Botanical Sciences 103 (2): 483-497. 2025
DOI: 10.17129/botsci.3660

Received: January 21, 2025, Accepted: February 21, 2025
On line first: March 15, 2025

Phytochemistry / Fitoquímica

Phytochemical compositions and cytotoxic activity of *Conamomum vietnamense* rhizome fractionated extract: *in vitro* and *in silico* screenings

Chen Tran Van[1], Minh Kiep Do[2], Nguyen Bao Tran Pham[3], Linh Tu Vo[1], Nguyen Cong Luan Pham[4], Hien Nguyen Thi Thu[5], Thanh Triet Nguyen[1]*

[1] Faculty of Traditional Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.
[2] Faculty of Pharmacy, Nam Can Tho University, Can Tho, Vietnam.
[3] Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.
[4] Quang Nam Central General Hospital, Quang Nam Province, Vietnam.
[5] Faculty of Pharmacy, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam.
*Corresponding author: nguyenthanhtriet1702@ump.edu.vn

Abstract

Background: *Conamomum vietnamense* is a new species discovered in Vietnam with important pharmacological potential.
Questions: What are the major phytochemical constituents of *C. vietnamense* rhizomes? Does the n-hexane fraction have cytotoxic effects against five human cancer cell lines (MCF-7, SK-LU-1, HeLa, MKN-7, and HL-60)?
Studied species: *Conamomum vietnamense* N.S.Lý & T.S.Hoang (Zingiberaceae).
Study site and dates: Loc Bac, Bao Lam, Lam Dong, Vietnam, 2022-2023.
Methods: Volatile components and secondary metabolite groups were identified using gas chromatography-mass spectrometry analysis and color/precipitation reactions, respectively. Rhizome n-hexane fractionated extract of *C. vietnamense* was tested against cancer cell lines *in vitro* and *in silico*.
Results: Twenty-three compounds were identified in the rhizome fraction of *C. vietnamense*, where in α-eudesmol (26.84 %), β-eudesmol (15.02 %), cryptomeridiol (14.36 %), γ-eudesmol (6.21 %), eucalyptol (4.38 %), and eudesm-7(11)-en-4-ol (3.11 %) were proved as major compounds. This n-hexane fractionated extract showed a cytotoxic effect against five human cancer cell lines, namely MCF-7, SK-LU-1, HeLa, MKN-7, and HL-60, with IC_{50} values varying from 59.04 to 172.43 µg/mL. Along with the *in vitro* activity test, the docking study demonstrated that α-eudesmol, guaiol, and nerolidol showed the most potential binding affinities to human PTPN2 with binding energies of -29.71, -29.29, and -28.87 kcal/mol, respectively. Furthermore, β-eudesmol, guaiol, and cryptomeridiol exhibited the strongest affinity for the binding site with human IGF-1R kinase with docking scores of -29.29, -28.87, and -32.64 kcal/mol.
Conclusions: The current results implied that *C. vietnamense* rhizomes and its dominant components could be a source of therapeutic interest for cancer.
Keywords: anticancer, bioactivity, gas chromatography-mass spectrometry, molecular docking simulation.

Resumen

Antecedentes: *Conamomum vietnamense* es una nueva especie descubierta en Vietnam con potencial farmacológico.
Preguntas: ¿Cuáles son los principales componentes fitoquímicos de los rizomas de *C. vietnamense*? ¿Tiene la fracción de n-hexano efectos citotóxicos contra cinco líneas celulares de cáncer humano (MCF-7, SK-LU-1, HeLa, MKN-7 y HL-60)?
Especies estudiadas: *Conamomum vietnamense* N.S.Lý & T.S.Hoang (Zingiberaceae).
Sitio y fechas del estudio: Loc Bac, Bao Lam, Lam Dong, Vietnam, 2022-2023.
Métodos: Se identificaron componentes volátiles y metabolitos secundarios mediante cromatografía de gases-espectrometría de masas y reacciones de color/precipitación. El extracto fraccionado con n-hexano del rizoma de *C. vietnamense* se probó contra líneas celulares de cáncer *in vitro* e *in silico*.
Resultados: Se identificaron 23 compuestos en la fracción de rizoma de *C. vietnamense*, siendo los mayoritarios α-eudesmol (26,84 %), β-eudesmol (15,02 %), cryptomeridiol (14,36 %), γ-eudesmol (6,21 %), eucaliptol (4,38 %) y eudesm-7(11)-en-4-ol (3,11 %). Este extracto mostró efecto citotóxico contra cinco líneas celulares de cáncer humano (MCF-7, SK-LU-1, HeLa, MKN-7 y HL-60) con valores de IC_{50} de 59,04 a 172,43 µg/mL. El estudio de acoplamiento demostró que α-eudesmol, guaiol y nerolidol mostraron altas afinidades de unión al PTPN2 humano con energías de -29,71, -29,29 y -28,87 kcal/mol, respectivamente. β-eudesmol, guaiol y criptomeridiol exhibieron afinidad fuerte por el sitio de unión con la quinasa IGF-1R humana con puntajes de -29,29, -28,87 y -32,64 kcal/mol.
Conclusiones: Los rizomas de *C. vietnamense* y sus componentes dominantes podrían ser de interés terapéutico para el cáncer.
Palabras clave: anticancerígeno, bioactividad, cromatografía de gases-espectrometría de masas, simulación de acoplamiento molecular.

Currently, alongside the continuous advancements in science and technology, human living standards have significantly improved, with indispensable contributions from the field of medicine. Over the decades, human awareness regarding health has undergone substantial changes as the burden of disease has gradually shifted towards non-communicable diseases, especially cancer (Wagner & Brath 2012). This is a highly complex condition that poses a severe threat to human life, arising from abnormalities in cellular functioning. The etiology of cancer is believed to result from the independent or combined effects of genetic factors and environmental influences. In 2020, 19.3 million new cancer cases and over 10 million cancer-related deaths were reported worldwide (Sung *et al.* 2021). Among these, breast cancer is the most common type in women, while lung cancer is known to be the leading cause of cancer-related mortality. Along with population growth and aging, the global trends in cancer incidence not only reflect issues associated with modern lifestyles but also underscore the urgent need to explore new, sustainable, and comprehensive solutions (Torre *et al.* 2016). Advancements in surgery, chemotherapy, radiotherapy, and newer approaches such as molecularly targeted therapy and immunotherapy have significantly reduced cancer incidence and improved patient survival rates. However, cancer treatment continues to face considerable challenges, including alarming recurrence rates and the toxicity or inefficacy of certain drugs, which negatively impact patients' quality of life during and after treatment (Mahvi *et al.* 2018). Concurrently with efforts to discover new treatments, complementary and alternative medicine (CAM) has gained recognition as a supportive treatment in managing malignancies, particularly in supportive and palliative care for cancer patients. In developing countries, up to 80 % of the population utilizes natural herbs as a health-friendly therapy (Balaji *et al.* 2022), including cancer management.

Several plant species have been demonstrated to possess antitumor properties, particularly the Zingiberaceae family, one of the largest plant families, comprises approximately 1,300 species of aromatic, flowering, perennial herbs with characteristic creeping or tuberous rhizomes (Alolga *et al.* 2022). Certain notable members of this plant family, such as ginger (*Zingiber officinale* Roscoe), turmeric (*Curcuma longa L.*), etc. possess remarkable biological properties, including anti-inflammatory, antioxidant, antibacterial, and particularly anticancer activities (Alolga *et al.* 2022). Among them, species within the genus *Conamomum Ridl.* have recently garnered increasing attention from the scientific community. Currently, a total of 12 species within this genus are recognized worldwide, with four species (namely *C. odorum* Luu, H.Đ.Trần & G.Tran, *C. pierreanum* (Gagnep.) Škorničk. & A.D.Poulsen, *C. rubidum* (Lamxay & N.S.Lý) Škorničk. & A.D.Poulsen, *C. vietnamense* N.S.Lý & T.S.Hoang) identified in Vietnam (Chen *et al.* 2024). Notably, *C. vietnamense* is considered endemic to primary evergreen and lowland mountain forests in the The Central Highlands region of Vietnam. Recent botanical studies have identified *C. vietnamense* as a herbaceous plant, growing in bushes, reaching heights of 1.2-2.0 m (Nhi *et al.* 2023). Previous studies discovered that the essential oils extracted from *C. vietnamense* leaves and rhizomes were primarily composed of 1,8-cineole and limonene (Nguyen *et al.* 2023, Huong *et al.* 2023, Chen *et al.* 2024). These oils exhibited strong inhibitory effects against the growth of Gram-positive bacteria such as *Staphylococcus aureus* ATCC 29213 and *Bacillus subtilis* ATCC 6501 (Huong *et al.* 2023, Chen *et al.* 2024). Another species, *C. rubidum*, found in Vietnam, contained compounds conarubins A-D. These monoterpenoid chalcones are believed to possess anti-inflammatory and cytotoxic properties (Hoang *et al.* 2023). This presents a promising foundation for further research into the potential anticancer properties of *C. vietnamense.*

The *in silico* method is currently gaining interest as a screening study. This method reduces the cost and time of laboratory experiments by predicting the most promising compounds. Regarding ligand-protein interactions based on binding energy, molecular docking simulations are an effective method to study the potency of a ligand as an inhibitor for its target protein (Chen *et al.* 2022). PTPN2, or Protein Tyrosine Phosphatase Non-Receptor Type 2, is a signaling molecule responsible for multiple cellular activities, including cell proliferation, differentiation, and migration (Flosbach *et al.* 2020). Through various mechanisms, PTPN2 plays a pivotal role in tumorigenesis, inflammatory and immune response. The absence and/or deficiency of PTPN2 has been found to enhance the survival of short-lived activated T cells and to increase the expansion of transferred effector T cell populations (Flosbach *et al.* 2020). Moreover, PTPN2 has been recognized as a promising cancer immunotherapy target, as the loss of this protein can boost antigen presentation and IFNγ sensing of tumors, which in turn increases their sensitivity to im-

munotherapy (Manguso *et al.* 2017). Additionally, PTPN2 acts as a positive regulator of mitochondrial respiration in human colorectal cancer (HCT116) cells (Vinette *et al.* 2021). In PTPN2-null cells, an increase in the number of damaged mitochondria was observed, followed by mitochondrial stress, decreased ATP production, cellular proliferation, and migration. The insulin-like growth factor-1 receptor (IGF-1R) has been proven to significantly engage in cellular signaling transduction and physiological regulation, most notably the inhibition of tumor cell death (Riedemann *et al.* 2007). Hence, the overexpression of IGF-1R is a critical component promoting the proliferation of many established human cancer cells, such as cervical cancer, colorectal cancer, and lung cancer (Steller *et al*. 1996, Shiratsuchi *et al.* 2011, Alfaro-Arnedo *et al.* 2022). By reducing the signaling of IGF-1R, its inhibitors are gaining interest as promising tumor-suppressing agents for cancer therapy. In recent years, within phytochemical research, gas chromatography-mass spectrometry (GC-MS) has become a crucial technical foundation for constructing chemical constituent profiles and secondary metabolite profiles in both plant and non-plant species (Manurung *et al.* 2022).

Sesquiterpenes, natural compounds, show promise as potential anticancer candidates by targeting protein tyrosine phosphatases (Zhao *et al*. 2018), including PTPN2 (Yamazaki *et al.* 2021, Song *et al.* 2022). Additionally, some sesquiterpenes derivatives have also been shown to inhibit cancer cell growth, migration, and invasion or increase the sensitivity of these cells to radiotherapy by targeting IGF-1R (Zheng *et al*. 2017, Chen *et al*. 2018).

In this context, although *C. vietnamense* has been recognized for its medicinal potential, studies on its chemical composition and biological effects, especially its ability to inhibit cancer cell growth, remain limited. Therefore, the objective of this study is to identify the chemical constituents from the rhizomes of *C. vietnamense* via GC-MS techniques and to evaluate the cytotoxic activity of the n-hexane fraction from *C. vietnamense* rhizomes, contributing to the research foundation for herbal cancer therapy. Moreover, molecular docking simulations were also performed to provide deeper insights into the binding modes of the phytocompositions with the PTPN2 and IGF-1R kinase target proteins, as critical drivers in well-known cancer pathways.

Materials and methods

Plant material. *C. vietnamense* rhizomes were collected from Loc Bac Commune, Bao Lam District, Lam Dong Province, Vietnam in April 2022 (11° 47’ 31.9” N; 107° 35’ 47.2” E). This investigation was a continuation of the previous study (Nhi *et al.* 2023). The study sample was identified based on DNA and deposited in GenBank under the code ON923664.1 (https://www.ncbi.nlm.nih.gov/nuccore/ON923664; Supplementary material, Table S1). The experimental samples were washed and dried in the shade, then crushed into a coarse powder and prepared for test extraction. Figure 1 shows the morphology of the *C. vietnamense* species.

Chemicals and reagents. Dulbecco’s Modified Eagle Medium (DMEM), Minimum Essential Medium with Eagle salt (MEME), antibiotics (L-glutamine, penicillin G, streptomicin), tricloroacetic acid (TCA), sulforhodamine B (SRB), Tris-base, phosphate buffered saline (PBS), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), 10 % Fetal Bovine Serum (FBS), sodium pyruvate ($C_3H_3NaO_3$), Trypsin-EDTA (0.05 %), and ellipticine were obtained from Sigma, United States. Dimethylsulfoxide (DMSO, Merck, German), acetic acid and sodiume bicarbonate (China). All other reagents were analytical grade.

Testing cells. All cell lines (human acute leukemia: HL-60, human breast carcinoma: MCF-7, human gastric carcinoma: MKN-7, human cervical carcinoma: HeLa, and human lung carcinoma: SK-LU-1) using in this study were provided by Prof. JM Pezzuto (Long Island University, United States) and Prof. Jeanette Maier (University of Milan, Italy).

Preparation of plant extract. Dried powder of *C. vietnamense* rhizomes was macerated with 96 % ethanol for 48h. The solvent was then evaporated under low pressure to obtained a concentrated form before being partitioned successfully with n-hexane. After evaporating at low pressure, the n-hexane fractionated extract was utilized for screening chemical components by using gas chromatography-mass spectroscopic method as well as investigating for cytotoxic activity (Van Chen *et al.* 2024).

Figure 1. *Conamomum vietnamense* N.S.Lý & T.S.Hoang (Photos by Nguyen Danh Duc).

Preliminary phytochemical screening. Secondary metabolite groups, such as carbohydrates, essential oils, amino acids, fats, tannins, flavonoids, coumarins, alkaloids, steroids/cardiac glycosides, triterpenoids, and saponins, were qualitatively evaluated by color or precipitation reactions. Briefly, the test sample (50.0 g rhizome powder) was extracted by soaking in 100 mL of 96 % ethanol for 30 min. The extract was then subjected to preliminary phytochemical evaluation under the same conditions (Tran *et al*. 2023).

Analysis of the volatile compounds. The chemical components of *C. vietnamense* rhizomes were detected using GC-7890 gas chromatography coupled with a mass MS 5977C spectrometry detector (Agilent). The separation was achieved by an HP-5MS UI column (30 m × 0.25 mm × 0.25 mm, Agilent) and supplemented with helium as carrier gas at flow rate 1.5 mL/min. Initially, column temperature was set up at 80 °C for one min, and was increased 20 °C/min until reached 300 °C, the oven was then maintained at this temperature for 15 min. Furthermore, the injector, MS Quad, and transfer line temperatures were programmed at 300, 150, and 300 °C, respectively. The MS was run at an ionization voltage 70 Ev and ion source temperature at 230 °C. The scan mass range of MS was 50-550 *m/z* with the scanning frequently of 2.0 scans/sec. To search volatile compounds, 1.0 µL aliquot of sample (20 mg mL^{-1}) was injected into clolumn at a split ratio of 1:25. The chemical components in the n-hexane fractionated extract were identified based on a comparison of their mass spectra values with those in the NIST17 database (Van Chen *et al.* 2022).

In vitro cytotoxic activity assay. The cytotoxic effects of the n-hexane fractionated extract were performed according to previously reported with some modifications (Van Chen *et al.* 2024). Four tested cell lines, including MCF-7, SK-LU-1, HeLa, and MKN-7 were cultured in MEME, while HL-60 was maintained in DMEM medium. Both mediums were supplemented with 2.0 mL L-glutamine, 1mM sodium pyruvate, penicillin G (100 IU/mL), streptomycin (100 µg/mL), and 10 % FBS, and was incubated at 37 °C and 5 % CO_2 in an incubator. The n-hexane fractionated extract was dissolved in DMSO to make a stock solution of 20 mg/mL. Serial dilutions of sample (500, 100, 20.0, 4.0, and

0.8 μg/mL) were prepared in cell culture medium. Afterwards, cells were treated with or without sample at a final volume of 200 μL/well (10 μL sample and 190 μL cell suspension) and incubated for 72 h. The line cells (MCF-7, SK-LU-1, HeLa, and MKN-7) were then fixed with 20 % TCA solution and stained with 0.2 % SRB for 30 min at 37 °C before washing with acetic acid (3 times) and drying at room temperature. 10 mM Tris-base was buffer was added to dissolve the SRB. In terms of HL-60 cell line, 10 μL aliquot of MTT solution (500 μg/mL) was added to each well and incubated for 4 h. Then, the culture media was discarded before adding 50 μL of DMSO to each well to dissolve the formazan crystals. All above mixtures were gently shaken for 10 min and the optical density (OD) was recorded by using an ELISA plate reader (Biotek, USA) at a wavelength of 540 nm. The 1 % DMSO and ellipticine (10, 2.0, 0.4, and 0.08 μg/mL) were used as blank and positive control, respectively. The inhibition rate of tumor cell lines was calculated by the following formula (Van Chen *et al.* 2024):

$$\% \, I = \left[1 - \frac{(ODsp - ODbl)}{(ODdmso - ODbl)}\right] \times 100 \, \%$$

Whereas, I: inhibition rate of tumor cells. OD_{sp}: average optical density value of testing sample; OD_{bl}: average optical density value of blank sample; OD_{dmso}: average optical density value of DMSO.

Molecular docking study. PTPN2 (PDB ID: 7UAD) and IGF-1R kinase (PDB ID: 2OJ9) were used in this study. Molecular docking studies were performed using AutoDock Vina v. 1.2.3 (Eberhardt *et al.* 2021) with AutoDock4 forcefield (Morris *et al.* 2009). This study used a basic molecular docking protocol throughout the process (Forli *et al.* 2016). Ligand structures were retrieved from the IMPPAT database (https://cb.imsc.res.in/imppat/) in the 3D conformer format (.pdbqt). A box-shaped grid, centered on the co-crystallized ligand of each protein (x = -22.629, y = -18.548, z = -12.201 for PTPN2, and x = 5.514, y = -6.490, z = 21.182 for IGF-1R kinase), was created to define the search space for docking simulations. The dimensions of this grid were set to 40 angstroms (Å) along each side. The redocking process was used for docking model validation. Redocking PTPN2 results revealed that the interacting residues of the two conformations share many similarities, including an attractive charge with Asp182, fluorine with Gln260, hydrogen bond with Asp50, Lys122, Phe183, Ser217, Ala218, and Gln264, and hydrophobic interactions with Tyr48, Val51, Phe183, Ala218, Ile220, and Met256. The RMSD value between the ABBV-CLS-484 conformation after redocking and the initial conformation was 0.6751 Å (under 2.0 Å), which showed that the docking model was reliable and suitable. Meanwhile, the redocking results of IGF-1R kinase showed that the RMSD value of the co-crystallized ligand before and after was 0.6080 Å (under 2.0 Å), the main interactions of the ligand with the residues at the active site included hydrogen bonds with Asp50, Lys122, Phe183, Ser217, Ala218, Gln264, attractive charge interaction with Asp182, fluorine bond with Gln260 and stacked Pi-Pi stacked interaction with Phe183.

Data analysis. Experimental data was analyzed and measured. The results were performed in triplicates, presented as the mean value ± standard deviation (S.D), and calculated using Microsoft Excel 2023 software. The IC_{50} value was accessed utilizing TableCurve 2Dv4 software (Van Chen *et al.* 2024).

Results

Phytochemical evaluation. The preliminary phytochemical screening of *C. vietnamense* rhizome ethanol extract showed the presence of fats, carbohydrates, carotenoids, essential oil, triterpenoids, alkaloids, amino acid, coumarins, flavonoids, and tannins. In contrast, steroids/cardiac glycosides and saponins were absence in this rhizome extract under the same analytical conditions (Table 1). Furthermore, the GC-MS analysis of the n-hexane fractionated extract of *C. vietnamense* rhizome led to the identification of total twenty-three volatile compounds, accounting for 87.61 % (Table 2 and Figure 2). Among them, *α*-eudesmol was dominant (26.84 %), followed by *β*-eudesmol (15.02 %), cryptomeridiol (14.36 %), *γ*-eudesmol (6.21 %), eucalyptol (4.38 %), and eudesm-7(11)-en-4-ol (3.11 %) (Tables 2 and S2, Figures 2 and 3).

Table 1. Phytochemical screening of *C. vietnamense* rhizome extract.

Chemical Constituents	The test's name	Results
Fats	Stain test	+
Carbohydrates	Fehling's test, Molisch's test	+
Carotenoids	H_2SO_4 test	+
Essential oil	Scent test	+
Triterpenoids	Salkowski test	+
Alkaloids	Dragendoff's test, Wagner's test	+
Amino acids	Na_2CO_3 test	+
Steroid/Cardiac glycosides	Liebermann Burchard test/ Raymond's test, Xanthydrol's test	-
Saponins	Foam test	-
Coumarins	Lactone ring test	+
Flavonoids	Cyanidin's test	+
Tannins	Gelatin's test, $FeCl_3$ test	+

Note: "+" indicates the presence and "-" indicates the absence of the phytocompositions.

Table 2. Volatile constituents of the n-hexane fractionated extract from *C. vietnamense* rhizomes.

No.	RT (min)	Compounds	MF	MW (g/mol)	Area (%)
1	5.171	*α*-Phellandrene	$C_{10}H_{16}$	136.23	1.10
2	5.484	2-Carene	$C_{10}H_{16}$	136.23	2.19
3	5.844	Eucalyptol	$C_{10}H_{18}O$	154.25	4.38
4	8.708	Camphor	$C_{10}H_{16}O$	152.23	0.69
5	9.089	Benzenepropanal	$C_9H_{10}O$	134.17	0.47
6	9.184	*endo*-Borneol	$C_{10}H_{18}O$	154.25	0.44
7	9.733	*α*-Terpineol	$C_{10}H_{18}O$	154.25	0.83
8	10.867	Benzylacetone	$C_{10}H_{12}O$	148.20	0.77
9	11.729	Acetic acid, 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester	$C_{12}H_{20}O_2$	196.29	0.38
10	13.440	Germacrene D	$C_{15}H_{24}$	204.35	0.37
11	15.762	*γ*-Cadinene	$C_{15}H_{24}$	204.35	0.77
12	15.898	*cis*-Calamenene	$C_{15}H_{22}$	202.33	2.36
13	16.448	Nerolidol	$C_{15}H_{26}O$	222.37	0.78
14	16.868	Mayurone	$C_{14}H_{20}O$	204.31	1.10
15	17.038	Guaiol	$C_{15}H_{26}O$	222.37	0.39
16	17.167	Viridiflorol	$C_{15}H_{26}O$	222.37	0.56
17	17.561	*γ*-Eudesmol	$C_{15}H_{26}O$	222.37	6.21
18	17.697	*epi*-Cubebol	$C_{15}H_{24}O$	220.35	2.77
19	17.751	*δ*-Cedrol	$C_{15}H_{26}O$	222.37	1.72
20	17.846	*β*-Eudesmol	$C_{15}H_{26}O$	222.37	15.02
21	17.887	*α*-Eudesmol	$C_{15}H_{26}O$	222.37	26.84
22	17.982	Eudesm-7(11)-en-4-ol	$C_{15}H_{26}O$	222.37	3.11
23	20.079	Cryptomeridiol	$C_{15}H_{28}O_2$	240.38	14.36
		Total (%)			87.61

Note: MW: Molecular Weight; MF: Molecular Formula; RT: Retention time (min); Area (%) in "Bold" shows major compounds (> 3.0 %).

Cytotoxic effect evaluation. The cytotoxic activity of the n-hexane fractionated extract of *C. vietnamsese* against five cancer cell lines was shown in Table 3. Accordingly, the strongest cytotoxic effect was favorable for the human acute leukemia (HL-60) with the IC_{50} value of 59.04 ± 2.32 μg/mL, followed by human breast carcinoma (MCF-7; IC_{50} = 61.99 ± 3.02 μg/mL) and human gastric carcinoma cell lines (MKN-7; IC_{50} = 64.60 ± 3.40 μg/mL). On the other hand, this extract also showed weak cytotoxic effects on human cervical carcinoma (HeLa) and human lung carcinoma (SK-LU-1) cell lines with the IC_{50} values of 109.41 ± 6.43 μg/mL and 172.43 ± 13.26 μg/mL, respectively, which were compared with the positive control, ellipticine, with the IC_{50} values ranging from 0.31 ± 0.03 to 0.5 ± 0.04 μg/mL (Table 3 and Figure S1).

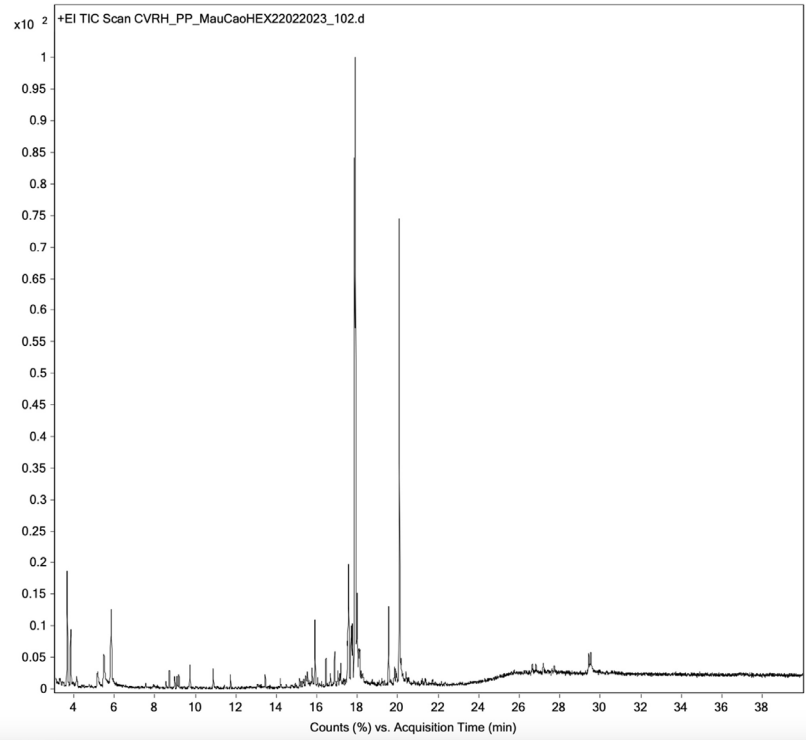

Figure 2. GC-MS chromatogram of the n-hexane fractionated extract from *C. vietnamense* rhizomes.

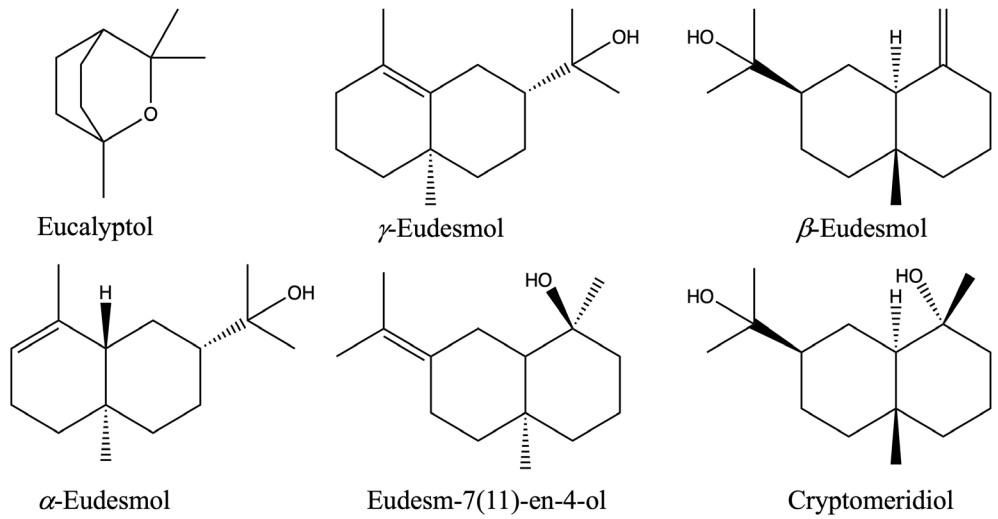

Figure 3. Chemical structure of the major identified components in the n-hexane fractionated extract from *C. vietnamense* rhizomes.

Table 3. Cytotoxic potential of *C. vietnamense* rhizome n-hexane extract and Ellipticine.

% inhibition of cell growth of rhizome n-hexane fractionated extract					
Concentration (µg/mL)	**MCF-7**	**SK-LU-1**	**Hela**	**MKN-7**	**HL-60**
500	81.05 ± 2.81	74.86 ± 3.38	80.50 ± 3.34	89.43 ± 2.14	90.88 ± 2.53
100	74.37 ± 1.71	44.94 ± 1.29	56.46 ± 2.00	69.59 ± 1.46	87.99 ± 1.60
20.0	21.97 ± 1.31	8.70 ± 0.81	12.79 ± 0.81	16.25 ± 0.61	15.95 ± 1.39
4.0	5.75 ± 1.08	5.05 ± 0.37	7.49 ± 0.22	4.77 ± 0.38	3.03 ± 0.29
0.8	4.81 ± 0.49	3.11 ± 0.28	1.35 ± 0.17	1.82 ± 0.16	1.19 ± 0.14
IC_{50}	61.99 ± 3.02	172.43 ± 13.26	109.41 ± 6.43	64.60 ± 3.40	59.04 ± 2.32
Ellipticine (IC_{50})	0.50 ± 0.04	0.51 ± 0.03	0.39 ± 0.05	0.42 ± 0.04	0.31 ± 0.03

Table 4. Docking score of ligands with PTPN2 and IGF-1R kinase.

No.	**Compounds**	**Docking score (kcal/mol)**	
		PTPN2	**IGF-1R kinase**
1	*α*-Phellandrene	-5.4	-5.1
2	2-Carene	-5.4	-5.1
3	Eucalyptol	-5.6	-5.0
4	Camphor	-6.3	-4.7
5	Benzenepropanal	-5.3	-4.5
6	*endo*-Borneol	-5.9	-4.8
7	*α*-Terpineol	-6.5	-5.1
8	Benzylacetone	-5.9	-5.0
9	Acetic acid, 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester	-6.1	-5.4
10	Germacrene D	-6.7	-6.4
11	*γ*-Cadinene	-6.4	-6.4
12	*cis*-Calamenene	-6.3	-6.4
13	Nerolidol	-6.9	-6.6
14	Mayurone	-5.2	-5.9
15	Guaiol	-7.0	-6.9
16	Viridiflorol	-6.0	-6.4
17	*γ*-Eudesmol	-6.9	-6.8
18	*epi*-Cubebol	-6.0	-6.7
19	*δ*-Cedrol	-6.2	-6.8
20	*β*-Eudesmol	-6.5	-7.0
21	*α*-Eudesmol	-7.1	-6.8
22	Eudesm-7(11)-en-4-ol	-5.9	-6.3
23	Cryptomeridiol	-6.9	-6.8

Molecular docking study. The docking scores of 23 ligands with PTPN2 (PDB ID: 7UAD) and IGF-1R kinase (PDB ID: 2OJ9) are presented in Table 4. A total of 23 compounds were successfully docked into the pockets of human PTPN2 (PDB ID: 7UAD) with binding affinities ranging from -5.2 to -7.1 kcal/mol. Among them, *α*-eudesmol (21), guaiol (15), and nerolidol (13) were the three most potential compounds with the binding affinities of -7.1, -7.0, and -6.9 kcal/mol, respectively.

Discussion

In this study, the chemical components of the n-hexane fractionated extract of *C. vietnamense* rhizomes were investigated by using the GC-MS analysis. Relative amounts of each one of the twenty-three named structures are shown in Table 2. Different chemical classes of identified compounds were found in this extract, such as monoterpene, sesquiterpene, oxygenated monoterpene and sesquiterpene, and benzene derivatives and they accounted for 87.61 % of total volatile contents with some dominant constituents being *α*-eudesmol, *β*-eudesmol, cryptomeridiol, *γ*-eudesmol, eucalyptol, and eudesm-7(11)-en-4-ol. The chemical components from *C. vietnamense* rhizomes extract accessed by us were quite like those previously reported in which the major compound in leaf, flower, and rhizome of *C. vietnamense* was eucalyptol (21.90, 13.29, and 9.98 %, respectively) (Pham *et al.* 2024). Similarly, both our and previous studies showed that *α*-eudesmol, *β*-eudesmol, and *γ*-eudesmol were present in the *C. vietnamense* rhizomes. However, there were still some differences in relative amounts of identified compounds. For example, the current study demonstrated that *α*-eudesmol, *β*-eudesmol, and *γ*-eudesmol comprised 26.84, 15.02, and 6.21 %, respectively, while these compounds were detected in very low content in *C. vietnamense* rhizome from a prior study (1.52, 0.68, and 0.63 %, respectively) (Nguyen *et al.* 2023). This can be explained that different extraction method, extraction solvents, and analytical methods as well as different sample collected locations resulted in different amounts of volatile compounds. Among the various compounds identified from the n-hexane fractionated extract, three of the six main components were eudesmol isomers (*α*-, *β*-, and *γ*-eudesmols), which were also presented in many essential oils of *Satureja isophylla* Rech.f. (Sefidkon & Jamzad 2004), *Thuja occidentalis* L. (Swetha *et al.* 2024), and to name a few. These structures exhibited multiple activities, such as anti-angiogenic (Tsuneki *et al*. 2005), antitumor (Bomfim *et al.* 2013), and anti-inflammatory properties (Seo *et al.* 2011). Furthermore, these compounds have been also shown cytotoxic effects againt several human cancer cell lines, such as human hepatocellular carcinoma (HepG2) (Bomfim *et al.* 2013), human colon cancer (HCT-8) and HL-60 (Martins *et al.* 2015), HCT116 and RKO (Murata *et al.* 2013), human erythroleukemic (K562) (Sghaier *et al.* 2011), and human colon adenocarcinoma (HT29) cell lines (Ali *et al.* 2012).

Additionally, eucalyptol or 1,8-cineole is one of the major compounds in *C. vietnamense* rhizomes, which was also extracted from the essential oils of plants, especially in Zingiberaceae family (Nguyen *et al.* 2023). Eucalyptol was not only used in traditional medicine for decades but also played an important role in the treatment of various diseases. In detail, it has therapeutic effects on many respiratory diseases, such as influenza, bronchitis, pneumonia, and asthma. Furthermore, eucalyptol was served as a potential cancer inhibitor against leukemia, skin, oral, colon, breast, liver, and ovarian cancer both *in vitro* and *in vivo* (Cai *et al.* 2021). Eudesm-7(11)-en-4-ol, another compound of the rhizome of *C. vietnamense*, was also existed in essential oils of *Asarum geophilum* Hemsl., *A. splendens* (F.Maek.) C.Y.Chen & C.S.Yang (Minh *et al.* 2023), *Z. zerumbet* (L.) Roscoe ex Sm. (Dash *et al.* 2020), etc. It has been reported for antimicrobial, anti-inflammatory activities, etc (Minh *et al.* 2023). Cryptomeridiol is an oxygenated sesquiterpene present in the essential oils or extracts of several species, such as *Blumea balsamifera* (L.) DC. (Ragasa *et al.* 2005), *Juniperus thurifera* L. (Lafraxo *et al.* 2023), etc. This compound has various effects, especially antifungal (Ragasa *et al.* 2005), antioxidant, and antimicrobial activities (Lafraxo *et al.* 2023).

In recent reports, the leaf oil of this plant displayed moderate antibacterial effects against *Enterococcus faecalis* and weak activities against *S. aureus*, *B. cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enterica*, while the rhizome oil showed effects on *E. faecalis*, *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, *and S. enterica* (Nguyen *et al.* 2023). Another study on the acetone extracts obtained from different parts of *C. vietnamense* leaf has been reported that the leaf extract inhibited eight bacterial strains, namely *E. coli*, *S. typhimurium*, *S. saprophyticus*,

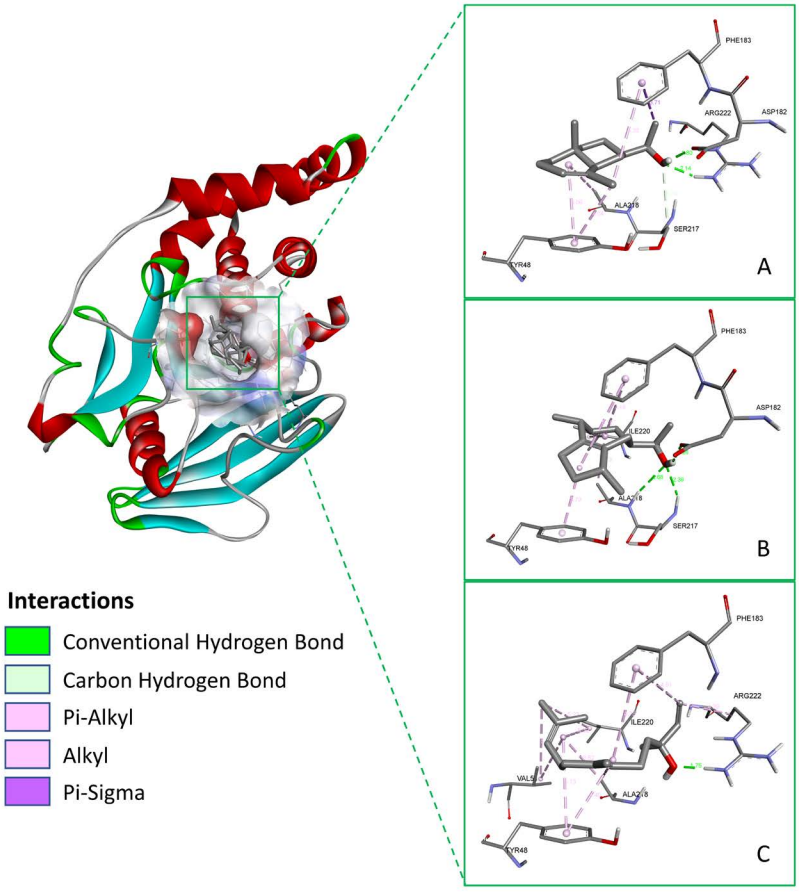

Figure 4. 3D-ligand interaction diagram of *α*-eudesmol (A), guaiol (B), and nerolidol (C) and residues in the active sites of PTPN2 (PDB ID: 7UAD).

B. cereus, *Klebsiella pneumoniae*, *Shigella flexneri*, *S. aureus* ATCC 29213, and *S. aureus* ATCC 25923, while the flower and rhizome extracts were active for *S. saprophyticus*, *B. cereus*, *S. aureus* ATCC 29213, and *S. aureus* ATCC 25923 (Pham *et al.* 2024). In addition, *C. vietnamense* leaf and rhizome essential oils showed strong mosquito larvicidal activity against *Aedes aegypti* and *A. albopictus* (Huong *et al.* 2023).

In this study, the cytotoxic property of the n-hexane fractionated extract of the *C. vietnamense* rhizomes was shown in Table 3. Accordingly, the cytotoxic effect of rhizome fractionated extract displayed concentration-dependent inhibition of the growth of tumor cell lines. For instance, at 100 μg/mL, *C. vietnamense* rhizome extract exhibited its inhibition on all of the tested cell lines, including MCF-7, SK-LU-1, HeLa, MKN-7, and HL-60 with percentages of inhibition being 74.37 ± 1.71, 44.94 ± 1.29, 56.46 ± 2.00, 69.59 ± 1.46, and 87.99 ± 1.60 %, respectively. Interestingly, the rhizome fractionated extract was most active against HL-60, MCF-7, and MKN-7 with IC_{50} values of 59.04 ± 2.32, 61.99 ± 3.02, and 64.60 ± 3.40 μg/mL, respectively. Furthermore, this rhizome fractionated extract was also exhibited weak cytotoxicity towards HeLa and KS-LU-1 with the IC_{50} values ranging from 109.41 to 172.43 μg/mL, which were compared to that of the positive control, ellipticine (IC_{50} values ranging from 0.31 ± 0.03 to 0.5±0.04 μL/mL) (Table 3). From these above evidences, it can be hypothesized that different extraction methods and extraction solvents will influence the chemical constituents which play an important role in enhancing biological properties of *C. vietnamense*. To the best of our knowledge, the cytotoxic activity against some specific tumor cell lines of *C. vietnamense* was addressed for the first time. This result somehow fills a gap in the knowledge of the *Conamomum* genus in relation to not only the chemical compounds but also the cytotoxic effects.

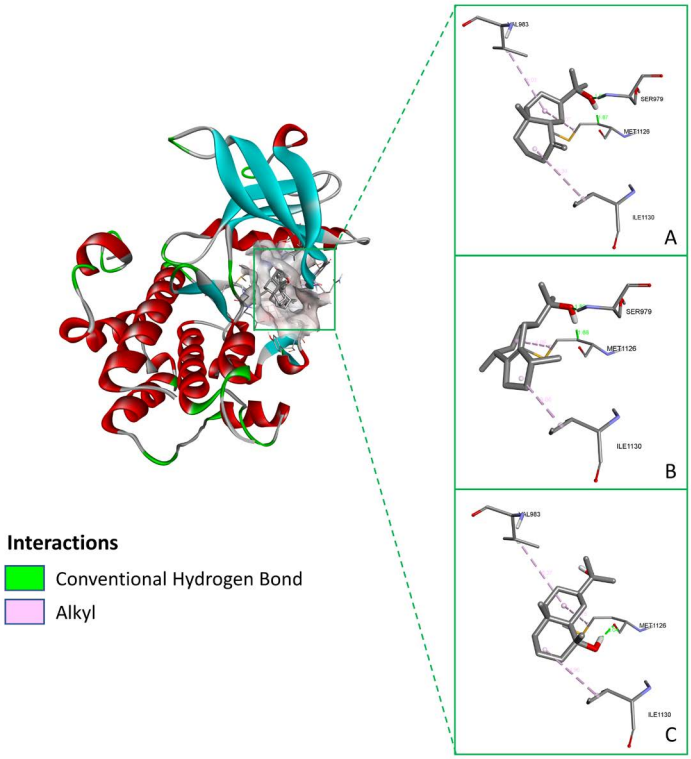

Figure 5. 3D-ligand interaction diagram of *β*-eudesmol (A), guaiol (B), and cryptomeridiol (C) and residues in the active sites of IGF-1R kinase (PDB ID: 2OJ9).

As in *α*-eudesmol (21), the O of the hydroxyl group acts as a hydrogen bond acceptor to Arg222 (2.14 pm) and Ser217 (3.74 pm) (Figure 4A). The H atom of said group also forms a hydrogen bond with the carbonyl group of Asp182 (1.80 pm). Meanwhile, the eudesmane framework plays an important role in hydrophobic interactions with Tyr48, Ala218, and Phe183, their lengths ranging from 3.71 to 5.32 pm. The strong affinity of guaiol (15) can be attributed to the guaiane skeleton creating alkyl and pi-alkyl bonds with Phe183, Ile220, and Tyr48 (Figure 4B). The distances between them range from 3.73 to 5.43 pm. Additionally, the hydroxyl group forms hydrogen bonds with Asp182, Ser217, and Ala218; these reach the lengths of 2.26, 2.39, and 2.68 pm correspondingly. Our docking study suggests that nerolidol (13) achieves good binding affinity with the receptor mainly through hydrophobic interactions with Arg222, Tyr48, Phe183, Val51, and Ile220. Their bond distances vary between 3.78 and 5.40 pm. Furthermore, the O atom of the hydroxyl group receives electrons from the amine group of Arg222, creating a hydrogen bond with a span of 1.75 pm (Figure 4C).

The same 23 compounds were also explored to bind well into the IGF-1R kinase (PDB ID: 2OJ9) with docking scores ranging from -18.83 to -29.29 kcal/mol. Out of them, *β*-eudesmol (20), guaiol (15), and cryptomeridiol (23) exhibited the strongest affinity for the binding site with the corresponding docking scores of -29.29, -28.87, and -28.45 kcal/mol.

The eudesmane framework of *β*-eudesmol (20) has a pivotal role in the alkyl interactions with amino acids like Met1126 (5.07 pm), Ile1130 (5.30 pm), and Val983 (5.03 pm) (Figure 5A). The H atom of the hydroxyl group serves as the electron donor to Met1126. On the other hand, the O atom of the same group receives electrons from the amine group of Ser979. These two hydrogen bonds have lengths of 1.87 and 1.62 pm respectively. The receptor-ligand interactions between IGF-1R kinase and guaiol (15) (Figure 5B) are quite similar to that of *β*-eudesmol (20). The differences in binding affinity between these two seems to be caused by the absence of hydrophobic interaction with Val983. Aside from that, guaiol (15) still displays hydrophobic bonds with Ile1130 (3.86 pm) and Met1126 (4.69

pm), as well as hydrogen bonds with Met1126 (1.88 pm) and Ser979 (1.82 pm). Compared to the compounds above, cryptomeridiol (23) only creates one hydrogen bond with Met1126 (2.04 pm) (Figure 5C). Nevertheless, because of the shared eudesmane skeleton with *β*-eudesmol (20), it also forms hydrophobic interactions with Met1126 (4.78 pm), Ile1130 (4.96 pm), and Val983 (5.37 pm). These findings highlight the therapeutic potential of cancer-related diseases as well as the medicinal value of the major constituents found in the *C. vietnamense* rhizome, which may pave the way for future experimental studies.

In conclusion, the phytochemical analysis of the n-hexane rhizome extract of *C. vietnamense* led to the identification of 23 compounds. Among them, *α*-eudesmol, *β*-eudesmol, cryptomeridiol, *γ*-eudesmol, eucalyptol, and eudesm-7(11)-en-4-ol were dominated. The cytotoxic activity against five human tumor cell lines MCF-7, SK-LU-1, HeLa, MKN-7, and HL-6 was observed from this extract. In molecular docking, nerolidol, guaiol, *α*-eudesmol, *β*-eudesmol, and cryptomeridiol are substances with strong affinities for the binding sites of PTPN2 and IGF-1R kinase, with docking scores ranging from -29.71 to -27.61 kcal/mol. These results suggest that *C. vietnamense* could be a potential source for anti-tumor agents.

Supplementary material

Supplemental data for this article can be accessed here: https://doi.org/10.17129/botsci.3660

Acknowledgments

We are grateful to Mr. Nguyen Danh Duc and MSc. Nguyen Thanh To Nhi for their assistance in collecting research samples and identifying plants using DNA barcodes.

Literature cited

Alfaro-Arnedo E, López IP, Piñeiro-Hermida S, Canalejo M, Gotera C, Sola JJ, Roncero A, Peces-Barba G, Ruíz-Martínez C, Pichel JG. 2022. IGF1R acts as a cancer-promoting factor in the tumor microenvironment facilitating lung metastasis implantation and progression. *Oncogene* **41**: 3625-3639. DOI: https://doi.org/10.1038/s41388-022-02376-w

Ali NAA, Wurster M, Denkert A, Arnold N, Fadail I, Al-Didamony G, Lindequist U, Wessjohann L, Setzer WN. 2012. Chemical composition, antimicrobial, antioxidant and cytotoxic activity of essential oils of *Plectranthus cylindraceus* and *Meriandra benghalensis* from Yemen. *Natural Product Communications* **7**: 1934578X1200700834. DOI: https://doi.org/10.1177/1934578X1200700834

Alolga RN, Wang F, Zhang X, Li J, Tran LSP, Yin X. 2022. Bioactive compounds from the Zingiberaceae Family with known antioxidant activities for possible therapeutic uses. *Antioxidants* **11**: 1281. DOI: https://doi.org/10.3390/antiox11071281

Balaji AP, Bhuvaneswari S, Raj LS, Bupesh G, Meenakshisundaram KK, Saravanan KM. 2022. A review on the potential species of the Zingiberaceae family with anti-viral efficacy towards enveloped viruses. *Journal of Pure and Applied Microbiology* **16**: 796-813. DOI: https://doi.org/10.22207/JPAM.16.2.35

Bomfim DS, Ferraz RP, Carvalho NC, Soares MB, Pinheiro ML, Costa EV, Bezerra DP. 2013. Eudesmol isomers induce caspase-mediated apoptosis in human hepatocellular carcinoma H ep G2 Cells. *Basic & Clinical Pharmacology & Toxicology* **113**: 300-306. DOI: https://doi.org/10.1111/bcpt.12097

Cai ZM, Peng JQ, Chen Y, Tao L, Zhang YY, Fu LY, Long QD, Shen XC. 2021. 1,8-Cineole: A review of source, biological activities, and application. *Journal of Asian Natural Products Research* **23**: 938-954. DOI: https://doi.org/10.1080/10286020.2020.1839432

Chen TV, Boonma T, Triet NT, Phan Nguyen Duc D, Trong Nghia N, Saensouk S, Thi Thu Hien N. 2024. Exploring the botany and pharmacology of the genus *Conamomum* Ridl.(Zingiberaceae). *Nordic Journal of Botany* **2024**: e04504. DOI: https://doi.org/10.1111/njb.04504

Chen YA, Tzeng DT, Huang YP, Lin CJ, Lo UG, Wu CL, Lin H, Hsieh JT, Tang CH, Lai CH. 2018. Antrocin sensitizes prostate cancer cells to radiotherapy through inhibiting PI3K/AKT and MAPK signaling pathways. *Cancers* **11**: 34. DOI: https://doi.org/10.3390/cancers11010034

Dash B, Sahoo A, Ray A, Jena S, Nayak S. 2020. Identification of chemical constituents of *Zingiber zerumbet* rhizome extract using GC/MS. *Journal of Biologically Active Products from Nature* **10**: 411-417. DOI: https://doi.org/10.1080/22311866.2020.1821775

Eberhardt J, Santos-Martins D, Tillack AF, Forli S. 2021. AutoDock Vina 1.2. 0: New docking methods, expanded force field, and python bindings. *Journal of Chemical Information and Modeling* **61**: 3891-3898. DOI: https://doi.org/10.1021/acs.jcim.1c00203

Flosbach M, Oberle SG, Scherer S, Zecha J, von Hoesslin M, Wiede F, Chennupati V, Cullen JG, List M, Pauling JK, Baumbach J, Kuster B, Tiganis T, Zehn D. 2020. PTPN2 deficiency enhances programmed T cell expansion and survival capacity of activated T cells. *Cell Reports* **32**: 107957. DOI: https://doi.org/10.1016/j.celrep.2020.107957

Forli S, Huey R, Pique ME, Sanner MF, Goodsell DS, Olson AJ. 2016. Computational protein–ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols* **11**: 905-919. DOI: https://doi.org/10.1038/nprot.2016.051

Hoang HNT, Vo HQ, Tran LTT, Nguyen HT, Ho DV. 2023. Conarubins A-D: Four monoterpene-chalcone conjugates from *Conamomum rubidum* and their anti-inflammatory and cytotoxic activities. *The Journal of Organic Chemistry* **88**: 15318-15325. DOI: https://doi.org/10.1021/acs.joc.3c01825

Huong LT, The Son N, Sam LN, Minh PN, Luyen ND, Hung NH, Dai DN. 2023. Essential oils of the ginger plants *Meistera caudata* and *Conamomum vietnamense*: chemical compositions, antimicrobial, and mosquito larvicidal activities. *Zeitschrift für Naturforschung C* **78**: 337-344. DOI: https://doi.org/10.1515/znc-2022-0244

Lafraxo S, Zouirech O, El Barnossi A, Chelouati T, Chebaibi M, Chebbac K, Nafidi HA, Salamatullah AM, Bourhia M, Aboul-Soud MA,Bari A. 2023. Promising antioxidant and antimicrobial effects of essential oils extracted from fruits of *Juniperus thurifera*: *In vitro* and *in silico* investigations. *Open Chemistry* **21**: 20220332. DOI: https://doi.org/10.1515/chem-2022-0332

Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. 2018. Local cancer recurrence: the realities, challenges, and opportunities for new therapies. *CA: A Cancer Journal For Clinicians* **68**: 488-505. DOI: https://doi.org/10.3322/caac.21498

Manguso RT, Pope HW, Zimmer MD, Brown FD, Yates KB, Miller BC, Collins NB, Bi K, LaFleur MW, Juneja VR, Weiss SA, Lo J, Fisher DE, Miao D, Allen EV, Root DE, Sharpe AH, Doench JG, Haining WN. 2017. *In vivo* CRISPR screening identifies Ptpn2 as a cancer immunotherapy target. *Nature* **547**: 413-418. DOI: https://doi.org/10.1038/nature23270

Manurung H, Susanto D, Kusumawati E, Aryani R, Nugroho RA, Kusuma R, Rahmawati Z, Sari RD. 2022. Phytochemical, GC-MS analysis and antioxidant activities of leaf methanolic extract of Lai (Durio kutejensis), the endemic plant of Kalimantan, Indonesia. *Biodiversitas Journal of Biological Diversity* **23**: 5566-5573. DOI: https://doi.org/10.13057/biodiv/d231104

Martins CDM, Nascimento EAD, de Morais SA, de Oliveira A, Chang R, Cunha LC, Martins MM, Martins CHG, Moraes TDS, Rodrigues PV, da Silva CV, de Aquino FJ. 2015. Chemical constituents and evaluation of antimicrobial and cytotoxic activities of *Kielmeyera coriacea* Mart. & Zucc. essential oils. *Evidence-Based Complementary and Alternative Medicine* 2015: 842047. DOI: https://doi.org/10.1155/2015/842047

Minh PTH, Tuan NT, Van NTH, Bich HT, Lam DT. 2023. Chemical composition and biological activities of essential oils of four Asarum species growing in Vietnam. *Molecules* **28**: 2580. DOI: https://doi.org/10.3390/molecules28062580

Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. 2009. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry* **30**: 2785-2791. DOI: https://doi.org/10.1002/jcc.21256

Murata S, Shiragami R, Kosugi C, Tezuka T, Yamazaki M, Hirano A, Yoshimura Y, Suzuki M, Shuto K, Ohkohchi

N, Koda K. 2013. Antitumor effect of 1, 8-cineole against colon cancer. *Oncology Reports* **30**: 2647-2652. DOI: https://doi.org/10.3892/or.2013.2763

Nguyen DD, Nguyen-Ngoc H, Tran-Trung H, Nguyen DK, Nguyen LTT. 2023. Limonene and eucalyptol rich essential oils with their antimicrobial activity from the leaves and rhizomes of *Conamomum vietnamense* NS Lý & TS Hoang (Zingiberaceae). *Pharmacia* **70**: 91-97. DOI: https://doi.org/10.3897/pharmacia.70.e96946

Nhi NTT, Van Chen TRAN, Lam DNX, Nguyen DD, Dinh QD, Linh NHK. 2023. Morphological and anatomical studies of *Conamomum vietnamense* NS Lý & TS Hoang: An endemic plant from Vietnam. *Biodiversitas Journal of Biological Diversity*, **24**: 5022-5034. DOI: https://doi.org/10.13057/biodiv/d240946

Pham TV, Quoc LPT, Nguyen MP, Nguyen HN, Nguyen QH, Le TT, Nguyen VH, Van HT. 2024. Chemical components and biological properties from acetone extracts of *Conamomum vietnamense*. *Journal of Applied Botany and Food Quality* **97**: 79. DOI: (https://doi.org/10.5073/JABFQ.2024.097.010

Ragasa CY, Kristin C Co AL, Rideout JA. 2005. Antifungal metabolites from Blumea balsamifera. *Natural Product Research* **19**: 231-237. DOI: https://doi.org/10.1080/14786410410001709773

Riedemann J, Sohail M, Macaulay VM. 2007. Dual silencing of the EGF and type 1 IGF receptors suggests dominance of IGF signaling in human breast cancer cells. *Biochemical and Biophysical Research Communications* **355**: 700-706. DOI: https://doi.org/10.1016/j.bbrc.2007.02.041

Sefidkon F, Jam ZZ. 2004. Chemical composition of the essential oil of two iranian *Satureja* species (*S. edmondi* and *S. isophylla*). *Iranian Journal of Pharmaceutical Research* **3**: 91.

Seo MJ, Kim SJ, Kang TH, Rim HK, Jeong HJ, Um JY, Hong SH, Kim HM. 2011. The regulatory mechanism of β-eudesmol is through the suppression of caspase-1 activation in mast cell-mediated inflammatory response. *Immunopharmacology and Immunotoxicology* **33**: 178-185. DOI: https://doi.org/10.3109/08923973.2010.491082

Sghaier MB, Skandrani I, Nasr N, Franca MGD, Chekir-Ghedira L, Ghedira K. 2011. Flavonoids and sesquiterpenes from *Tecurium ramosissimum* promote antiproliferation of human cancer cells and enhance antioxidant activity: A structure–activity relationship study. *Environmental Toxicology and Pharmacology* **32**: 336-348. DOI: https://doi.org/10.1016/j.etap.2011.07.003

Shiratsuchi I, Akagi Y, Kawahara A, Kinugasa T, Romeo K, Yoshida T, Ryu Y, Gotanda Y, Kage M, Shirouzu K. 2011. Expression of IGF-1 and IGF-1R and their relation to clinicopathological factors in colorectal cancer. *Anticancer Research* **31**: 2541-2545.

Song J, Lan J, Tang J, Luo N. 2022. PTPN2 in the immunity and tumor immunotherapy: a concise review. *International Journal of Molecular Sciences* **23**: 10025. DOI: https://doi.org/10.3390/ijms231710025

Steller MA, Delgado CH, Bartels CJ, Woodworth CD, Zou Z. 1996. Overexpression of the insulin-like growth factor-1 receptor and autocrine stimulation in human cervical cancer cells. *Cancer Research* **56**: 1761-1765.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal For Clinicians* **71**: 209-249. DOI: https://doi.org/10.3322/caac.21660

Swetha S, Manivannan HP, Francis AP, Veeraraghavan VP, Gayathri R, Sankaran K. 2024. Identification of potential lead compound from *Thuja occidentalis* as an inhibitor of FMS-like tyrosine kinase 3 (FLT3) in acute myeloid leukemia through virtual screening. *Indian Journal of Biochemistry and Biophysics* **61**: 472-484. DOI: https://doi.org/10.56042/ijbb.v61i8.4569

Torre LA, Siegel RL, Ward EM, Jemal A. 2016. Global cancer incidence and mortality rates and trends -an update. *Cancer Epidemiology, Biomarkers & Prevention* **25**: 16-27. DOI: https://doi.org/10.1158/1055-9965.EPI-15-0578

Tran CV, Vo TM, Bui PT, Duong DN, Duong LX, Dinh DQ, Nguyen HTT. 2023. Phytochemical screening, antioxidant activity and α-glucosidase inhibitability of *Bauhinia* × *blakeana* Dunn leaf and flower extracts from Vietnam. *Tropical Journal of Natural Product Research* **7**: 2737-2743. DOI: http://www.doi.org/10.26538/tjnpr/v7i4.11

Tsuneki H, Ma EL, Kobayashi S, Sekizaki N, Maekawa K, Sasaoka T, Wang M, Kimura I. 2005. Antiangiogenic activity of β-eudesmol *in vitro* and *in vivo*. *European Journal of Pharmacology* **512**: 105-115. DOI: https://doi.org/10.1016/j.ejphar.2005.02.035

Van Chen T, Cuong TD, Quy PT, Bui TQ, Van TL, Van HN, Triet NT, Duc VH, Chi BN, Nhung NTA. 2022. Antioxidant activity and α-glucosidase inhibitability of *Distichochlamys citrea* MF Newman rhizome fractionated extracts: *In vitro* and *in silico* screenings. *Chemical Papers* **76**: 5655-5675. DOI: https://doi.org/10.1007/s11696-022-02273-2

Van Chen T, Truong MN, Quynh TTT, Nhi NTT, Linh NHK. 2024. GC-MS analysis and cytotoxic activity of the n-hexane fraction from *Curcuma sahuynhensis* Škornick. & NS Lý leaves collected in Vietnam. *Plant Science Today* **11**: 308-315. DOI: https://doi.org/10.14719/pst.2881

Vinette V, Aubry I, Insull H, Uetani N, Hardy S, Tremblay ML. 2021. Protein tyrosine phosphatome metabolic screen identifies TC-PTP as a positive regulator of cancer cell bioenergetics and mitochondrial dynamics. *The FASEB Journal* **35**: e21708. DOI: https://doi.org/10.1096/fj.202100207R

Wagner KH, Brath, H. 2012. A global view on the development of non communicable diseases. *Preventive Medicine* **54**: S38-S41. DOI: https://doi.org/10.1016/j.ypmed.2011.11.012

Yamazaki H, Tsuge H, Takahashi O, Uchida R. 2021. Germacrane sesquiterpenes from leaves of *Eupatorium chinense* inhibit protein tyrosine phosphatase. *Bioorganic & Medicinal Chemistry Letters* **53**: 128422. DOI: https://doi.org/10.1016/j.bmcl.2021.128422

Zhao BT, Nguyen DH, Le DD, Choi JS, Min BS, Woo MH. 2018. Protein tyrosine phosphatase 1B inhibitors from natural sources. *Archives of Pharmacal Research* **41**: 130-161. DOI: https://doi.org/10.1007/s12272-017-0997-8

Zheng SW, Wan WG, Miao HX, Tang R, Wang B, Huang QZ, Liu WL, Zheng JP, Chen CQ, Zhong HB, Li SF, Sun CH. 2017. Leptocarpin suppresses proliferation, migration, and invasion of human osteosarcoma by targeting type-1 insulin-like growth factor receptor (IGF-1R). *Medical Science Monitor* **23**: 4132-4140. DOI: https://doi.org/10.12659/MSM.903427

Supporting agencies: Not applicable.

Associate editor: Juan Rodrigo Salazar

Author contributions: TVC, data curation, formal analysis, investigation, methodology, writing - review and editing; DMK, formal analysis, writing - original draft; PNBT, data curation, methodology; VLT, data curation; methodology; PNCL, writing - original draft; NTTH, writing–original draft; NTT, supervision, validation, writing–review and editing. All authors read and approved the final manuscript. The authors declare that there is no conflict of interest, financial or personal, in the information, presentation of data and results of this article.