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Research Article

Chemical Composition and Biological Activity of the Essential Oil Isolated from the Leaves of *Achillea fragrantissima* Growing Wild in Yemen

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ABSTRACT

Background: Yemen is diverse in its geography and rich in its natural flora. *Achillea fragrantissima* grown wild in Yemen is widely used in folkloric medicine. **Objectives:** To investigate the chemical composition, cytotoxicity, xanthine oxidase inhibitory and tyrosinase inhibitory activities of the essential oil isolated form the leaves of *Achillea fragrantissima* (Forssk.) Sch. Bip. growing wild in Yemen. **Materials and Methods:** The oil was collected after hydrodistillation for 3 h, the oil composition was analyzed by GC-MS and assayed for biological activities. **Results:** Artemisia ketone (49.53%), camphor (14.73%), α-bisabolol (11.20%), α-bisabolol oxide B (2.62%) were the main components of the oil. The MTT assay of the oil on two human colorectal cancer cell lines (SW480 and HCT-116) showed IC_{50} values of 110.1 and 134.6 μg ml^{-1}, respectively. Xanthine oxidase inhibitory and tyrosinase inhibitory activity assays were performed but exhibited only marginal activities. **Conclusion:** the components of the essential oil could be excellent anticancer drugs for treatment of colon cancer

Key words: *Achillea fragrantissima*, Artemisia ketone, Essential oil, Cytotoxicity, GC-MS.

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INTRODUCTION

Essential oils (EO) are natural aromatic oils obtained from different parts of the plant material. Steam distillation is the most common method for commercial production of EOs. EOs have been used for many applications including food flavoring agent, aromatherapy, perfumes, in addition to their medical uses including antioxidants, antimicrobial, antiviral, antifungal, insecticidal and anticancer activity.[1]

Yemen is characterized by its diversity in topography and climate. It is divided into five geographical regions; mountains, coastal plains, inland plains, desert and islands. This diversity is the reason behind the complicated vegetation and floristic richness of Yemen.[1-3]

Achillea is a genus belonging to Asteraceae, represented by around 115 species in the temperate regions in the world, five of which have been recorded in Yemen.[3-5] Species of *Achillea* are used in folkloric medicine as antibacterial, antifungal, anti-inflammatory, antiulcer, hypoglycemic, contraceptive, emmenagogue and abortifacient.[6] *A. fragrantissima* (known by its Arabic name Qaysoom) has been employed in folkloric medicine as stomachic and anthelmintic and for treating chronic diseases as arthritis and diabetes.[7-9] In addition, *A. fragrantissima* was found to protect against brain damage and to delay the onset of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[10] Several papers have reported the chemical composition of *A. fragrantissima* essential oil (AFEO) that was characterized mainly by high amounts of oxygenated terpenoids either with artemisia ketone, α-thujone, β-thujone, terpinen-4-ol or caryophyllene oxide as main components.[7,11-16] Cytotoxic, antimicrobial, antiviral and antioxidant activities of AFEO were also reported.[7,13-18] In this work, we report for the first time the essential oil composition, cytotoxicity, xanthine oxidase and tyrosinase inhibitory activities of *A. fragrantissima* growing wild in Yemen.

MATERIALS AND METHODS

Plant material

Ten kg of the leaves of *A. fragrantissima* were collected during the flowering stage in May 2013, from Dhamar province (14.0° 32.0′23.4″ N, 44.0° 18.0′ 0.7″E, altitude 2341.0 m), Yemen. The plant was identified by Dr. Hassan M. Ibrahim of the Botany Department, Faculty of Sciences, Sana'a University. A voucher specimen of the plant material (YMP-com-11) has been deposited at the Pharmacognosy Department, Sana'a University, Yemen.

Isolation of essential oil

The dried leaves were hydrodistilled for 3 h in a Clevenger type apparatus according to the European Pharmacopoeia.[19] The obtained oil was subsequently dried over anhydrous Na_2SO_4 and kept at 4°C until analysis.

Gas chromatography – mass spectrometry

The *A. fragrantissima* essential oil was analyzed by GC-MS using an Agilent 6890 GC with an Agilent

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5973 mass selective detector [MSD, operated in the EI mode (electron energy = 70 eV), scan range = 45-400 amu and scan rate = 3.99 scans/sec] and an Agilent Chem Station data system. The GC column was an HP-5ms fused silica capillary with a (5% phenyl)-polymethylsiloxane stationary phase, film thickness of 0.25 µm, a length of 30 m and an internal diameter of 0.25 mm. The carrier gas was helium with a column head pressure of 48.7 kPa and a flow rate of 1.0 mL/min. Inlet temperature was 200°C and interface temperature was 280°C. The GC oven temperature program was used as follows: 40°C initial temperature, held for 10 min; increased at 3°C/min to 200°C; increased 2°/min to 220°C. A 1 %, w/v, solution of the sample in CH_2Cl_2 was prepared and 1 µL was injected using a splitless injection technique. Identification of the oil components was based on their retention indices determined by reference to a homologous series of *n*-alkanes (C8-C40) and by comparison of their mass spectral fragmentation patterns with those reported in the literature[20] and stored on the MS library [NIST database (G1036A, revision D.01.00)/Chem Station data system (G1701CA, version C.00.01.080]. The percentages of each component are reported as raw percentages based on total ion current without standardization.

Cytotoxicity screening

Human colorectal cancer cell lines (SW480 and HCT116) cultured in DMEM to which 10% fetal calf serum (Bio Whittaker, Belgium) was added. The Yamani AFEO was tested for acute cytotoxic effect; the essential oil was dissolved in DMSO and different dilutions in culture buffer were prepared (DMSO end concentration <1%). The acute cytotoxic effect of AFEO on colorectal cancer cells was determined using the MTT assay.[21] Briefly, 5000 cells/well were seeded onto 96-well, flat-bottomed culture plates and allowed to grow for 24 h before the oil treatment. Cells were then incubated with 200 µL of essential oil concentrations (0–200 µg/mL) for 72 h, labeled with MTT from the Vybrant MTT Cell Proliferation Assay Kit (Molecular Probes, Eugene, USA) according to the manufacturer's instruction and the resulting formazan was solubilized with DMSO and the absorbance was read at 540 nm.

Xanthine oxidase inhibition assay

Using xanthine as substrate, the xanthine oxidase activity of *A. fragrantissima* oil from Yemen was assayed spectrophotometrically according to Apaya and Hernandez.[22] A mixture containing 1 mL of 100 μg/mL of AFEO or allopurinol standard inhibitor, 1.9 mL of 50 mM potassium phosphate buffer and 1 mL of xanthine substrate (0.6 mM) was preincubated for 10 min at 25°C and the reaction was started by the addition of 0.1 mL of XO enzyme (0.1 U/mL in phosphate buffer). The reaction was incubated at 25°C for 30 min and the absorbance was measured against phosphate buffer as blank at 295 nm. The xanthine oxidase inhibition was calculated according to the following: % inhibition = $100 - (A_1 - B) \times 100/(A_o - B)$; where A_1 is the activity of the enzyme in presence of AFEO, B is the absorbance in absence of the enzyme and A_o is the absorbance in absence of the oil or inhibitor

Tyrosinase inhibition assay

In vitro mushroom tyrosinase inhibitory activity of *A. fragrantissima* oil from Yemen was determined by a spectrophotometric approach using L-tyrosine as the substrate.[23] In a total volume of 200 μL, the enzyme activity was measured in buffer containing 50 mM phosphate buffer, pH 6.5, 50 U/mL mushroom tyrosinase and 50 μg/mL L-tyrosine. The reaction (conversion of L-tyrosine to DOPAchrome) was conducted at 37°C for 30 min and absorbance was measured at 490 nm using a microplate reader in the presence and absence of 100 μg/mL of AFEO. Kojic acid was used as positive control inhibitor. The tyrosinase inhibitory activity was calculated as follows:

% inhibition = $((A - B)/A) \times 100)$

Where A is the absorbance difference at 490 nm of the negative control (no AFEO); B is the absorbance of test sample (with AFEO).

RESULTS AND DISCUSSION

Hydrodistillation of the dried leaves of *A. fragrantissima* collected from Yemen gave a yield of 0.92% w/w of yellow oil (calculated on the dry weight and after drying over Na_2SO4). The essential oil was subject to GC-MS analysis. The chemical composition is summarized in Table 1, where the compounds are listed in the order of elution on HP-5ms column. GC-MS analysis of the oil disclosed the presence of 37 compounds accounting for 94.84% oil composition. The oxygenated monoterpenoids represented the highest percentage (70.06%) among which artemisia ketone (49.53%), camphor (14.73%) were dominant, whereas the monoterpene hydrocarbons constituted only 6.46% of the total oil with *p*-cymene (1.62%) and camphene (1.18%), while the oxygenated sesquiterpenes formed 14.64% of the oil composition with α-bisabolol (11.20%), α-bisabolol oxide B (2.62%) as the main components; the sesquiterpene hydrocarbons were the poorest fraction (1.5%). Higher amount of oxygenated monoterpenes was reported in Egyptian AFEO with artemisia ketone as the main active component.[17,18] Conversely, Choucry reported the AFEO composition with caryophyllene oxide (23.50%) and terpinen-4-ol (11.15%) as main components,[7] which were found in our study in minor quantities. The essential oil collected from Sinai Peninsula was analyzed to have α-thujone (33.97%) and *trans*-2,7-dimethyl-4,6-octandien-2-ol (24.40%) as main component.[18] Another recent study on AFEO collected from the Jordanian desert, Alsohaili evaluated the effect of harvesting time on the composition of AFEO. The major components were artemisia ketone (20.50-31.86%), 1,8-cineole (8.31-16.85%) and β-thujone (11.34-22.11%).[14] While another study on Jordanian AFEO determined very low percentage of artemisia ketone (2.99%) but α-thujone (33.77%) and β-thujone (20.73%) as main components.[15] The Lebanese AFEO was also analyzed by GC-MS and contained artemisia ketone (29.97%) and α -thujone (13.34%) as main compounds.[16] The difference in the active constituents could be due to difference in the extraction method of the essential oil, geographical region, climate and humidity, in addition to the time of plant collection and other environmental differences.

The cytotoxic activity of AFEO was studied against human colorectal cancer cell lines (SW480 and HCT116). AFEO showed anticancer activity against SW480 and HCT116-cell lines with IC_{50}s of 110.1 and 134.6 μg.mL^{-1}, respectively. The dose dependent inhibition of cell line survival and IC_{50}'s are shown in Figure 1. As reported in other studies, IC_{50} values less than 30 μg/mL possess a marked chemopreventive potential for the essential oils.[24] However AFEO contains high amount of monoterpenes and major compounds with reported cytotoxic activity such as camphor and α-bisabolol; they showed weak to moderate cytotoxic activity.[25] Camphor was found to have a dose-dependent cytotoxic effect against HCT116 cell line with IC_{50} value of 4.5 mM[26] while α-Bisabolol was reported to possess cytotoxic activity against glioma, pancreatic, ovarian and kidney carcinoma cells and as a chemopreventive agent in rat mammary carcinogenesis.[27-30] A previous study reported highest cytotoxic activity of Egyptian AFEO (IC_{50} = 0.51 µg.mL-1) against the HCT116 cell line,[7] which can be related to the high β-caryophyllene oxide content, that exhibited excellent cytotoxic activity against five different cell lines.[31] This cytotoxic activity variation could be attributed to the qualitative and quantitative oil compositions that may be explained in the light of the impact of the environmental factors during plant growth. Besides, the synergistic cytotoxic effects among the Egyptian AFEO components may be more potent than among our oil components.

Table 1: The Composition of essential oil isolated from the leaves of *Achillea Fragrantissima*, their retention time (Rt), Ri literature, Ri observed and their percentage in the oil.

No.	RT	RI literature[17]	RI Observed	Compound	%
1	9.28	906	902	Santolina triene	0.97
2	10.81	932	932	α-Pinene	0.43
3	11.46	945	944	4-Methyl-2-pentenolide	0.12
4	11.66	946	948	Camphene	1.18
5	13.15	974	976	β-Pinene	0.70
6	13.79	988	989	Myrcene	0.98
7	14.13	999	995	Yomogi alcohol	1.41
8	14.98	---	1009	Methyl 2-oxohexanoate	0.09
9	15.89	1020	1024	*p*-Cymene	1.62
10	16.17	1024	1028	Limonene	0.35
11	16.27	1025	1030	β-Phellandrene	0.23
12	18.09	1056	1058	**Artemisia ketone**	49.53
13	18.79	1065	1069	*cis*-Sabinene hydrate	0.26
14	19.41	1080	1079	Artemisia alcohol	1.21
15	20.22	---	1092	2,4-Dimethyl-2,4-heptadienal	0.13
16	20.77	1098	1100	*trans*-Sabinene hydrate	0.30
17	23.61	---	1142	Epoxyterpinolene	0.22
18	21.91	1141	1146	**Camphor**	14.77
19	24.50	1160	1155	*cis*-Chrysenthemol	0.14
20	25.03	1165	1163	Lavandulol	0.45
21	25.58	1165	1171	Borneol	0.83
22	26.17	1174	1179	Terpinen-4-ol	0.34
23	26.41	1179	1183	4-Methylacetophenone	0.12
24	26.56	1183	1185	Cryptone	1.18
25	26.61	1179	1186	*p*-Cymen-8-ol	0.68
26	27.17	1186	1194	α-Terpineol	0.16
27	30.34	1238	1241	Cuminal	0.13
28	30.77	1244	1247	Carvotanacetone	0.19
29	33.67	1289	1290	Cuminol	0.21
30	36.74	1330	1336	3-Oxo-*p*-menth-1-en-7-al	0.22
31	45.42	1475	1472	*trans*-Cadina-1(6),4-diene	0.31
32	45.85	1479	1479	α-Curcumene	0.55
33	47.75	1511	1510	δ-Amorphene	0.17
34	50.70	1561	1560	(*E*)-Nerolidol	0.60
35	51.78	1582	1578	Caryophyllene oxide	0.22
36	56.01	---	1652	α-Bisabolol oxide B	2.62
37	57.82	1685	1684	**α-Bisabolol**	11.20
				Monoterpene hydrocarbons (1, 2, 4, 5, 6, 9, 10, 11)	6.46
				Oxygenated monoterpenoids (7, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30)	72.23
				Sesquiterpene hydrocarbons (31, 32, 33)	1.03
				Oxygenated sesquiterpenoids (34, 35, 36, 37)	14.64
				Others (3, 8, 15, 23)	0.46
				Total Identified	94.82

RT: Retention time, compounds were ordered according to their retention time; **RI:** Retention index, both from literature and experimentally determined.

AFEO was tested for tyrosinase inhibitory activity and xanthine oxidase inhibitory, but exhibited no activity in any of these bioassays. At concentration of 100 μg/mL, the % inhibition of xanthine oxidase and tyrosinase activity by AFEO are shown in Table 2. Tyrosinase inhibitory activity was reported for essential oils obtained from Yemeni aromatic plants. At concentrations of 100 μg/mL, essential oils of *Ocimum basillicum*, *Ocimum canum, Cymbopogon citratus*, *Artemisia abrotanum* and *Chenopodium ambrosioides* showed potent inhibition of tyrosinase with 83.76, 66.0, 69.0, 63.60 and 64.44%, respectively.[32,33] Tyrosinase is the key enzyme in the biosynthesis of melanin and tyrosinase inhibitors can be used in cosmetics as whitening agents, in addition to their use as antibrowning in food industry.[34]

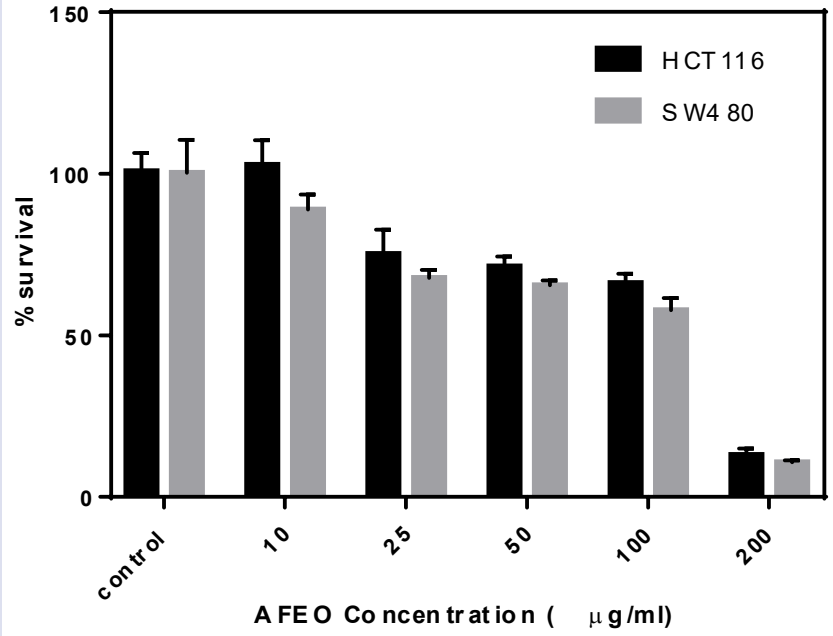

Figure 1: The dose dependent inhibition curve showing % Survival of SW480 and HCT116 cell lines following treatment with different concentrations of AFEO with IC_{50} of 110.1 µg/ml on SW480 and 134.6 µg/ml on HCT116.

Table 2: % inhibition of tyrosinase and xanthine oxidase inhibitory activities of AFEO.

Substance tested	%Tyrosinase inhibition	%Xanthine oxidase inhibition
AFEO	2.9±1.6	3.9±0.77
Kojic acid	98.1±1.1	-
Allopurinol	-	96.9±1.8

CONCLUSION

Achillea fragrantissima is widely used in folkloric medicine in Yemen. The leaves were collected from Dhamar region, and the essential oil was isolated by hydrodistillation and analyzed for its chemical composition by GC-MS. The cytotoxic activity and the inhibitory activities on two different enzymes (XO and tyrosinase) were also evaluated. Yemeni AFEO was characterized by a high content of oxygenated monoterpenes and rich in Artemisia ketone, which was reported in some Egyptian and Jordanian AFEO's as main component. Our results reveal also that AFEO exhibit weaker cytotoxic activity in comparison to Egyptian oil which can be related to the high content of β-caryophyllene oxide in the Egyptian oil and very weak inhibitory activities on the tested enzymes.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

EO: Essential oil; **AFEO**: *Achillea fragrantissima* essential oil; **DMEM**: Dulbeco's modified eagles medium; **XO**: Xanthine oxidase; **GC-MS**: Gas chromatography-mass spectroscopy; **DMSO:** Dimethyl sulfoxide; **MTT:** 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide.

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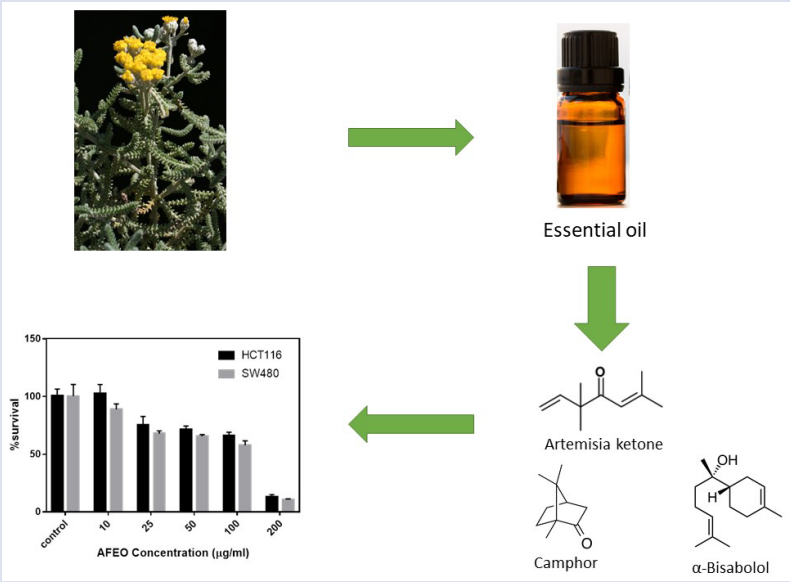
GRAPHICAL ABSTRACT



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