sunscreens, anti-aging face treatments, lotions, and tissue paper^[4-6]. The fleshy leaves, gel,

and latex of *Aloe* are the basis of its main commercial products, including pills, jellies, creams, drinks, liquids, sprays, ointments, and lotions, which are widely used across the food, cosmetics, and pharmaceutical industries^[7]. The identified nutrients and phytochemicals in *Aloe* plants include vitamins, amino acids, minerals, glucomannans, polysaccharides, fatty acids, enzymes, indoles, pyrimidines, alkanes, dicarboxylic acids, aldehydes, saponins, flavonoids, anthraquinones, ketones, phenolic compounds, sterols, and alkaloids^[8–11]. These compounds not only contribute to *Aloe*'s commercial value but also underpin its significant pharmacological properties. *Aloe* plants, for instance, is known for its immunomodulatory, anti-inflammatory, antioxidant, antimicrobial, and anticancer activities. The presence of compounds such as aloin and alo-emodin is associated with their well-documented effects as laxatives, anti-inflammatory agents, and anticancer agents^[7,12]. Acemannan, a key polysaccharide in *Aloe*, is noted for its immune-modulating and wound healing properties, making *Aloe* a crucial component in therapeutic products aimed at skin repair and immune support^[13]. Furthermore, the antioxidants and antimicrobial properties of *Aloe*'s flavonoids and phenolic compounds contribute to its use in reducing oxidative stress and treating infections^[7,14]. The important medicinal functions of these nutrients and phytochemicals confer to *Aloe* plants great value for research and use.

Aloe plants are widely recognized for their health, beauty, medicinal, and skincare benefits and may be used both topically and orally^[15]. Previous studies have highlighted the various medicinal applications of *Aloe* plants, such as their antibacterial^[16], anti-diabetic^[17], antioxidant^[18], anti-inflammatory^[19], hepatoprotective^[20], and anticancer properties^[21]. The polysaccharides and glycoproteins found in the leaf pulp of *Aloe vera* have anti-inflammatory and wound healing properties. *Aloe* gel not only increases the collagen content in wounds but also enhances the protein's cross-linking tendency of proteins^[22,23]. Its healing effect is attributed chiefly to the presence of glucomannan, which promotes the growth of fibroblast cells and stimulates their proliferation and activity, leading to enhanced collagen production and secretion^[24]. In addition, some *Aloe* species are commonly used for ornamental purposes and landscaping. The main species utilized in health and medical domains include, but are not limited to, *Aloe barbadensis* Miller, *Aloe arborescens* Miller, *Aloe perryi* Baker, *Aloe andongensis*, and *Aloe ferox*. Of these, *A. barbadensis* Miller, better known as *A. vera*, is arguably the most widely used species^[25]. It is included in the Chinese pharmacopoeia and is utilized as both a skin ointment and for treating dermatitis^[12].

Considering the immense value and benefits of *Aloe* to the pharmaceutical and cosmetic industries, this study aimed to guide its prospective applications for improving human welfare by evaluating the chemical profiles of 15 typical *Aloe* species. A multivariate statistical approach, including correlation analysis, clustering, principal component analysis (PCA), algorithms, and partial least squares discriminant analysis (PLS-DA), was employed. From the metabolome results, the main differential metabolites were selected for a heatmap analysis. According to the chemodiversity classification via the PLS-DA analysis, those main metabolites yielded three distinguishable groups that exhibited functional components harboring a wide range of chemodiversity. Overview of enriched metabolite sets of *Aloe* species revealed the prominently enriched differing metabolic pathways. The findings of this study will contribute to functional investigations of new and promising chemical components in *Aloe* species.

2 Materials and methods

2.1 Plant materials

In order to analyze all the functional components of *Aloe* plants with important global trade values, we selected fifteen species for metabolome (Table 1). *Aloe arborescens* (AL01), *A. vera* (AL02), *A. vera* var. *chinensis* (AL03), *Aloe kedongensis* (AL04), *Aloe marlothii* (AL05), *A. ferox* (AL06), *Aloe divaricata* (AL07), *Aloe secundiflora* (AL08), *Aloe rupestris* (AL09), *Aloe petricola* (AL10), *Aloe africana* (AL11), *Aloe excelsa* (AL12), *Aloe greatheadii* var. *davyana* (AL13), *Aloe zebrina* (AL14), and *Aloe dewetii* (AL15) were used in this study (Table 1).

A. petricola (AL10) and *A. dewetii* (AL15) were introduced from Cape Town, South Africa (introduction No. 2011-W1143 and 2011-W1129, respectively); *A. ferox* (AL15) was introduced from Eastern Cape, South Africa (introduction No. 2017-0275); *A. arborescens* (AL01) was introduced from South Africa (introduction No. 2001-w0036); *A. marlothii* (AL05), *A. divaricata* (AL07), *A. rupestris* (AL09), and *A. zebrina* (AL14) were introduced from Mesa Garden, USA (introduction No. 2008-1768, 2008-1742, 2008-1781, and 2008-1796, respectively); *A. secundiflora* (AL08) was introduced from Prague, Czech Republic (introduction No. 2012-W0358); *A. kedongensis* (AL04) and *A. excelsa* (AL12) were introduced from Shanghai Botanical Garden, China (introduction No. 2010-0802 and 2010-1029, respectively); *A. greatheadii* var. *davyana* (AL13) was introduced from Beijing, China (introduction No. 2010-W1136); *A. vera* (AL02) was introduced from the former government's Beiping Institute of Botany, China (introduction No. 1949-0298); *A. vera* var. *chinensis* (AL03) was introduced from Xiamen Garden and Botanical Garden, Fujian Province, China (introduction No. 2018-0015); *A. africana* (AL11) was introduced from Xianhu Botanical Garden, Shenzhen City, Guangdong Province, China (introduction No. 2008-1929).

All the plant materials were grown in greenhouse, China National Botanical Garden, Beijing, China. Fresh mature leaves of *Aloe* plants were collected from plants, immediately frozen in liquid nitrogen, and then stored at -80°C .

2.2 Metabolome analysis

2.2.1 Metabolite extraction

For each sample, fresh mature leaves were collected from fifteen individual plants. The samples were vacuum freeze-dried using a lyophilizer, then ground into powder with a grinder. A 100 mg portion of the powder was dissolved in 1.2 mL of 70% methanol extract and vortexed every 30 min for 30 s, repeated 6 times. The sample was stored at 4°C overnight in a refrigerator. After centrifugation, the supernatant was collected, filtered through a microporous membrane, and stored in an injection vial for ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) analysis.

2.2.2 UPLC conditions

Chromatographic column: Agilent SB-C₁₈ (2.1 mm $\times$ 100 mm, 1.8 μm). Mobile phase: A–0.1% formic acid in water; B–0.1% formic acid in acetonitrile. Elution gradient: phase B starts at 5% at 0.00 min, linearly increases to 95% by 9.00 min, held at 95% for 1 min, then decreases back to 5% from 10.00 min to 11.10 min, and equilibrates at 5% until 14 min. Column temperature: 40°C ; Flow rate: 0.35 mL/min; Injection volume: 4 μL .

Table 1 Detailed information of 15 *Aloe* species

Sample ID	Species	Introduction No.	Introduction source	Chinese name	Trading area	Medicinal function
AL01	<i>A. arborescence</i>	2001-w0036	South Africa	'Muli' Lu Hui	Southern Africa (South Africa, Eswatini, Malawi, Mozambique, Zimbabwe), Japan, China	Anti-diabetes; Anti-cancer (lung, stomach, colon); inhibition of pain-producing substances; anti-lymphocyte mitotic activity; arthritis control; reduction of asthma; reduction of gastric damage and gastric ulcers; anti-liver cancer; skin; heart problems in rats; food addition Plants are scorched over a fire to make a wet plaster on the outside of a broken bone or as a disinfectant for a wound; antibacterial and anti-inflammatory promote callus; immune regulation; food addition
AL02	<i>A. vera</i>	1949-0298	The former government's Beijing Institute of Botany, China	'Kulasu' Lu Hui	All over the world	
AL03	<i>A. vera</i> var. <i>chinensis</i>	2018-0015	Xiamen Garden and Botanical Garden, Fujian Province, China	'Hua' Lu Hui	China	Medicinal plant
AL04	<i>A. kedongensis</i>	2010-0802	Shanghai Botanical Garden, China	'Kedeng' Lu Hui	Kenya	Trauma, skin problems; respiratory disease, typhoid fever, venereal disease, vomiting, relieve diarrhea, ear disease
AL05	<i>A. marlothii</i>	2008-1768	Mesa Garden, USA	'Mashi' Lu Hui	Southern Africa	Wounds, burns, tapeworms, roundworms and other parasites; stomach pain; adhesive Diarrhea, trauma, X-ray radiation injury, rheumatoid arthritis, conjunctivitis; tonic, labor pain medicine; skin, arthritis, rheumatism, dental abscess, promotion of labor, lymphatic system; nutrition; anesthetic component; toxicity; make jam; a source of honey; adhesive; kill insects; food addition
AL06	<i>A. ferox</i>	2017-0275	Eastern Cape, South Africa	'Haowangjiao' Lu Hui	South Africa, Lesotho	Medicinal plant
AL07	<i>A. divaricata</i>	2008-1742	Mesa Garden, USA	'Duohuaxu' Lu Hui	Madagascar	Wounds, burns, skin infections, itching, cough, cold, chest pain, headache, loss of appetite, stomach pain, nausea, arthritis, bile problems, diabetes, diarrhea, eye disease, venereal disease, headache, hypertension, kidney disease, liver disease, malaria; nervous system, urinary, respiratory, parasitic, metabolic, infection, gastrointestinal, eye, food, skin, cardiovascular, etc; curare ingredient; a source of honey; disinsectization
AL08	<i>A. secundiflora</i>	2012-W0358	Prague, Czech Republic	'Cehua' Lu Hui	Kenya, Uganda, Tanzania, Rwanda, Ethiopia	Boost fertility, tonic
AL09	<i>A. rupestris</i>	2008-1781	Mesa Garden, USA	'Shidi' Lu Hui	Southern Africa	
AL10	<i>A. petricola</i>	2011-W1143	Cape Town, South Africa	'Shisheng' Lu Hui	South Africa	Trauma, burns, stomach pain
AL11	<i>A. africana</i>	2008-1929	Xianhu Botanical Garden, Shenzhen City, Guangdong Province, China	'Feizhou' Lu Hui	South Africa	Relieve diarrhea
AL12	<i>A. excelsa</i>	2010-1029	Shanghai Botanical Garden, China	'Gao' Lu Hui	Southern Africa	Asthma, jaundice, infant chin depression
AL13	<i>A. greatheadii</i> var. <i>davyana</i>	2010-W1136	Beijing, China	'Sheweijin' Lu Hui	South Africa	Burns, swelling pain, trauma, laxative, snake medicine; skin; nectar source
AL14	<i>A. zebrina</i>	2008-1796	Mesa Garden, USA	'Banma' Lu Hui	Southern Africa	Kidney disease, urinary disease; curare ingredient; anamorphose; nectar source
AL15	<i>A. dewetii</i>	2011-W1129	Cape Town, South Africa	'Deweishi' Lu Hui	South Africa, Eswatini	Medicinal plant

2.2.3 LC-MS/MS analysis

Linear ion trap (LIT) and triple quadrupole (QQQ) scans were conducted using a triple quadrupole-linear ion trap mass spectrometer equipped with an electrospray ionization (ESI) Turbo Ion-Spray interface. The system operated in both positive and negative ion modes and was controlled by SCIEX Analyst software (Versions 1.6.3). ESI source parameters were as follows: source temperature at 500 °C, ion spray voltage set to 5,500 V for positive mode and −4,500 V for negative mode. Multi reaction monitoring (MRM) transitions were specifically monitored for each period based on the elution time of metabolites.

2.2.4 Qualitative and quantitative metabolites

Using the local metabolic database, the metabolites in the samples were qualitatively and quantitatively analyzed through mass spectrometry. The characteristic ions of each compound were identified using a triple quadrupole system, and the signal intensity (CPS) of these ions was recorded by the detector. The mass spectrometry data were processed with MultiaQuant software, where chromatographic peaks were integrated and corrected. The peak area indicated the relative content of the corresponding compound.

After peak alignment and noise filtering, the data was processed using Thermo Fisher SIEVE software. The data was then

normalized and organized into a two-dimensional matrix based on retention time, compound molecular weight, sample observations, and peak intensity. PCA was subsequently applied to this matrix for further analysis^[26].

2.3 Metabolite annotation

The exact molecular mass and m/z values were used to identify metabolites through the Human Metabolome Database (HMDB, <http://www.hmdb.ca/>) and Lipid Metabolites and Pathways Strategy (LIPID MAPS, <http://www.lipidmaps.org/>). Metabolite identification was confirmed by comparing their accurate mass, retention time, and fragment patterns with commercial standards. Potential biomarkers were analyzed using MetPA (<http://metpa.metabolomics.ca/MetPA/faces/Home.jsp>) for pathway analysis, based on the Kyoto Encyclopedia of Genes and Genomes Pathway Database (KEGG, <http://www.genome.jp/kegg/pathway.html>) to determine the associated metabolic pathways^[27].

2.4 Data analysis

PCA and Spearman correlation analysis were applied to assess the repeatability of the sample groups and quality control samples. Heatmap and dendrogram analyses were performed using the R platform. Supervised statistical analysis was conducted with PLS-DA using SIMCA 14.1 (Umetrics, Umea, Sweden). The model's variable importance in the projection (VIP) value was calculated through multiple cross-validation. The significance of differential metabolite enrichment in KEGG pathways was determined using the hypergeometric distribution test.

3 Result

3.1 Information of the fifteen typical medicinal *Aloe* species

We chose 15 typical medicinal plants from the collection of *Aloe* plant resources for their metabolome analysis (Table 1,

Fig. 1). The Chinese name of *A. arborescence* (AL01) is 'Muli' Lu Hui; it these characteristics or uses: anti-diabetes and, anti-cancer properties, inhibition of pain-producing substances, anti-lymphocyte mitotic activity, arthritis control, reduction of asthma, reduction of gastric damage and gastric ulcers, anti-liver cancer effects, skin care, reducing heart problems in rats, and use as food additive roles (Fig. 1A).

The Chinese name of *A. vera* (AL02) is 'Kulasu' Lu Hui. This plant is scorched over a fire to produce a wet plaster that can be applied to the outside of a broken bone or as a wound disinfectant, in addition to its antibacterial and anti-inflammatory promote callus, immune regulation, and food additive roles (Fig. 1B).

The Chinese name of *A. vera* var. *chinensis* (AL03) is 'Hua' Lu Hui, predominately a medicinal plant (Fig. 1C). The Chinese name of *A. kedongensis* (AL04) is 'Kedeng' Lu Hui which can be effective against trauma, skin problems, respiratory disease, typhoid fever, venereal disease, vomiting, diarrhea, and ear disease (Fig. 1D). The Chinese name of *A. marlothii* (AL05) is 'Mashi' Lu Hui which could treat wounds, burns, tapeworms, roundworms and other parasites, as well as stomach pain, in addition to being an adhesive (Fig. 1E).

The Chinese name of *A. ferox* (AL06) is 'Haowangjiao' Lu Hui. This plant is noted for helping with the following: diarrhea, trauma, X-ray radiation injury, rheumatoid arthritis, conjunctivitis; tonic, labor pain, skin, arthritis, rheumatism, dental abscess, childbirth, lymphatic system, nutrition, anesthetic component, and toxicity. It is used in jam making and is a source of honey, being also an adhesive, insecticide and food additive (Fig. 1F).

The Chinese name of *A. divaricata* (AL07) is 'Duohuaxu' Lu Hui, a medicinal plant (Fig. 1G). The Chinese name of *A. secundiflora* (AL08) is 'Cehua' Lu Hui; it is applicable to wounds, burns, skin infections, itching, cough, cold, chest pain, headache, loss of appetite, stomach pain, nausea, arthritis, bile problems, diabetes, diarrhea, eye disease, venereal disease, headache, hypertension, kidney disease, liver disease, malaria, nervous system, urinary and respiratory issues, parasites,

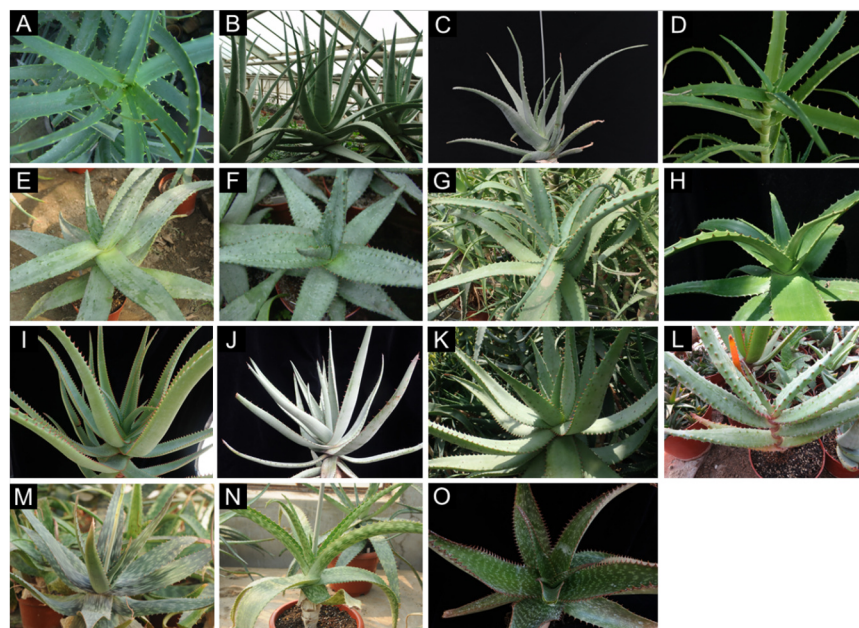


Figure 1 Morphological characteristics of 15 typical medicinal *Aloe* species. (A) AL01, *A. arborescence*. (B) AL02, *A. vera*. (C) AL03, *A. vera* var. *chinensis*. (D) AL04, *A. marlothii*. (E) AL05, *A. marlothii*. (F) AL06, *A. ferox*. (G) AL07, *A. divaricata*. (H) AL08, *A. secundiflora*. (I) AL09, *A. rupestris*. (J) AL10, *A. petricola*. (K) AL11, *A. africana*. (L) AL12, *A. excelsa*. (M) AL13, *A. greatheadii* var. *davyana*. (N) AL14, *A. zebrina*. (O) AL15, *A. dewetii*.

metabolic ailments, infections, the gastrointestinal tract, and eye, food, skin, cardiovascular system, while also a curare ingredient, honey source, and insecticide (Fig. 1H).

The Chinese name of *A. rupestris* (AL09) is 'Shidi' Lu Hui which can boost fertility and is also a tonic (Fig. 1I). The Chinese name of *A. petricola* (AL10) is 'Shisheng' Lu Hui, which can treat trauma, burns, and stomach pain (Fig. 1G). The Chinese name of *A. africana* (AL11) is 'Feizhou' Lu Hui which is able to relieve diarrhea (Fig. 1K). The Chinese name of *A. excelsa* (AL12) is 'Gao' Lu Hui, which can alleviate asthma, jaundice, and infant chin depression (Fig. 1L). The Chinese name of *A. greatheadii* var. *davyana* (AL13) is 'Shewejin' Lu Hui, it relevant to reducing burns, swelling pain, and trauma, being also a laxative, snake medicine, good for skin care, and a nectar source (Fig. 1M). The Chinese name of *A. zebrina* (AL14) is 'Banma' Lu Hui; it helps with kidney and urinary diseases, and is a curare ingredient, anamorphous, and a nectar source (Fig. 1N). The Chinese name of *A. dewettii* (AL15) is 'Deweishi' Lu Hui, this being another medicinal plant (Fig. 1O).

Additionally, *A. vera* (Fig. 1B) is the most commercially utilized species of the *Aloe* genus, valued broadly for its medicinal, cosmetic, and nutritional properties^[28]. Morphologically, there is no significant difference in the number or thickness of its leaves; it has either no stem or a very short one and grows to a height of 80–100 cm, spreading via basal offsets and root shoots (Fig. 1B). This cactus-like plant features green, sword-shaped, fleshy leaves that are serrated, pointed, and filled with a clear, viscous gel, as seen in Fig. 1B.

3.2 Metabolic differences among the 15 typical medicinal *Aloe* species

Based on LC-QTRAP platform UPLC, all 15 species were qualitatively and quantitatively analyzed. A total of 813 peaks were detected, corresponding to 813 metabolites. These consisted of 108 amino acids and derivatives, 106 phenolic acids, 37 nucleotides and derivatives, 3 tannins, 47 organic acids, along with 178 flavonoids (8 chalcones, 16 flavanones, 77 flavones, 54 flavonols, 2 flavanols, and 21 other flavonoids), 23 quinones (anthraquinones), 23 lignans and coumarins (5 lignans and 18 coumarins), 110 others (4 alcohol compounds, 5 lactones, 10 others, 3 aldehyde compounds, 14 chromones, 56 saccharides, 4 ketone compounds, and 14 vitamins), 59 alkaloids (4 pyridine alkaloids, 1 pyrrole alkaloid, 5 phenolamines, 2 quinoline alkaloids, 1 tropan alkaloid, 2 piperidine alkaloids, 28 alkaloids, 10 plumeranes, and 6 steroid

alkaloids), 16 terpenoids (7 sesquiterpenoids, 6 diterpenoids, and 3 triterpenes), 21 steroids (1 cardiac glycoside, 1 steroid, and 19 steroidal saponins), 82 lipids (12 glycerol esters, 1 phosphatidylcholines (PC), 5 sphingolipids, 13 lyso-phosphatidylcholines (LPCs), 17 lyso-phosphatidylethanolamines (LPEs), and 34 free fatty acids).

Flavonoids included 7-*O*-methylaloesin, aloeresin A, aloeresin C, aloeresin D, aloeresin E, aloeresin G, 2'-*O*-feruloyl aloesin, 6"-*O*-*p*-coumaroyl-aloesin, etc. Quinones included 2'-*O*-feruloyl-aloesin, 8-*O*-methyl-7-hydroxyaloin B, 6'-malonylnataloin, 5-hydroxyaloin A, aloin B, 5-hydroxyaloin, 10-hydroxyaloin A, 7-hydroxyaloin, hydroxyaloe-emodin-8-*O*-glucoside, aloe emodin, aloin A, etc. Others included feralolide, aloesin, 7-*O*-methylaloesin A, etc.

However, the identified *Aloe* metabolites differed significantly among the 15 species (Fig. 2A). PCA showed that the first contribution rate (PC1) was 15.74% and the second contribution rate (PC2) was 10.81% (Fig. 2B). The metabolic pathway cluster analysis was carried out according to the KEGG, HMDB and LIPID MAPS databases (Fig. 3). KEGG analysis clustered the metabolites into various categories, including amino acid metabolism galactose metabolism, ATP-Binding Cassette (ABC) transporters, and aminoacyl tRNA biosynthesis (Fig. 3A). The HMDB analysis clustered the metabolites into categories such as benzene and substituted derivatives, fatty acyls, carboxylic acids and derivatives, and organooxygen compounds (Fig. 3B). The metabolites were clustered by the LIPID MAPS analysis into glycerolipids, polyketides, prenol lipids, and sphingolipids (Fig. 3C).

3.3 The main differential metabolites analysis of 15 typical medicinal *Aloe* species

According to the metabolome results, 105 main metabolites of the 15 *Aloe* species were selected for their heatmap analysis (Fig. 4, Table 2). These 105 main metabolites included 3 alkaloids (1 alkaloid and 2 pyridine alkaloids), 13 amino acids and derivatives, 34 flavonoids (4 flavanones, 10 flavones, 11 flavonols, and 8 other flavonoids), 2 lignans and coumarins (2 coumarins), 5 lipids (4 free fatty acids and 1 LPC), 6 organic acids, 13 others (7 chromones, 1 lactone, 3 saccharides, and 2 others), 13 phenolic acids, and 16 quinones (anthraquinones) (Fig. 4A). According to their cluster analysis, the main differential metabolites constituted three main groups (Fig. 4B).

The three alkaloids were histidinol, 3-carbamyl-1-methylpyridinium (1-methylnicotinamide), and trigonelline. The

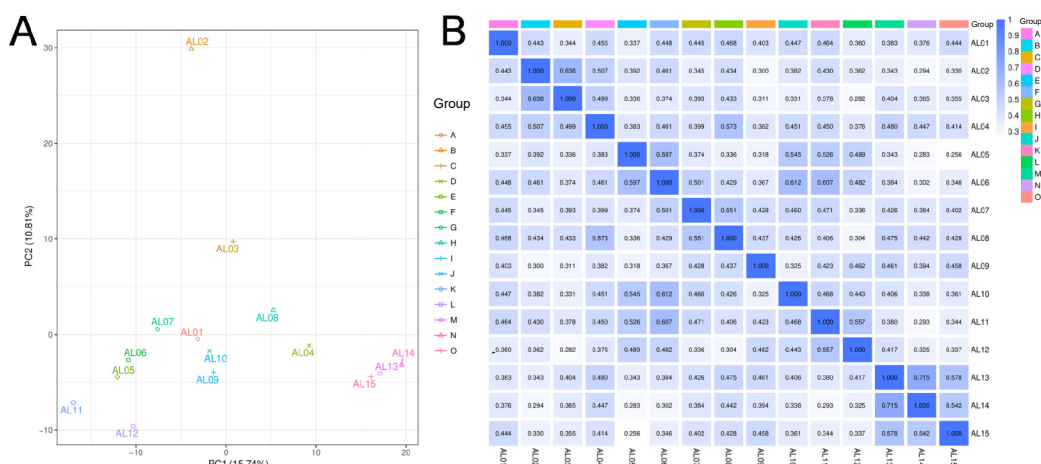


Figure 2 PCA and correlation analysis of fifteen typical medicinal *Aloe* species. (A) PCA. (B) Correlation analysis of fifteen typical medicinal *Aloe* species.

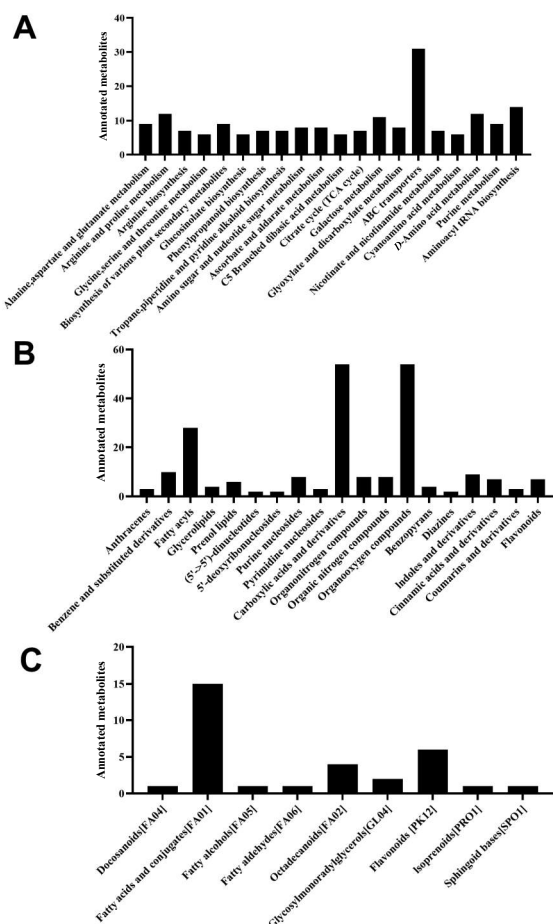


Figure 3 Metabolites cluster analysis of 15 typical medicinal *Aloe* species. (A) KEGG enrichment analysis of metabolites in *Aloe* species. (B) HMDB enrichment analysis of metabolites in *Aloe* species. (C) LIPID MAPS enrichment analysis of metabolites in *Aloe* species.

13 amino acids and derivatives were *L*-phenylalanine, *L*-cyclopentylglycine, *L*-norleucine, His-Thr-Ser-Asp, *L*-tryptophan, *L*-isoleucine, Cyclo-(Gly-Phe), Trp-Phe, Trp-Ala, TyrMe-Asp-OH, Met-Tyr, Nap-Ser-OH, and His-Ala-Val-Asp.

The 34 flavonoids were hydroxy isoliquiritigenin glucoside, liquiritigenin-4'-*O*-glucoside (liquiritin), isohemiphloin, naringenin-4'-*O*-glucoside, naringenin-7-*O*-glucoside (prunin), luteolin-6-*C*-glucoside (isoorientin), luteolin-8-*C*-glucoside (orientin), apigenin-5-*O*-glucoside, chrysoeriol-5-*O*-glucoside, apigenin-6-*C*-glucoside (isovitexin), tricetin-7-*O*-(6"-*O*-malonyl) glucoside, luteolin-7-*O*-rutinoside, isovitexin-2"-*O*-xyloside, apigenin-6-*C*-(2"-xylosyl) glucoside, luteolin-6-*C*-glucoside-7-*O*-rhamnoside, quercetin-3-*O*-(2"-*O*-*p*-coumaroyl) glucoside, kaempferol-3-*O*-neohesperidoside, aloeresin A, kaempferol-3-*O*-glucorhamnoside, quercetin-3-*O*-glucoside-7-*O*-rhamnoside, kaempferol-3-*O*-rutinoside (nicotiflorin), tamarixetin-3-*O*-glucoside-7-*O*-rhamnoside, quercetin-3-*O*-rutinoside (rutin), kaempferol-3-*O*-glucoside-7-*O*-rhamnoside, isorhamnetin-3-*O*-neohesperidoside, sexangularetin-3-*O*-glucoside-7-*O*-rhamnoside, 7-*O*-methylaloesin, aloeresin C, 2"-*O*-feruloyl aloesin, 3'-methoxyquercetin-3-*O*-*L*-rhamnosyl(1→2)-glucopyranoside, aloeresin E, aloeresin D, 6"-*O*-*p*-coumaroyl-aloesin, and aloeresin G.

The 2 coumarins and lignans were coumarin and hydrangenol-*O*-glucoside-*O*-glucoside, respectively. The 5 lipids were γ -linolenic acid, palmitaldehyde, elaidic acid, α -linolenic acid, and

LysoPC 18:2. The 6 organic acids were quinic acid, muconic acid, *cis*-aconitic acid, citric acid, homocitrate, and *L*-malic acid. Regarding the 13 other metabolites, these consisted of were 2-methyl-5-acetyl-7-hydroxychromone glucoside, 8-*C*-glucosyl-7-*O*-methyl-(*R*)-aloesol, feralolide, 8-*C*-glucosyl-(*R*)-aloesol, 2,5-dimethyl-7-hydroxychromone glucoside, 3-dehydro-*L*-threonic acid, 5-acetyl-6-glucosyl-7-hydroxy-2,6-methylchromone, aloesin, 7-*O*-methylaloesin A, 4-(β -*D*-glucopyranosyloxy)-2,4',6-trihydroxybenzophenone, glucarate *O*-phosphoric acid, 4-*O*-acetyl-3-*O*-caffeoyl-2-*C*-methyl-*D*-erythronate, and maltotriose.

The 13 phenolic acids found were 1-*O*-*p*-coumaroylquinic acid, dimethyl phthalate, 4-nitrophenol, 1-*O*-*p*-coumaroyl- β -*D*-glucose, 3-*O*-feruloylquinic acid, 3-*O*-*p*-coumaroylquinic acid, 5-*O*-*p*-coumaroylquinic acid, chlorogenic acid (3-*O*-caffeoylquinic acid), neochlorogenic acid, 1-caffeoylquinic acid, (7*S*,8*R*)-dehydrodiconiferylalcohol-9'-*O*- β -*D*-glucopyranoside, 6-*O*-caffeoylarbutin, and cryptochlorogenic acid.

The 16 quinones found were 2"-*O*-feruloyl-aloesin, 8-*O*-Methyl-7-hydroxyaloin B, 6'-malonylnataloin, aloin B, 5-hydroxyaloin, 10-hydroxyaloin A, 7-hydroxyaloin, emodin-6-*O*-glucoside, emodin-8-*O*-glucoside, 5-hydroxyaloin A, nataloin, aloin A, 3,8-dihydroxy-1-methoxy-9,10-anthraquinone glucoside, aloesin emodin, danthron, 1,8-dihydroxyanthraquinone, and hydroxy aloesin emodin-8-*O*-glucoside.

3.4 Chemodiversity classification of 15 typical medicinal *Aloe* species

To further classify the typical medicinal *Aloe* species, a dendrogram analysis was then carried out (Fig. 5). The 15 species got distinctly classified, indicating significant interspecific differences in the main functional components. According to the dendrogram analysis, those components grouped into three primary clusters, these designated Groups 1, 2, and 3 (Fig. 5A). Group 1 had a single species *A. vera* (AL02). Six species *A. arborescens* (AL01), *A. kedongensis* (AL04), *A. secundiflora* (AL08), *A. greatheadii* var. *davyana* (AL13), *A. zebrina* (AL14), and *A. dewettii* (AL15) represented Group 2. To Group 3 belonged *A. vera* var. *chinensis* (AL03), *A. marlothii* (AL05), *A. ferox* (AL06), *A. divaricata* (AL07), *A. rupestris* (AL09), *A. petricola* (AL10), *A. africana* (AL11), and *A. excelsa* (AL12). To sum up, the dendrogram analysis revealed broadly ranging chemodiversity among different functional components. The composition of each *Aloe* species was further distinguished by a supervised PLS-DA statistical method, as indicated by the dendrogram analysis (Fig. 5B).

Chemical markers were identified according to the values for VIP scores obtained from the PLS-DA model, which also serves as a key parameter for assessing the contribution of various chemical compositions to the fitted model^[29]. Depicted in Fig. 5C are VIP values of each typical medicinal *Aloe* species' metabolites; vital metabolites were defined as those with higher VIP values (≥ 1). Among these, aloeresin E (1.794,5), isohemiphloin (1.794,0), 10-hydroxyaloin A (1.793,7), 8-*O*-methyl-7-hydroxyaloin B (1.782,7), feralolide (1.720,4), 5-hydroxyaloin (1.711,6), chrysoeriol-5-*O*-glucoside (1.540,0), 8-*C*-glucosyl-7-*O*-methyl-(*R*)-aloesol (1.523,6), *L*-phenylalanine (1.500,6), aloesin emodin (1.289,3), aloeresin D (1.208,3), and aloeresin G (1.079,8) all stood out markedly in having substantial effects on the PLS-DA model's classification. Crucially, these metabolites might function as suitable chemical markers to identify the chemodiversity of certain *Aloe* species.

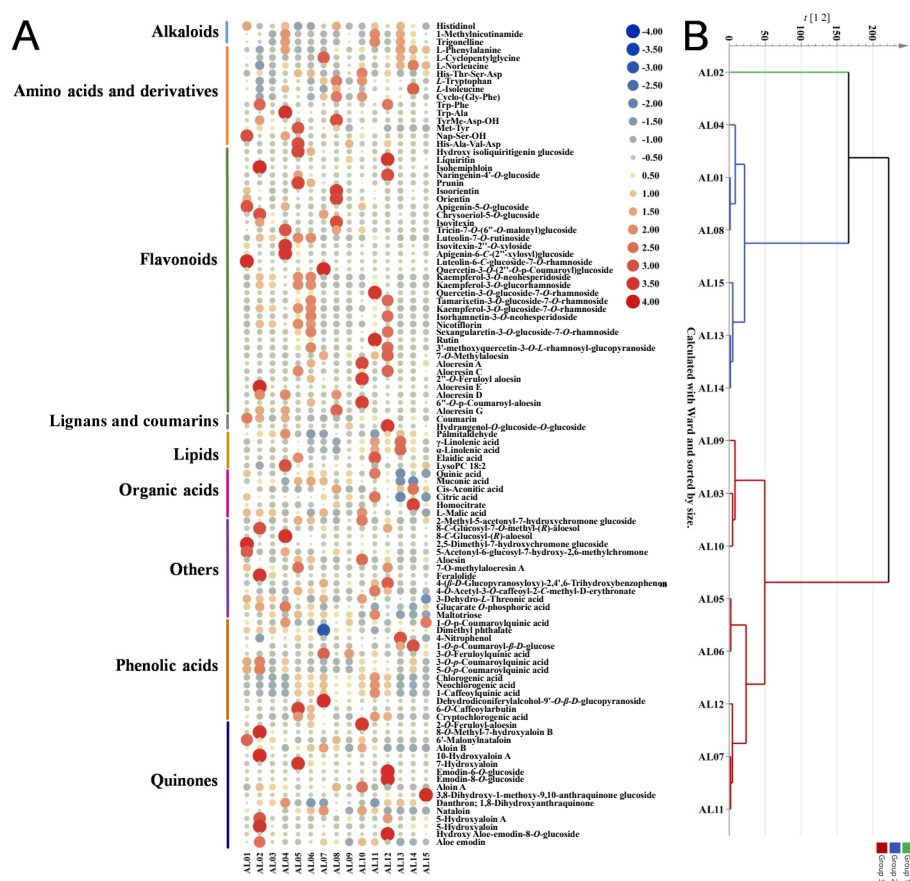


Figure 4 Heatmap and cluster analysis of 15 typical medicinal *Aloe* species. (A) Heatmap analysis of the 105 main functional components. (B) Cluster analysis of 15 typical medicinal *Aloe* species, based on their main functional components.

Table 2 Main metabolites of 15 *Aloe* species

Compounds	Class I	Class II
Histidinol	Alkaloids	Alkaloids
3-Carbamyl-1-methylpyridinium (1-Methylnicotinamide)	Alkaloids	Pyridine alkaloids
Trigonelline	Alkaloids	Pyridine alkaloids
L-Phenylalanine	Amino acids and derivatives	Amino acids and derivatives
L-Cyclopentylglycine	Amino acids and derivatives	Amino acids and derivatives
L-Norleucine	Amino acids and derivatives	Amino acids and derivatives
His-Thr-Ser-Asp	Amino acids and derivatives	Amino acids and derivatives
L-Tryptophan	Amino acids and derivatives	Amino acids and derivatives
L-Isoleucine	Amino acids and derivatives	Amino acids and derivatives
Cyclo-(Gly-Phe)	Amino acids and derivatives	Amino acids and derivatives
Trp-Phe	Amino acids and derivatives	Amino acids and derivatives
Trp-Ala	Amino acids and derivatives	Amino acids and derivatives
TyrMe-Asp-OH	Amino acids and derivatives	Amino acids and derivatives
Met-Tyr	Amino acids and derivatives	Amino acids and derivatives
Nap-Ser-OH	Amino acids and derivatives	Amino acids and derivatives
His-Ala-Val-Asp	Amino acids and derivatives	Amino acids and derivatives
Hydroxy isoliquiritigenin glucoside	Flavonoids	Chalcones
Liquiritigenin-4'-O-Glucoside (Liquiritin)	Flavonoids	Flavanones
Isohemiphloin	Flavonoids	Flavanones
Naringenin-4'-O-glucoside	Flavonoids	Flavanones
Naringenin-7-O-glucoside (Prunin)	Flavonoids	Flavanones
Luteolin-6-C-glucoside (Isoorientin)	Flavonoids	Flavones
Luteolin-8-C-glucoside (Orientin)	Flavonoids	Flavones

(Continued)

Compounds	Class I	Class II
Apigenin-5- <i>O</i> -glucoside	Flavonoids	Flavones
Chrysoeriol-5- <i>O</i> -glucoside	Flavonoids	Flavones
Apigenin-6- <i>C</i> -glucoside (Isovitexin)	Flavonoids	Flavones
Tricin-7- <i>O</i> -(6"- <i>O</i> -malonyl)glucoside	Flavonoids	Flavones
Luteolin-7- <i>O</i> -rutinoside	Flavonoids	Flavones
Isovitexin-2"- <i>O</i> -xyloside	Flavonoids	Flavones
Apigenin-6- <i>C</i> -(2"-xylosyl)glucoside	Flavonoids	Flavones
Luteolin-6- <i>C</i> -glucoside-7- <i>O</i> -rhamnoside	Flavonoids	Flavones
Quercetin-3- <i>O</i> -(2"- <i>O</i> - <i>p</i> -Coumaroyl)glucoside	Flavonoids	Flavonols
Kaempferol-3- <i>O</i> -neohesperidoside	Flavonoids	Flavonols
Kaempferol-3- <i>O</i> -glucorhamnoside	Flavonoids	Flavonols
Quercetin-3- <i>O</i> -glucoside-7- <i>O</i> -rhamnoside	Flavonoids	Flavonols
Tamarixetin-3- <i>O</i> -glucoside-7- <i>O</i> -rhamnoside	Flavonoids	Flavonols
Kaempferol-3- <i>O</i> -glucoside-7- <i>O</i> -rhamnoside	Flavonoids	Flavonols
Isorhamnetin-3- <i>O</i> -neohesperidoside	Flavonoids	Flavonols
Kaempferol-3- <i>O</i> -rutinoside (Nicotiflorin)	Flavonoids	Flavonols
Sexangularetin-3- <i>O</i> -glucoside-7- <i>O</i> -rhamnoside	Flavonoids	Flavonols
Quercetin-3- <i>O</i> -rutinoside (Rutin)*	Flavonoids	Flavonols
3'-methoxyquercetin-3- <i>O</i> -L-rhamnosyl(1→2)-glucopyranoside	Flavonoids	Flavonols
7- <i>O</i> -Methylaloesin	Flavonoids	Other flavonoids
Aloeresin A	Flavonoids	Other flavonoids
Aloeresin C	Flavonoids	Other flavonoids
2"- <i>O</i> -Feruloyl aloesin	Flavonoids	Other flavonoids
Aloeresin E	Flavonoids	Other flavonoids
Aloeresin D	Flavonoids	Other flavonoids
6"- <i>O</i> - <i>p</i> -Coumaroyl-aloesin	Flavonoids	Other flavonoids
Aloeresin G	Flavonoids	Other flavonoids
Coumarin	Lignans and coumarins	Coumarins
Hydrangenol- <i>O</i> -glucoside- <i>O</i> -glucoside	Lignans and coumarins	Coumarins
Palmitaldehyde	Lipids	Free fatty acids
γ -Linolenic acid	Lipids	Free fatty acids
α -Linolenic acid	Lipids	Free fatty acids
Elaidic acid	Lipids	Free fatty acids
LysoPC 18:2(2n isomer)	Lipids	LPC
Quinic acid	Organic acids	Organic acids
Muconic acid	Organic acids	Organic acids
<i>cis</i> -Aconitic acid	Organic acids	Organic acids
Citric acid	Organic acids	Organic acids
Homocitrate	Organic acids	Organic acids
<i>L</i> -Malic acid	Organic acids	Organic acids
2-Methyl-5-acetonyl-7-hydroxychromone glucoside	Others	Chromone
8- <i>C</i> -Glucosyl-7- <i>O</i> -methyl-(<i>R</i>)-aloesol	Others	Chromone
8- <i>C</i> -Glucosyl-(<i>R</i>)-aloesol	Others	Chromone
2,5-Dimethyl-7-hydroxychromone glucoside	Others	Chromone
5-Acetonyl-6-glucosyl-7-hydroxy-2,6-methylchromone	Others	Chromone
Aloesin	Others	Chromone
7- <i>O</i> -methylaloesin A	Others	Chromone
Feralolide	Others	Lactones
4-(β - <i>D</i> -Glucopyranosyloxy)-2,4',6-Trihydroxybenzophenone	Others	Others
4- <i>O</i> -Acetyl-3- <i>O</i> -caffeoyl-2- <i>C</i> -methyl- <i>D</i> -erythronate	Others	Others
3-Dehydro- <i>L</i> -threonic acid	Others	Saccharides

(Continued)

Compounds	Class I	Class II
Glucarate- <i>O</i> -phosphoric acid	Others	Saccharides
Maltotriose	Others	Saccharides
1- <i>O-p</i> -Coumaroylquinic acid	Phenolic acids	Phenolic acids
Dimethyl phthalate	Phenolic acids	Phenolic acids
4-Nitrophenol	Phenolic acids	Phenolic acids
1- <i>O-p</i> -Coumaroyl- β - <i>D</i> -glucose	Phenolic acids	Phenolic acids
3- <i>O</i> -Feruloylquinic acid	Phenolic acids	Phenolic acids
3- <i>O-p</i> -Coumaroylquinic acid	Phenolic acids	Phenolic acids
5- <i>O-p</i> -Coumaroylquinic acid	Phenolic acids	Phenolic acids
Chlorogenic acid (3- <i>O</i> -Caffeoylquinic acid)	Phenolic acids	Phenolic acids
Neochlorogenic acid (5- <i>O</i> -Caffeoylquinic acid)	Phenolic acids	Phenolic acids
1-Caffeoylquinic acid	Phenolic acids	Phenolic acids
(7 <i>S</i> ,8 <i>R</i>)-dehydrodiconiferylalcohol-9'- <i>O</i> - β - <i>D</i> -glucopyranoside	Phenolic acids	Phenolic acids
6- <i>O</i> -Caffeoylarbutin	Phenolic acids	Phenolic acids
Cryptochlorogenic acid (4- <i>O</i> -Caffeoylquinic acid)	Phenolic acids	Phenolic acids
2''- <i>O</i> -Feruloyl-aloesin	Quinones	Anthraquinone
8- <i>O</i> -Methyl-7-hydroxyaloin B	Quinones	Anthraquinone
6'-Malonylnataloin	Quinones	Anthraquinone
Aloin B	Quinones	Anthraquinone
10-Hydroxyaloin A	Quinones	Anthraquinone
7-Hydroxyaloin	Quinones	Anthraquinone
Emodin-6- <i>O</i> -glucoside	Quinones	Anthraquinone
Emodin-8- <i>O</i> -glucoside	Quinones	Anthraquinone
Aloin A	Quinones	Anthraquinone
3,8-Dihydroxy-1-methoxy-9,10-anthraquinone glucoside	Quinones	Anthraquinone
Danthron; 1,8-Dihydroxyanthraquinone	Quinones	Anthraquinone
Nataloin	Quinones	Anthraquinone
5-Hydroxyaloin A	Quinones	Anthraquinone
5-Hydroxyaloin	Quinones	Anthraquinone
Hydroxy aloes-emodin-8- <i>O</i> -glucoside	Quinones	Anthraquinone
Aloe emodin	Quinones	Anthraquinone

3.5 Metabolites enrichment analysis of 15 typical medicinal *Aloe* species

According to dendrogram results, the top 25 main functional components of Group 1 were as follows: isohemiphloin, aloin B, 8-*O*-methyl-7-hydroxyaloin B, aloin A, 10-hydroxyaloin A, aloeresin D, 3-*O-p*-coumaroylquinic acid, 5-*O-p*-coumaroylquinic acid, 8-*C*-glucosyl-7-*O*-methyl-(*R*)-aloesol, quinic acid, aloeresin E, dimethyl phthalate, 3-dehydro-*L*-threonic acid, histidinol, nataloin, kaempferol-3-*O*-glucoside-7-*O*-rhamnoside, kaempferol-3-*O*-rutinoside(nicotiflorin), luteolin-7-*O*-rutinoside, kaempferol-3-*O*-glucorhamnoside, kaempferol-3-*O*-neohesperidoside, muconic acid, 2-methyl-5-acetonyl-7-hydroxychromone glucoside, danthron, 4-nitrophenol, and palmitaldehyde (Fig. 4B).

Six species, namely *A. arborescence* (AL01), *A. kedongensis* (AL04), *A. secundiflora* (AL08), *A. greatheadii* var. *davyana* (AL13), *A. zebrina* (AL14), and *A. dewetii* (AL15), constituted Group 2 (Fig. 4). The top 25 main functional components in Group 1 were 1-*O-p*-coumaroylquinic acid, dimethyl phthalate, histidinol, quinic acid, 4-nitrophenol, muconic acid, danthron, palmitaldehyde, *L*-phenylalanine, *cis*-aconitic acid, 3-dehydro-*L*-threonic acid, citric acid, 3-carbamyl-1-

methylpyridinium (1-methylnicotinamide), trigonelline, homocitrate, 3-*O-p*-coumaroylquinic acid, 5-*O-p*-coumaroylquinic acid, 6'-malonylnataloin, aloin B, apigenin-5-*O*-glucoside, nataloin, tricin-7-*O*-(6''-*O*-malonyl) glucoside, Nap-Ser-OH, aloeresin A, and aloeresin C (Fig. 4B).

Group 3 chiefly contained *A. vera* var. *chinensis* (AL03), *A. marlothii* (AL05), *A. ferox* (AL06), *A. divaricata* (AL07), *A. rupestris* (AL09), *A. petricola* (AL10), *A. africana* (AL11), and *A. excelsa* (AL12) (Fig. 4B). The top 25 main functional components in this group were 7-*O*-methylaloesin, quinic acid, 2-methyl-5-acetonyl-7-hydroxychromone glucoside, histidinol, dimethyl phthalate, 4-nitrophenol, danthron, muconic acid, 3-dehydro-*L*-threonic acid, palmitaldehyde, citric acid, 5-*O-p*-coumaroylquinic acid, 3-*O-p*-coumaroylquinic acid, kaempferol-3-*O*-neohesperidoside, *L*-malic acid, kaempferol-3-*O*-glucoside-7-*O*-rhamnoside, kaempferol-3-*O*-rutinoside (Nicotiflorin), luteolin-7-*O*-rutinoside, kaempferol-3-*O*-glucorhamnoside, 7-hydroxyaloin, aloin B, aloin A, aloeresin C, 7-*O*-methylaloesin A, and aloeresin A (Fig. 4).

In summary, KEGG cluster analysis of the dominant medicinal components revealed significantly enriched pathways, such as those for aminoacyl-tRNA biosynthesis; phenylalanine, tyrosine,

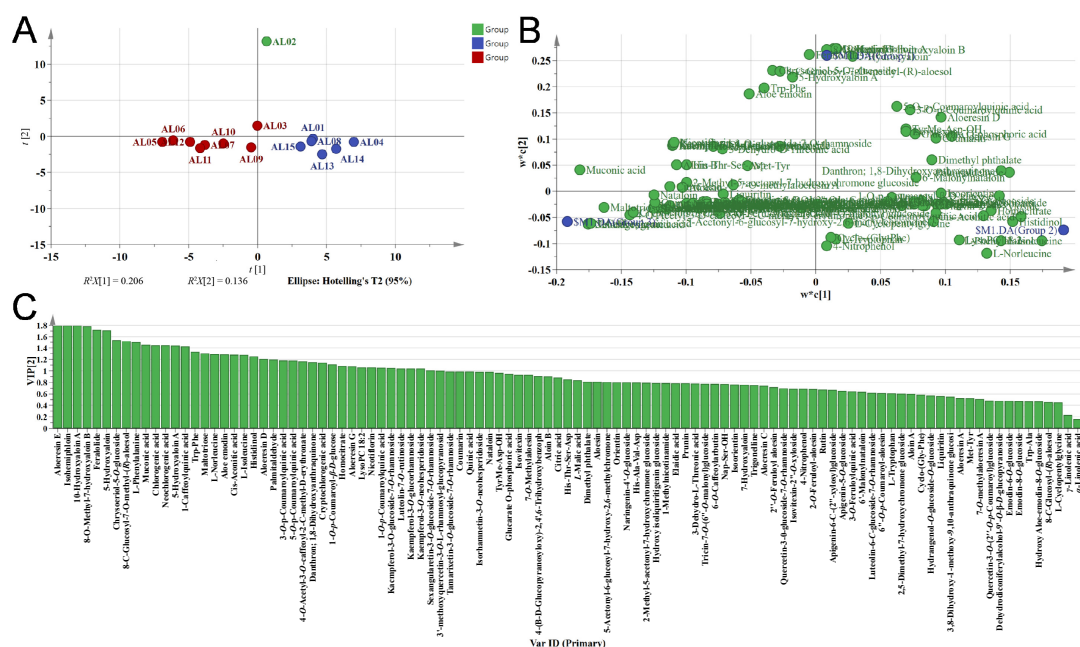


Figure 5 Chemodiversity classification of fifteen typical medicinal *Aloe* species. (A) Score plots, (B) loading plot, and (C) VIP values from PLS-DA analysis based on the main functional components of the three groups.

and tryptophan biosynthesis; valine, leucine, and isoleucine biosynthesis; phenylalanine metabolism; the citrate cycle; glyoxylate and dicarboxylate metabolism; as well as that for valine, leucine, and isoleucine degradation. (Fig. 6). These medicinal

functional component analyses thus provide robust foundation for harnessing and developing the applied functions of *Aloe* species in the future.

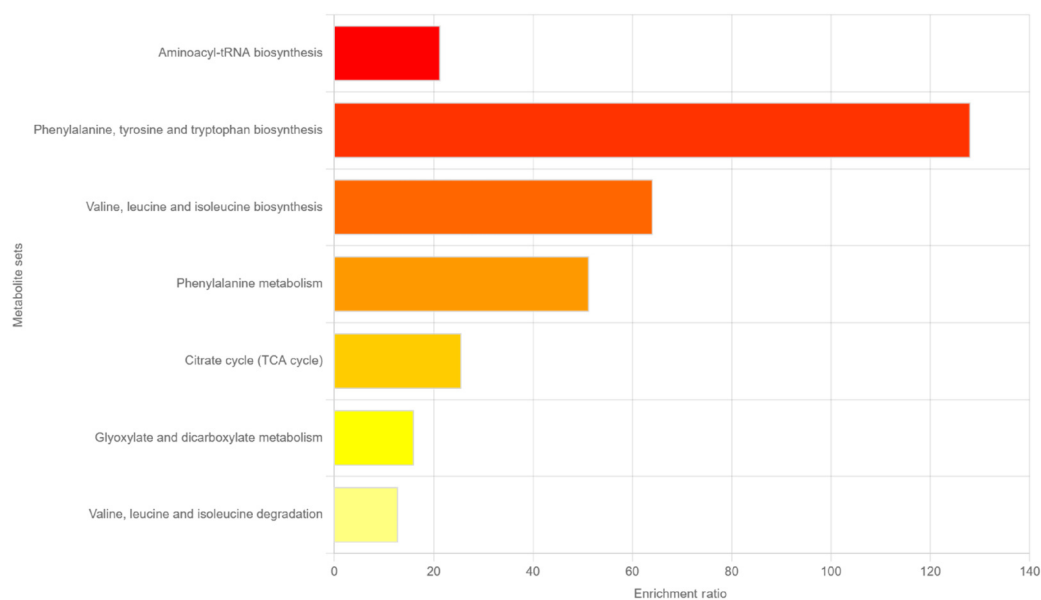


Figure 6 Overview of enriched metabolite sets of fifteen typical medicinal *Aloe* species.

4 Discussion

Several studies have demonstrated that certain *Aloe* species, including *A. vera*, *A. arborescens*, *A. ferox*, and *A. saponaria* (Fig. 1), possess anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and other therapeutic properties. In particular, *A. arborescens*, *A. barbadensis*, *A. ferox*, and *A. vera* are among the most extensively studied species to date. These currently rank among the most economically significant medicinal plants and are

widely utilized in primary healthcare, where they play a crucial role in treating various diseases by modulating biochemical and molecular pathways^[30]. The gel of *A. maculata* is rich in polysaccharides, while also containing a small amount of phenolic compounds. Among its non-cellulosic polysaccharides, pectins and acemannan have been identified as the main components^[31]. The composition and concentration of components in gel differ based on geographic origin or species. Therefore, identifying the active compounds in *Aloe* is crucial for its optimal use^[24]. The

melatonin and anthraquinone present in *Aloe* are key contributors to glycogen synthesis, beta cell recovery, insulin release, and carbohydrate metabolism^[32]. The flowers of *Aloe* plants contain volatile compounds and ascorbic acid, while their leaves are rich in organic acids, phenolics, enzymes, vitamins, and minerals; the rind, on the other hand, contains pectin, lignin, cellulose, hemicellulose, and polysaccharides^[10,28]. Due to the presence of various bioactive compounds, *A. vera* leaves have long been linked to numerous medicinal benefits^[33].

The gel is produced in the thin middle layer of *A. vera* leaf, contains a variety of physiologically active components, including vitamins, enzymes, lignin, sugars, minerals, saponins, amino acids, and salicylic acids^[7,13]. The glycoprotein fraction in *A. vera* gel is known to promote cellular proliferation and growth in human fibroblasts and keratinocytes^[34,35]. The tissue-regenerating function of *A. vera* is chiefly due to the synergistic action of its many bioactive compounds^[36]. In Chinese medicine, *A. vera* is employed for a wide range of purposes, which include treating diabetes, reducing hypertension, and infection control^[37]. Fresh leaves of *A. vera* consist of two major components: anthraquinones and a clear mucilaginous gel extracted from the leaf pulp, the latter commonly used for the topical treatment of skin wounds and burns^[8]. Phenolic compounds in *Aloe* include anthraquinone C- and O-glycosides, anthrones, and other hydroxyanthraquinone derivatives (HADs). The primary C-glycoside, aloin A, which happens to be the dominant HAD in aloe latex, yields aloe-emodin upon oxidation^[25].

The metabolic profiles of different *Aloe* species are closely related to their pharmacological activities. For example, aloin and aloe-emodin are well-known for their laxative, anti-inflammatory, and anticancer activities^[38,39]. Variations in the concentrations of these compounds among different *Aloe* species could influence their therapeutic potential and guide their selection for specific health benefits. Additionally, the presence of flavonoids and phenolic acids, known for their antioxidant, antimicrobial, and anti-inflammatory properties, and their differing concentrations could impact the antimicrobial potential of *Aloe*-based products^[7,24,40]. The levels of phenols, flavonoids, and tannins in plants and their corresponding biological activities depend on a suite of factors, such as the source species, the plant part used, as well as the extraction method^[41]. Thus, understanding these metabolic variations of *Aloe* species informs their future applications in food and medicine industry.

5 Conclusion

Aloe species possess extensive bioactive properties, including immune modulation, antioxidant, antimicrobial, antibacterial, antifungal, and antitumor activities, which make these plants valuable for use in cosmetics, therapeutics, tonics, health drinks, and other products. The rich content of secondary metabolites in *Aloe* plants contribute to their functional diversity. This study's results revealed the broad chemodiversity of *Aloe* species, leading to the identification of three core groups. Group 1 consists solely of species AL02, while group 2 is represented by six species: AL01, AL04, AL08, AL13, AL14, and AL15. Group 3 is predominantly comprised AL03, AL05, AL06, AL07, AL09, AL10, AL11, and AL12. Among these, aloeresin E, isohemiphloin, 10-hydroxyaloin A, 8-O-methyl-7-hydroxyaloin B, feralolide, and 5-hydroxyaloin are distinguishable as potential chemical classification markers. Furthermore, the metabolite enrichment analysis shows that the metabolite sets of *Aloe* species are primarily involved in pathways

such as aminoacyl-tRNA biosynthesis; phenylalanine, tyrosine, and tryptophan biosynthesis; valine, leucine, and isoleucine biosynthesis; phenylalanine metabolism; the citrate cycle; glyoxylate and dicarboxylate metabolism; and valine, leucine, and isoleucine degradation. Overall, this empirical study provides crucial insights for the development of distinct medicinal functions across various *Aloe* species, paving the way for their future applications.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgments

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