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Research Article

Chemical composition, enzyme inhibitory activities, and molecular docking studies of essential oil of *Knema globularia* leaves from Vietnam

Nguyen Thi Ngan[1], Trang H. D. Nguyen[1], Danh C. Vu[2], Nguyen Xuan Ha[3], Hieu Tran-Trung[4], Le Duc Giang[4], Phan Thi Thuy[4], Vi Thi Thuan[4], Bui Van Huong[5,6], Sy Vo Van[7] and Hoang Van Trung[8]*

[1] Institute of Biotechnology and Food Technology, Industrial University of Ho Chi Minh City, Ho Chi Minh City, Vietnam
[2] Institute of Applied Technology, Thu Dau Mot University, Binh Duong, Vietnam
[3] Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam
[4] Department of Chemistry, Vinh University, Vinh City, Nghean, Vietnam
[5] Vietnam National Museum of Nature, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam
[6] Graduate University of Science and Technology, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam
[7] Department of Pharmacy, Da Nang University of Medical Technology and Pharmacy, Vietnam
[8] School of Chemistry, Biology and Environment, Vinh University, Vinh City, Nghean, Vietnam

***Corresponding Author**
Hoang Van Trung
hoangtrungdhv@gmail.com

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Abstract
In the present work, chemical composition, enzyme inhibitory activities, and molecular docking studies of essential oil (EO) of *Knema globularia* leaves collected from Vinh Phuc Province, Vietnam, were investigated. The EO from the leaves of *K. globularia* was obtained by hydrodistillation and analyzed by gas chromatography-mass spectrometry (GC-MS) analysis. The leaf EO yield was 0.14 ± 0.01% (w/w), comprising 39 identified components, constituting 96.77% of the EO content. Notable constituents included β-caryophyllene (54.11%), α-humulene (12.67%), and (*E*)-β-ocimene (8.82%). Enzyme inhibitions were assessed via the α-amylase inhibitory assay (IC_{50} = 282.71 ± 10.06 µg/mL) and tyrosinase inhibitory assay (IC_{50} = 993.92 ± 37.40 µg/mL). The molecular docking method has been employed to observe valuable binding interactions and binding energy with the main compounds on the target enzymes α-amylase and tyrosinase. Caryophyllene oxide exhibits the strongest affinity with α-amylase among the other major compounds. Meanwhile, viridiflorene shows the best binding energy with the tyrosinase enzyme. This is the first study providing valuable scientific data on the *in vitro* inhibitory activities of α-amylase and tyrosinase enzymes of the leaf EO of *K. globularia* and evaluating its main compounds through a molecular docking approach on these enzyme targets.

Keywords
Knema globularia, Essential oil, GC-MS, Enzyme inhibitions, Molecular docking.

INTRODUCTION

Genus *Knema* Lour. belongs to the family Myristicaceae, which is abundant in regions spanning from Northern to Southern Vietnam. Among the over 60 species discovered worldwide, at least 13 have been found in various areas of Vietnam[1-3]. *Knema globularia* (Fig. S1), known as "Máu chó cầu" in Vietnamese, is often found in the wild in mountainous forested regions. In folk medicine, *K. globularia* is used to treat certain ailments. For example, the bark can address ulcers and boils[4], while the oil from the seeds is a topical treatment for skin conditions like scabies[1]. The chemical composition and pharmacological activities of *K. globularia* have been extensively documented in previous studies. Various classes of compounds including flavonoids, polyketides, steroids, and others extracted from this species have been reported[5-9]. Some previous studies have demonstrated that this species may exhibit inhibitory effects

against HepG2 (Hepatoblastoma cell line), MCF-7 (Breast cancer cell line), SK-LU-1 (Lung adenocarcinoma cell line), KKUM156 (Intrahepatic cholangiocarcinoma cell line), NCIH187 (Lung small cell carcinoma), and KB (A subline of the ubiquitous KERATIN-forming tumor cell line HeLa)[5-7]. Furthermore, the essential oil (EO) of *K. globularia* leaves from Thua Thien Hue, Vietnam has been investigated for its chemical composition. The main components of the EO include β-elemene, α-copaene, β-caryophyllene, and α-humulene, and this EO exhibits antioxidant activity[10].

In the current study, the chemical composition of the leaf EO of *K. globularia* growing wild from Vinh Phuc Province, Vietnam was reported, as well as *in vitro* α-amylase and tyrosinase inhibitory activities were investigated for the first time, which has been lacking in the literature. To give a deeper understanding of the interactions between the active constituents found in the *K. globularia* EO and the target enzymes, namely α-amylase and tyrosinase, *in silico* molecular docking studies were performed. This computational approach enabled us to investigate how these compounds bind to the enzymes, uncovering insights into their binding strengths and modes.

Materials and Methods

Plant materials

K. globularia leaves used in the current study were collected in July 2023 from Phuc Yen District, Vinh Phuc Province (21°23'19.7"N 105°42'54.2"E), Vietnam. The identification of species was identified by Msc. Bui Van Huong (Vietnam National Museum of Nature, VAST, Vietnam). A voucher specimen (BVH-05) was deposited at the Vietnam National Museum of Nature.

Chemicals

A hydrocarbon mixture (C_7-C_{30} *n*-alkanes), sodium sulfate (Na_2SO_4), and dichloromethane (CH_2Cl_2) were purchased from Merck (Darmstadt, Germany). Acarbose, kojic acid, L-DOPA (3,4-dihydroxy-L-phenylalanine), α-amylase from *Bacillus* sp., and tyrosinase from mushroom were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Essential oil isolation

The EO of fresh leaves of *K. globularia* (500 g) was obtained after hydrodistillation that lasted for 4.0 h utilizing a Clevenger-type apparatus. The process was performed in triplicate. Then the EO was subsequently dried over anhydrous sodium sulfate (Na_2SO_4) and collected in a sealed vial that was kept at 4°C till analyses. The yield was calculated as % w/w based on the fresh sample weight.

Gas chromatography-mass spectrometry (GC-MS) analysis

The GC-MS analysis of *K. globularia* EO was carried out by using a Gas Chromatograph (7890B GC) coupled with a Mass Selective Detector (5977B MSD). Analytical conditions of the GC-MS system are presented in Table 1.

Identification of chemical constituents of the EO was done based on the comparison of their mass spectral and retention indices (RIs) in the National Institute of Standards and Technology (NIST17) and Adams books[11].

Inhibition of α-amylase

The assay was based on a previously published method, with minor modifications[12]. A diluted EO from *K. globularia* leaves (0.75 mL) was combined with α-amylase (0.14 U/mL, 0.15 mL) in a phosphate buffer (pH 6.9) and incubated for 15 min at 37°C. Subsequently, 0.225 mL of a starch solution (0.25%) was introduced to initiate the reaction, followed by an additional 15-min incubation at the same temperature. The blank sample underwent the same process, excluding the addition of α-amylase. To stop the reaction, 0.75 mL of 1 M HCl was employed, followed by the addition of 1.5 mL of KI_3 solution. The absorbance was measured spectrophotometrically at 620 nm. The percentage of enzymatic activity inhibition was calculated using the formula:

Percentage of inhibition (%) = [1 - (As/Ab)] × 100%

where, As and Ab represent the absorbance of the sample and blank, respectively. Acarbose

Table 1. GC-MS analytical conditions

Instrument	Gas Chromatograph (7890B GC) linked with Mass Selective Detector (5977B MSD) (Agilent Technologies)
Column	HP-5MS UI (30 m × 0.25 mm × 0.25 µm)
Inlet-F and Aux-2 temperatures	300°C
MS Quad temperature	150°C
MS source	230°C
Oven temperature	Initial 60°C (hold for 1 min), rise to 240°C at 4°C/min (hold for 4 min)
Injection volume	1.0 µL (split ratio 25:1)
Carrier gas	Helium (flow rate 1.0 mL/min)
Ionization voltage	70 eV
Scanning range	50-550 amu

served as a reference standard. IC_{50} values (µg/mL) were used to assess the EO's activity.

Inhibition of tyrosinase

The capacity of the EO to inhibit tyrosinase was evaluated following a previously described report[13]. The diluted EO (125-1000 µg/mL, 100 µL) was mixed with tyrosinase (80 U/mL, 40 µL) and L-DOPA (0.5 mM, 40 µL). The mixture was then incubated at 37°C for 20 min, and the absorbance was recorded at 490 nm. Kojic acid served as a reference standard.

Molecular docking

The employment of molecular docking offers advantages as it enables the prediction of the structure of intermolecular complexes resulting from interactions among two or more molecules[14]. To assess the interaction between the primary compounds within the EO that possess inhibitory effects on α-amylase and tyrosinase, the AutoDock Vina v1.2.3 software was utilized[15,16]. The crystallographic data for α-amylase and tyrosinase enzymes were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/) under the respective identifiers 5E0F and 5M8M[17-19]. Subsequently, the protein structures underwent a preparation process involving adding hydrogen atoms, and removing unnecessary molecules (water, ions, and the co-crystallized ligands). The partial charges utilizing the Kollman-Gasteiger method were executed using the AutodockTools 1.5.7 software and converted to PDBQT format. The ligands selected for the study represent the principal constituents of the EO sample, specifically β-caryophyllene, α-humulene, *(E)*-β-ocimene, β-phellandrene, viridiflorene, and caryophyllene oxide. The three-dimensional (3D) structures of these ligands were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These compounds were then optimized using the MMFF94s force field and converted to the *.pdbqt format through the AutodockTools 1.5.7 software[20]. The target proteins were maintained in a rigid conformation during the docking process, while the studied compounds retained their flexibility. The docked poses and the 2D target-ligand interactions were visualized using the BIOVIA Discovery Studio software (https://www.3ds.com/products/biovia/discovery-studio/visualization).

Results and Discussion

The yield and volatile composition of the EO

The hydrodistillation of *K. globularia* leaves produced the EO with an average yield of 0.14 ± 0.01% (w/w), calculated on fresh weight basis. The GC chromatogram of the *K. globularia* leaf EO is displayed in Fig. S2. As presented in Table 2, a total of 39 volatile compounds (representing 96.77% of the content) were identified in the leaf EO.

Among these, fifteen sesquiterpene hydro-

carbons are the predominant constituents, reaching 75.32% of the *K. globularia* leaf EO. The other significant compound classes include monoterpene hydrocarbons (14.59%) and oxygenated sesquiterpenes (6.43%). Besides, oxygenated monoterpene and other compounds had lower concentrations, comprising 0.12 and 0.31%, respectively. The major compounds (> 5%) in the *K. globularia* leaf EO belong to the classes of sesquiterpene hydrocarbons and monoterpene hydrocarbons, with β-caryophyllene, α-humulene, and (*E*)-β-ocimene constituting 54.11, 12.67, and 8.82% of the total content. Furthermore, several prominent

Table 2. Chemical constituents of *K. globularia* leaf EO

No.	RT (min)	Compounds	RI (cal.)	RI (lit.)	Area (%)
1	5.553	α-Pinene	940	937	0.70
2	6.618	β-Pinene	982	979	0.64
3	6.944	β-Myrcene	993	991	0.58
4	7.327	Pseudolimonen	1007	1004	0.13
5	8.048	β-Phellandrene	1033	1031	3.24
6	8.271	(*Z*)-β-Ocimene	1042	1038	0.25
7	8.603	(*E*)-β-Ocimene	1053	1049	8.82
8	9.845	Terpinolene	1091	1088	0.15
9	10.183	Linalool	1100	1099	0.12
10	10.320	Nonanal	1105	1104	0.06
11	10.720	(*E*)-4,8-Dimethylnona-1,3,7-triene	1119	1116	0.20
12	11.127	Neo-allo-ocimene	1133	1131	0.08
13	13.021	*trans*-3-Hexenyl butyrate	1189	1185	0.05
14	17.982	δ-Elemene	1341	1338	0.59
15	19.229	α-Copaene	1380	1376	0.17
16	19.744	β-Elemene	1395	1391	0.94
17	20.225	(*Z*)-β-Caryophyllene	1410	1406	0.36
18	20.328	α-Gurjunene	1414	1409	0.08
19	20.740	(*E*)-β-Caryophyllene	1428	1419	54.11
20	21.215	Aromandendrene	1443	1440	0.58
21	21.695	α-Humulene	1459	1454	12.67
22	21.815	Valerena-4,7(11)-diene	1463	1460	0.21
23	22.662	β-Eudesmene	1490	1486	1.06
24	22.800	δ-Selinene	1494	1493	0.06
25	22.931	Viridiflorene	1498	1493	2.55
26	23.063	α-Muurolene	1503	1499	0.07
27	23.280	α-Farnesene	1510	1508	1.06
28	23.753	β-Sesquiphellandrene	1527	1524	0.81
29	24.911	(*E*)-Nerolidol	1567	1564	1.12
30	25.054	Maaliol	1572	1574	0.20
31	25.346	Spathulenol	1582	1577	0.36
32	25.523	Caryophyllene oxide	1587	1581	2.30
33	25.764	Viridiflorol	1595	1591	0.49
34	25.815	Guaiol	1597	1596	0.17
35	26.050	Rosifoliol	1605	1600	0.38

Table 2 ***cont***.

No.	RT (min)	Compounds	RI (cal.)	RI (lit.)	Area (%)
36	26.267	Humulene-1,2-epoxide	1613	1606	0.15
37	26.885	γ-Eudesmol	1636	1631	0.22
38	27.515	α-Eudesmol	1659	1653	0.66
39	27.967	β-Bisabolol	1675	1671	0.38
Total					**96.77**
Monoterpene hydrocarbons					14.59
Oxygenated monoterpenes					0.12
Sesquiterpene hydrocarbons					75.32
Oxygenated sesquiterpenes					6.43
Others					0.31

RT (min): Retention time (min); RI (cal.): Retention indices obtained in HP-5MS UI column; RI (lit.): Retention indices obtained from the literature

compounds (> 2%) were observed, including β-phellandrene (3.24%), viridiflorene (2.55%), and caryophyllene oxide (2.30%). In comparison with previous research, β-caryophyllene and α-humulene constituted lower percentages in the current study, with respective percentages of 9.37 and 8.42% in *K. globularia* leaf EO from Thua Thien Hue, Vietnam[10]. Meanwhile, the percentages of β-elemene and α-copaene in their study were significantly higher, at 25.48 and 17.05%, respectively, in contrast to our current study, which comprised only 0.94 and 0.17%, respectively. These differences can be attributed to various factors, such as the harvest season, environmental conditions, and geographic location[21].

Recently, some studies on the EOs of *Knema* species have been reported. The EOs of *K. hookeriana, K. kunstleri, and K. pierrei* all featured a predominant sesquiterpene hydrocarbon, β-caryophyllene, similar to *K. globularia* in our current study, with respective percentages of 26.2, 23.2, and 10.74%[22-24]. Similarly, with β-caryophyllene, α-humulene is also a significant component in the EOs of *K. kunstleri* and *K. pierrei*[22,24]. On the other hand, the two primary compounds found in *K. globularia*'s EO in this study were not present in *K. malayana* and *K. angustifolia* species[25,26]. These findings demonstrate the diversity in the chemical components of *Knema*'s essential oils recommending for the studies of potential uses of this genus in the future.

α-Amylase inhibitory activity of the EO

In the present study, the *K. globularia* leaf EO was tested for its α-amylase inhibitory activity, and the results are presented in Fig. 1. Within the examined concentration range (62.5-500 µg/mL), there was a consistent rise in the enzyme inhibition percentage with increasing concentration values. In other words, the inhibitory effect of the EO on *α*-amylase followed a concentration-dependent manner. The IC_{50} value estimated for the inhibitory effect of the EO was 282.71 ± 10.06 µg/mL. Compared to acarbose (IC_{50} = 88.79 ± 1.87 µg/mL), the EO exerted a weaker inhibitory activity against the enzyme. No information about α-amylase inhibitory activity of EO from *Knema* species has been reported. However, dichloromethane extracts of *K. glauca* were shown to strongly inhibit the enzyme[27]. Evidence has also indicated that some species belonging to the Myristicaceae family may possess anti-α-amylase activity, including *Myristica fragrans* and *Myristica fatua*[28,29].

As discussed earlier, β-caryophyllene was the most abundant compound in the EO. It has been found as a major constituent in EOs from *Aframomum melegueta*, *A. danielli*, and *Phlomis* species which possessed α-amylase inhibitory activity[30,31]. Another major compound in the

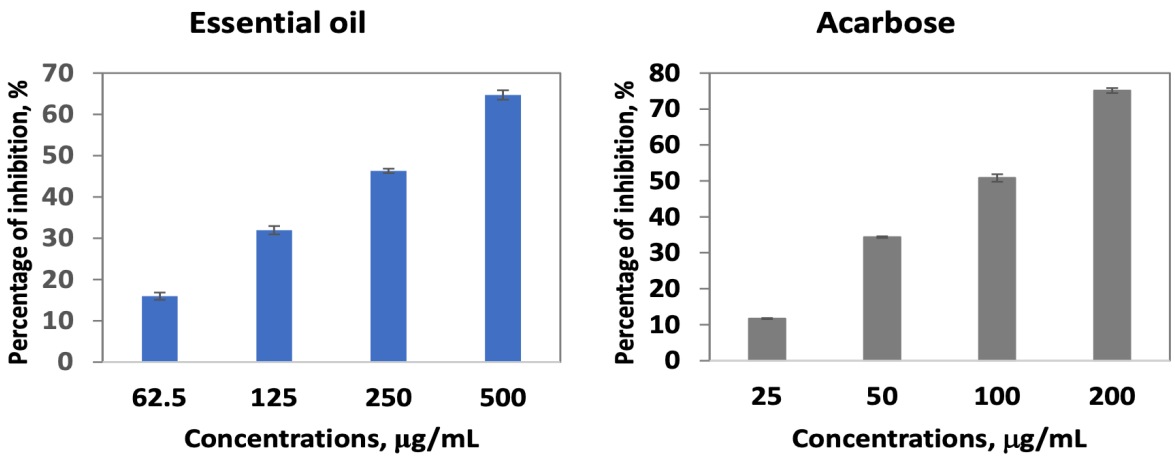

Figure 1. α-Amylase inhibitory activity of the *K. globularia* leaf EO and acarbose

EO is *(E)*-β-ocimene, which was previously reported to potentially contribute to α-amylase inhibition[32,33]. Thus, it is suggested that the inhibitory activity of the *K. globularia* leaf EO may be linked to the presence of these chemicals in its content.

Tyrosinase inhibitory activity of the EO

As presented in Fig. 2, in the tested concentration range (125-1000 µg/mL), a consistent increase in the percentage of enzyme inhibition was observed as the concentration values rose. This means that the inhibitory activity of the EO against tyrosinase demonstrated a concentration-dependent manner. The IC_{50} value determined for the inhibitory effect of the EO was 993.92 ± 37.40 µg/mL, which is much greater than kojic acid (IC_{50} = 62.03 ± 1.30 µg/mL). This showed a weaker inhibitory effect of the EO on tyrosinase in comparison with kojic acid, which is widely recognized as a tyrosinase inhibitor and commonly used as a skin-whitening ingredient in cosmetics[34]. Some volatile compounds, such as α-pinene, myrcene, and β-caryophyllene found to be present in the *K. globularia* EO were previously reported to have tyrosinase inhibitory activity[35-37]. The antityrosinase activity of EOs from other *Knema* species has been documented. For instance, *K. intermedia* and *K. malayana* EOs had moderate capacities to inhibit tyrosinase[26,38]. Moreover, this was reported to be attributed to the presence of δ-selinene and α-amorphene in their contents, respectively.

Molecular docking

Many studies have used molecular docking as an essential tool for predicting the binding energy and mode of ligands that have biological activity for target enzymes[39,40]. The process of the re-docking of co-crystallized ligands into the binding region of the specific proteins was performed to verify the active site as well as the reliability of the docking protocol. The two co-crystallized ligands, mini-montbretin A and kojic acid, were removed and re-docked in the active site of the downloaded complexes. Comparing the two states of co-crystallization and docked ligand shows that the position and ability to form interactions are within the allowable range (RMSD < 2Å), as demonstrated in Fig. S3.

In this section, we investigated docking simulation of the primary compounds in the EO of *K. globularia* to explore their potential in inhibiting α-amylase and tyrosinase enzymes. The results of the molecular docking process are presented in Fig. 3 and Fig. 4, illustrating the binding affinity values for the target proteins. The interactions between ligands and target proteins are depicted in Fig. S4 and Fig. S5.

The major components had binding affinities for the *α*-amylase enzyme ranging from -4.947 to -7.648 kcal/mol (Fig. 3). Of them, caryophyllene oxide is the ligand that can make the strongest interaction, with a binding energy of -7.648 kcal/mol, higher than that of the control compound acarbose (-7.632 kcal/mol). This compound exhibited four pi-alkyl interactions

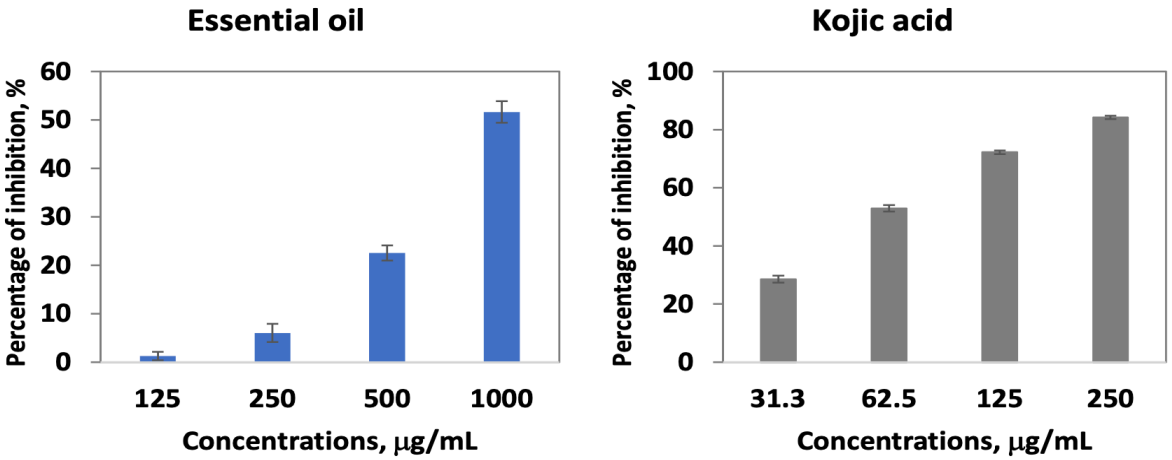

Figure 2. Tyrosinase inhibitory activity of the EO and kojic acid

at amino acid residues Trp58, Trp59, Tyr62, and His299, among other interactions with proteins. Similarly, β-caryophyllene and α-humulene also produce interactions with Trp59 and Tyr62 residues. Additionally, a Leu165 residue was observed within the complex that interacts with these compounds. As presented in Fig. 3, both compounds, β-caryophyllene and α-humulene showed binding energies of -7.569 and -7.097 kcal/mol, respectively. The compounds *(E)*-β-ocimene and viridiflorene showed main interactions including pi-sigma, pi-alkyl, and alkyl types. Specifically, *(E)*-β-ocimene forms only one pi-sigma interaction with Tyr62, while viridiflorene forms two pi-sigma interactions with Tyr62 and Trp59. Additionally, alkyl and pi-alkyl interactions are also indicated, such as those formed by *(E)*-β-ocimene with Ala198, His101, Trp59, His299, and Leu162. In contrast, viridiflorene interacts with Leu165, His101, Trp58, and His299. The active site of the α-amylase enzyme identified as previously documented had hydrogen bonds and hydrophobic interactions with the key amino acid residues of the α-amylase enzyme and inhibitors included Tyr62, Trp58, Trp59, Tyr62, Leu162, Leu165, His299, Asp300, and His305[41,42]. The establishment of connections at these crucial locations can show how well the main chemicals work to block the α-amylase enzymes.

Fig. 4 demonstrates that the most critical

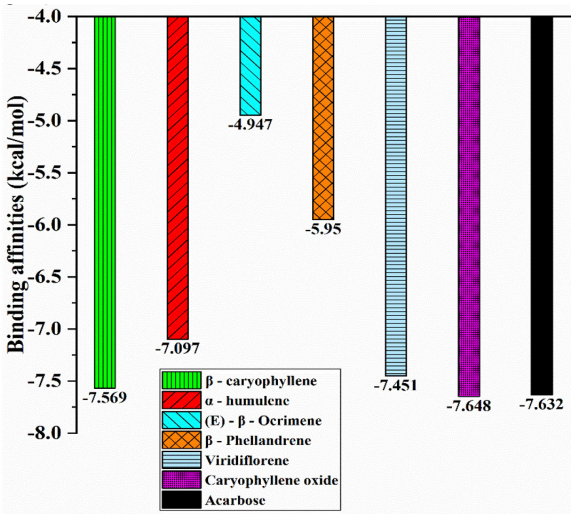

Figure 3. Binding energies of the significant components and control compounds in the active site of α-amylase enzyme calculated using the AutoDock Vina v1.2.3 program

components in the leaf EO exhibit binding affinities approximately comparable to the positive control compound, kojic acid (-5.381 kcal/mol), in the study of the tyrosinase enzyme. However, components with high concentrations such as *(E)*-β-ocimene (-4.605 kcal/mol), α-humulene (-5.347 kcal/mol), and β-caryophyllene (-5.343 kcal/mol) show a reduced interaction ability. In contrast, compounds with high binding affinities have lower concentrations, including β-phellandrene (-5.413 kcal/mol), caryophyllene oxide (-5.495 kcal/mol), and notably, viridiflorene (-5.893 kcal/mol).

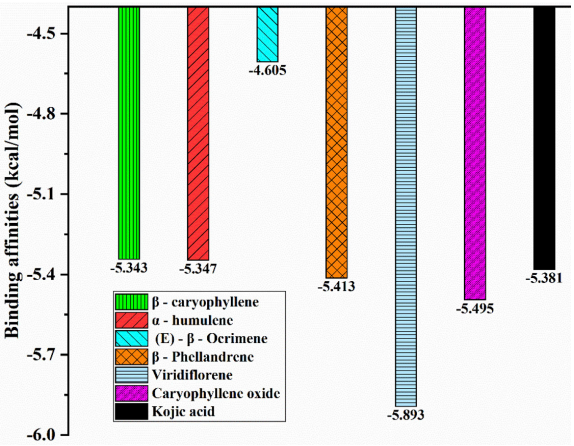

Figure 4. Binding energies of the significant components and control compounds in the active site of tyrosinase enzyme calculated using the AutoDock Vina v1.2.3 program

The interactions primarily involve alkyl and pi-alkyl interactions with amino acid residues in the active site of the tyrosinase enzyme, as illustrated in Fig.S5. β-Caryophyllene and α-humulene had all interacted with residues Tyr362, His215, His377, His381, and Leu382 similarly. Similar interactions with these amino acid residues are also shown by other compounds, along with an extra touch with His381. Notably, viridiflorene, β-phellandrene, and β-caryophyllene interact with important amino acid residue His381 in the active site of the tyrosinase enzyme[18,43]. This finding raises the possibility that some of the constituents of the EO may act as tyrosinase enzyme inhibitors, with a focus on inhibiting pigmentation. The results of the docking simulation show that, compared to tyrosinase, α-amylase activity is more pronounced.

Conclusion

The present study reveals that the chemical profile of the leaf EO of *K. globularia* from Vinh Phuc Province, Vietnam, was dominated by monoterpene hydrocarbons and sesquiterpene hydrocarbons among which β-caryophyllene, α-humulene, and (*E*)-β-ocimene were the most representative components. Moreover, *in vitro* anti-α-amylase, antityrosinase activities of the *K. globularia* leaf EO were reported for the first time, although these results show quite modest inhibitions. In addition, molecular docking study was carried out for the main six components of the leaf EO of *K. globularia* against α-amylase and tyrosinase enzymes. The obtained results attributed these activities to the presence of caryophyllene oxide and viridiflorene, which could be used as lead compounds for the discovery of anti-α-amylase and anti-tyrosinase properties. These findings provide additional scientific evidence regarding the biological activity of the leaf EO of *K. globularia*. Further studies will be conducted to gain a deeper understanding of its mechanism and explore other potential activities.

Competing interests

No potential conflict of interest was reported by the authors.

Supplementary Data

Figures S1 to S5 are given as supplementary data.

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