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Comparative Study on the Anticancer Potential of Apigenin and Syringic Acid Isolated from Parsley Leaves Against A375 cell line

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Parsley leaves (Petroselinum crispum) biennial herb native to the Mediterranean has diverse bioactive phytochemicals, like flavonoids and phenolic acids that known for their potent antioxidant and cytotoxic properties. This study aimed to isolate two phenolic compounds, Apigenin and Syringic acid from ethyl acetate fraction of parsley leaves extract and evaluate their cytotoxic activity against A375 cell line compared to normal cells. Ultrasonication was used to extract the active compounds using 90% ethanol, and PHPLC was used to isolate the two phenolic compounds. FT-IR was used to categorize the active functional groups comprising the two isolated phenolic compounds. The results showed the isolation of syringic acid and apigenin, apigenin exhibited cytotoxic activity with IC50% 40.8 μg /ml and Syringic acid exhibited cytotoxic activity with IC50 values 54.5 μg /ml, Apigenin showing a stronger cytotoxic activity than Syringic acid. Both isolated phenolic compounds exhibited strong cytotoxic activity depend on increasing concentration of each compound, and Apigenin showing particularly high cytotoxic activity against A375 cell line.

Keywords: A375cell line; Apigenin; Cancer; Parsley; Syringic acid.

Parsley (*Petroselinum crispum L.*) is a widely cultivated biennial herb native to the Mediterranean, thriving in rich, well-drained soils under full or partial sunlight, and often grown from seeds planted in early spring.[1] This vibrant green herb is celebrated for its diverse phytochemical profile, including abundant flavonoids like apigenin and luteolin glycosides, volatile oils such as apiol and myristicin, and phenolic acids like syringic and ferulic acids, which together confer potent antioxidant and anti-inflammatory properties.[2]

Traditionally, parsley has been used across cultures as a digestive aid, mild diuretic, breath freshener, and remedy for kidney or bladder issues, while in folk medicine it has also been employed to ease menstrual discomfort and reduce swelling, making it a plant of both culinary and medicinal significance .[3]

Cancer is a complex disease assigned by the unrestrained growth of abnormal cells, which can infiltrate neighboring tissues and spread to distant sites through metastasis.[4] Its development is driven by a combination of genetic mutations, epigenetic modifications, and disturbances in key signaling pathways that regulate cellular proliferation, programmed cell death, and differentiation .[5] Although conventional treatments like surgery, chemotherapy, and

radiation therapy have advanced, they still face significant drawbacks, such as serious side effects, the emergence of treatment resistance, and a lack of selectivity for cancer cells over healthy ones.[6,7] As a result, there is increasing interest in identifying new therapeutic agents, particularly natural compounds with potential anticancer properties, due to their promise of improved safety and effectiveness.[8]

Apigenin is a naturally occurring flavonoid found abundantly in many fruits, vegetables, and herbs. It is especially concentrated in parsley, chamomile, celery, and oranges, making these common dietary sources of this bioactive compound .[9,10] Traditionally, plants rich in apigenin have been used in folk medicine across various cultures to treat conditions such as inflammation, anxiety, insomnia, digestive issues, and skin disorders.[8] Chamomile tea, for example, is widely consumed as a calming remedy and owes much of its soothing effect to its apigenin content.[11,12]

Beyond its traditional applications, modern pharmacological research has revealed that apigenin possesses a varied spectrum of biological activities, as antioxidant, anti-inflammatory, antimicrobial, neuroprotective, and notably, anticancer activities.[13-15] Studies have shown that apigenin can inhibit the growth of cancer cells, induce apoptosis, and suppress tumor angiogenesis and metastasis by modulating various molecular pathways involved in cell cycle regulation and survival .[14,15]

Because of these promising properties, apigenin is increasingly being explored as a potential therapeutic agent in cancer prevention and treatment strategies.

Syringic acid is a naturally occurring phenolic acid that belongs to the class of hydroxybenzoic acids. It is widely distributed in the plant kingdom and can be found in various fruits, vegetables, and medicinal herbs, including grapes, olives, dates, honey, and spices like turmeric and parsley. [16,17] This compound is also abundant in the bark and heartwood of certain trees, such as maple and walnut, as well as in red wine and other plant-derived foods and beverages.[16-18]

In traditional medicine, syringic acid-rich plants have long been valued for their health-promoting properties. Remedies containing syringic acid sources have been used for centuries to manage inflammation, pain, infections, and digestive problems in different cultures around the world. [19,20] These traditional uses laid the foundation for scientific investigations into its potential health benefits.Modern pharmacological research has highlighted syringic acid's diverse biological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, neuroprotective, and anticancer effects.[21-23]

Studies show that syringic acid can neutralize free radicals, reduce inflammatory responses, modulate key metabolic enzymes, and even induce cancer cell apoptosis by influencing signaling pathways related to cell proliferation and survival.[22,23] These findings support syringic acid's promise as a natural therapeutic agent for various chronic diseases, including cancer and metabolic disorders. In this study, we hope to isolate two phenolic compounds Apigenin and Syringic acid from ethyl acetate fraction of parsley leaves extract and compared their cytotoxic effects on A375 cell line.

MATERIALS AND METHODS

Plant Collection and extraction

Parsley leaves were harvested from a home garden during the summer season and experienced authentication directed by expert Prof. Sukaena Abass. The collected leaves were thoroughly washed, shade-dried, and then mechanically ground into a fine powder. For extraction, 20 g of the powdered parsley leaves were mixed with 150 mL of 90% ethanol and subjected to ultrasonic-assisted extraction using an ultrasonic bath sonicator operating at (40 kHz and 45/ °C for 60 minutes) which relies on the principle of acoustic resonance, where small bubbles form and then burst near the plant cell wall, leading to its destruction and the release of active substances into the solution. These resulting cavities are a consequence of the conversion of electrical energy into high-frequency sound waves transmitted through the liquid inside the tank. The resulting mixture was filtered through Whatman filter paper. The filtrate was evaporated to dryness, and the dried extract was subsequently suspended in a biphasic system comprising 150 mL of distilled water and 150 mL of ethyl acetate. The ethyl acetate fraction (EtOAc) was then subjected to Preparative High-

performance Liquid Chromatography (PHPLC) for the isolation of phenolic compounds.[24]

Preparative High-performance Liquid Chromatography (PHPLC)Conditions

Quantitative analysis of phenolic compounds in the EtOAc was carried out using PHPLC. The phenolic constituents expected in the fractions were identified by comparing their retention times with those of standard compounds, namely apigenin and syringic acid. The chromatographic separation employed a mobile phase consisting of 1% aqueous acetic acid (solvent A) and acetonitrile (solvent B), with the flow rate set at 3 mL/min and an injection volume of 300 ìL. A gradient elution was applied, starting with 10% B and increasing linearly to 40% B over 28 min.then from 40% to 60% B by 39 min. and finally from 60% to 90% B by 50 min.After reaching 90% B, the gradient was returned to the initial composition of 10% B (B:A = 10:90) at 55 min.and the system was allowed to equilibrate for an additional 10 min. before concluding the run.[25,26]

Analysis by Fourier transform infrared (FT-IR)

FT-IR spectra of isolated compounds were subjected in the FTIR spectrometer (Shimadzu)in the range of 500 to 4000 cm^{-1}wave number

Materials

Apigenin and syringic acid St. Were from Sigma-Aldrich, A375 cell lines from Center for Biotechnology Research at Al-Nahrain University.

Cell Line Maintenance

The procedure of work was conducted for cell line maintenance according toFreshney RI [(27)].

MTT Assay

After treating the cells with apigenin and syringic acid for 72 hours, the culture medium in each well was gently removed. The wells were rinsed twice with phosphate-buffered saline to clear any residual compounds. Next, 100 ìL of fresh cell culture medium and 15 ìL of MTT staining solution were added to each well. Following a 4-hour incubation period, 100 ìL of stop solution was carefully introduced to halt the MTT reaction.[28] The plates were then kept in the incubator overnight to allow complete solubilization of the formazan crystals. Finally, cell viability was assessed by measuring at 570 nm optical density using a spectrophotometer ,Experiment was repeated three times .

Statistical analysis

Data analysis was performed with GraphPad Prism version 6, and results were appeared as the mean ± standard deviation depend on three independent replicates. Statistical comparisons between groups were made using an unpaired t-test, with differences considered statistically significant at $P < 0.05$.

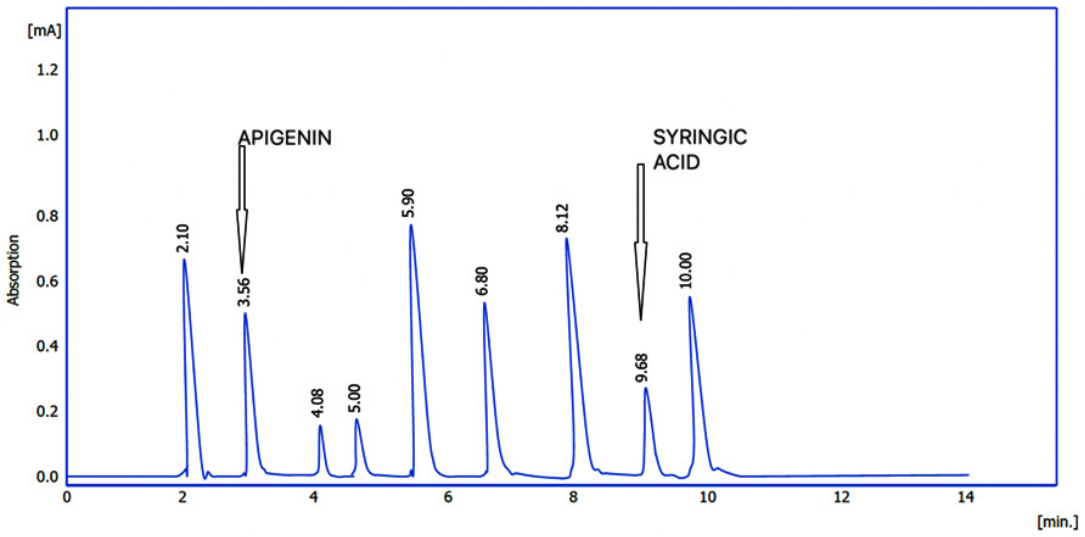

Fig. 1. HPLC chromatogram for EtOAc

RESULTS

Extraction by Ultrasonic bath sonicator

Ultrasound-assisted extraction was employed as the method of choice for processing the parsley leaves, yielding approximately 11 g of crude extract from 20 g of dried leaf material, representing a notably high extraction efficiency.

Isolation of Apigenin and syringic acid by PHPLC

Apigenin and Syringic acid were isolated by PHPLC using the chromatographic settings that cited in the earlier paragraphs, as in Figures. from 1 to 5

Analysis by FT-IR

FT-IR spectroscopy is generally used in phytochemical reports as a fingerprinting technique to compare normal compounds with synthetic standards. The IR spectra of the quarantined compound Apigenin is existing in figure 6. characteristic bands can be seen in the range of 3381-3000cm $^{-1}$ (O-H of alcohols stretching vibration),2904-2620 cm^{-1} (C-H stretching vibration for aliphatic),1650-1512 cm^{-1}(C=O)stretching vibration.[29]while the bands present in FT-IR spectrum of isolated syringic acid in figure 7 exhibited distinct peaks at

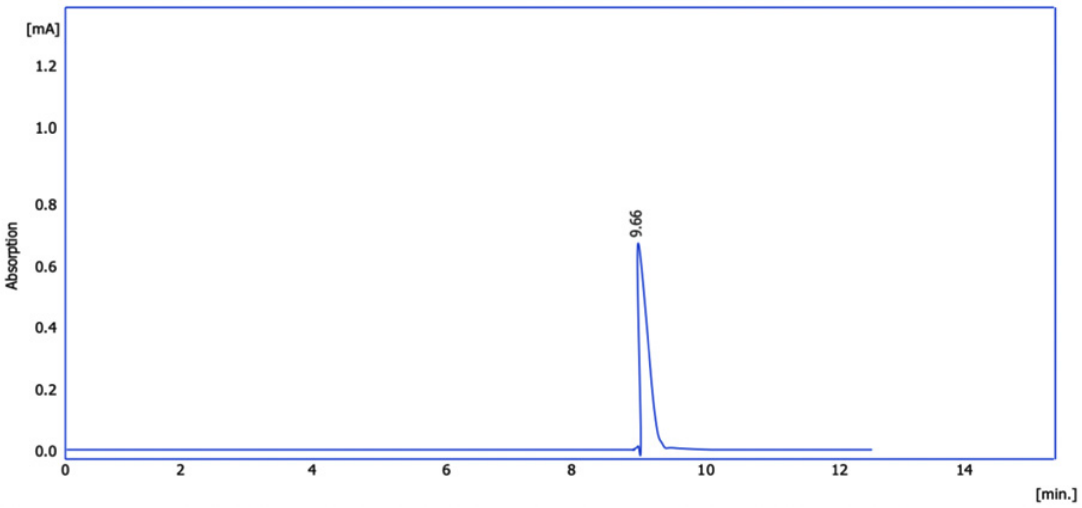

Fig. 2. HPLC chromatogram of Syringic acid standard

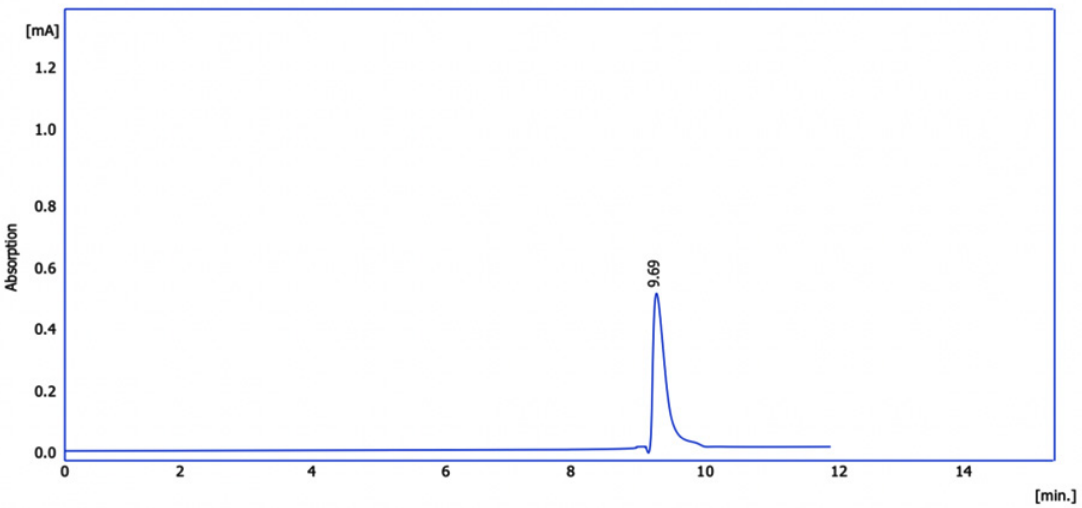

Fig. 3. HPLC chromatogram of isolated syringic acid

3361 cm^{-1} (corresponding to –OH vibrations), 1710 cm^{-1} (representing C=O stretching), and 1618 cm^{-1} (indicating aromatic ring group C = C stretching). Others peaks were seen at 1367 cm^{-1}, 1244 cm^{-1}, and 1203 cm^{-1}, which corresponded to CH3-, C-O-C, and C-OH groups, respectively as in previous studies.[30]

Table 1. Retention time in min. for phenolic compounds in EtOAc fraction

Phenolic compounds	Retention time forphenols in EtOAc fraction	Retention time of phenolic compounds standards
Syringic acid	9.68	9.69
Apigenin	3.56	3.58

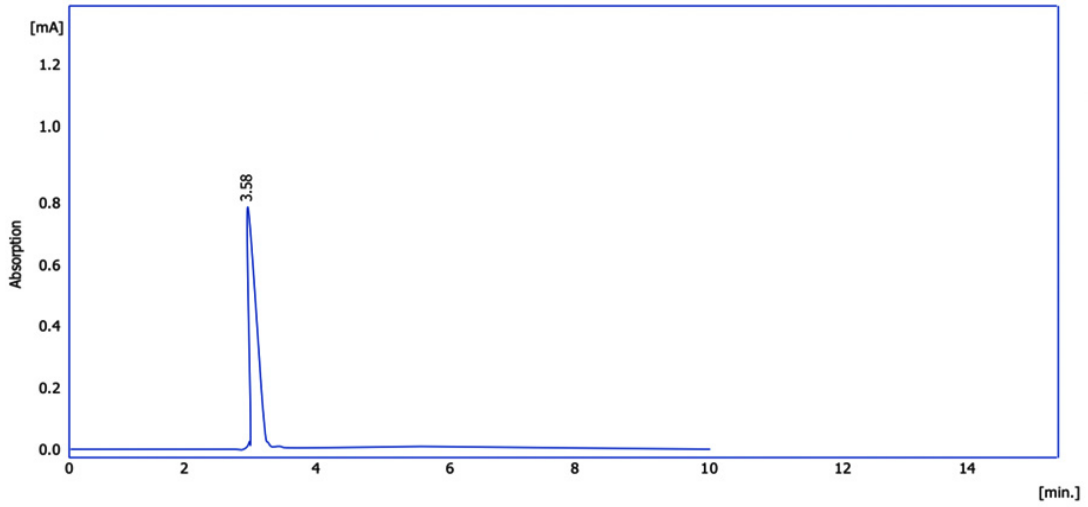

Fig. 4. HPLC chromatogram of Apigenin standard

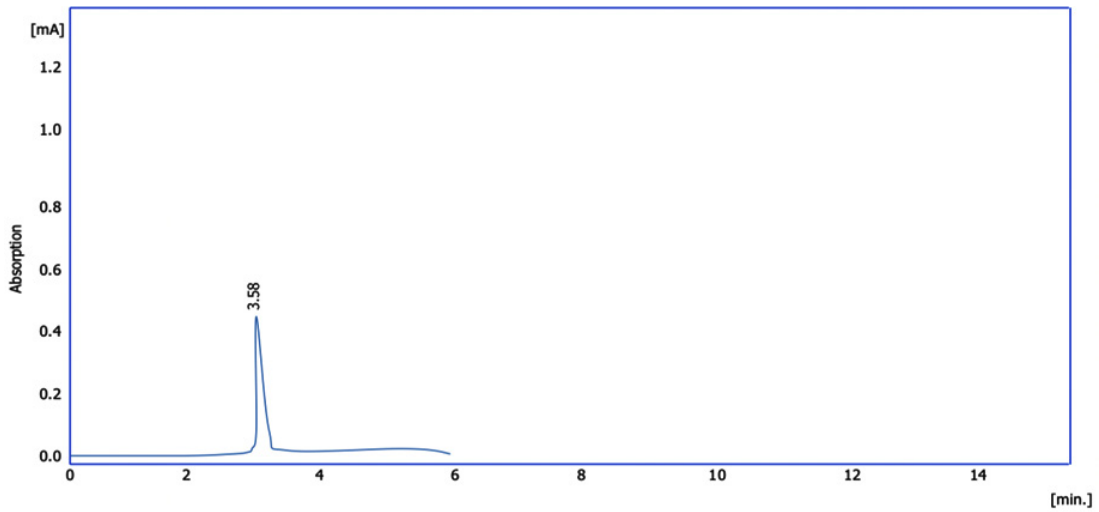

Fig. 5. HPLC chromatogram of isolated Apigenin

MTT Assay

The Cytotoxicity of Apigenin and Syringic acid isolated from plant leaves against A375 cell line compared with (Normal human dermal fibroblast) HdFn cell lines. both cell lines were exposed to serial concentrations from (6.25-400 ìg/ml) of the Apigenin and Syringic acid to assess their effects on the viability of cell line as shown

Table 2. Cytotoxicity of Apigenin on A375 cell line and HdFn Cell after 72 hours of Incubation at 37ºC

Conc. of Apigenin in µg /ml	HdFn viable cell count Mean ±SD	A375cell line count Mean ±SD
400	62.5386± 2.7419	22.3753 ±2.7365
200	74.4986 ±2.0764	29.9693± 2.5524
100	88.0846± 1.0499	39.3180± 1.5714
50	90.8653 ±1.1040	51.6603± 2.8454
25	93.6373± 0.4819	63.0000± 3.5990
12.5	94.0970 ±1.2520	76.2653 ±4.0336
6.25	95.0233 ±0.2315	85.5893± 1.1000

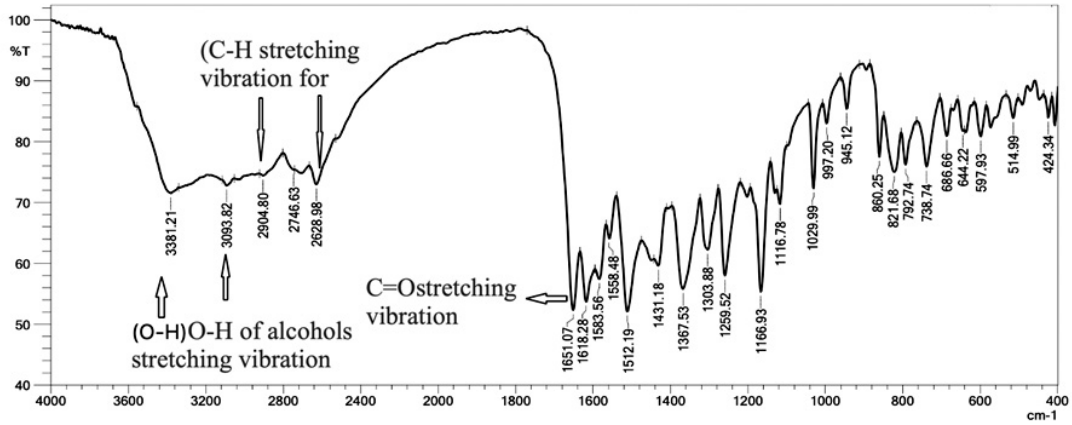

Fig. 6. FTIR spectrum of isolated Apigenin compound

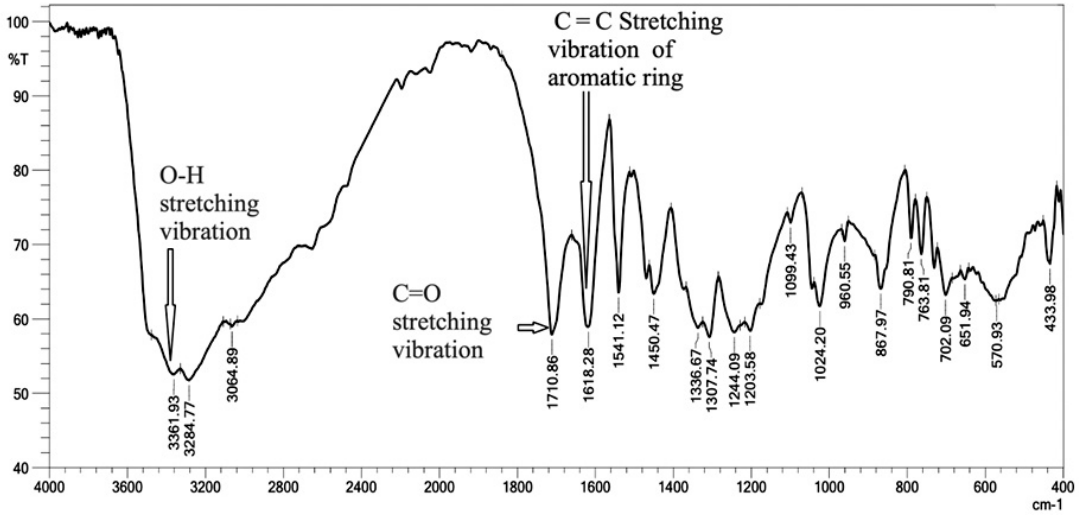

Fig. 7. FTIR spectrum of isolated Syringic acid compound

in figures (8 and 9) respectively. The decrease in A375 cell line viability (%) is represented in tables (2and3) respectively which exhibited a decrease in cell viability (%) with IC_{50} values of 40.8 ìg /ml for apigenin and IC_{50} values of 54.5 ìg /ml for syringic acid. These two compounds induced significant cell death that began at 25 ìg /mL ($P < 0.05$, $n = 6$).

DISCUSSION

The results were consistent with previous studies as ultrasonic analysis showed a significant increase in the conc.[31] of extracted material. Twenty grams of plant leaves yielded 11 grams of crude extract material this is high percentage compared to using the soaking method or the Soxhlet extraction method due to Ultrasound waves made fast formation and collapse of microscopic bubbles in the solvent these bubbles explode the plant cell walls, causing cell disruption and freedom of intracellular phytochemical compounds. Furthermore, using 90% ethanol is an ideal solvent for extracting and isolating the two phenolic compounds, apigenin and syringic acid. The PHPLC results showed high efficiency in isolating the two phenolic compounds, as they had the same retention times compared to the standards compounds. Apigenin had the same retention times was 3.56 as standard apigenin retention time 3.58, and syringic acid showed the same retention time was 9.68 as the standard apigenin retention time 9.69.FT-IR bands gave

Table 3. Cytotoxicity of Syringic acid on A375 cell line and HdFn Cell after 72 hours of Incubation at 37ºC

Conc. of Syringic acid in µg /ml	HdFn viable cell count Mean ±SD	A375cell line count Mean ±SD
400	65.5376± 3.7419	33.3653 ±2.7265
200	72.4976 ±3.07642	40.9593± 2.5424
100	90.0846± 1.04991	53.3180± 1.5724
50	92.8643 ±1.10405	62.6503± 1.8444
25	94.5373± 0.4819	73.0100± 3.5980
12.5	94.0970 ±1.2520	84.2643 ±4.0336
6.25	95.0433 ±0.2315	91.3893± 1.1000

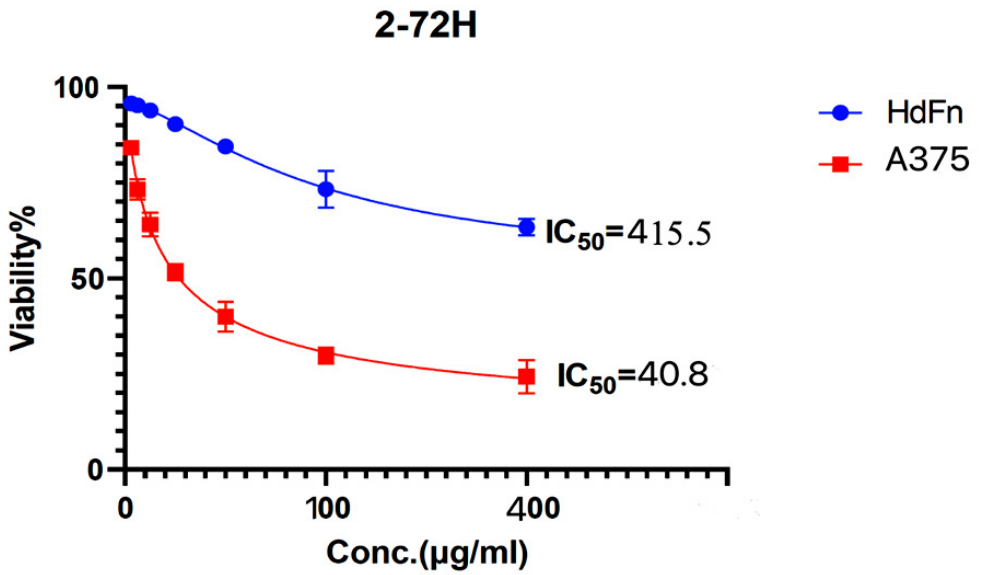

Fig. 8. IC_{50} of Apigenin on A375 cell line

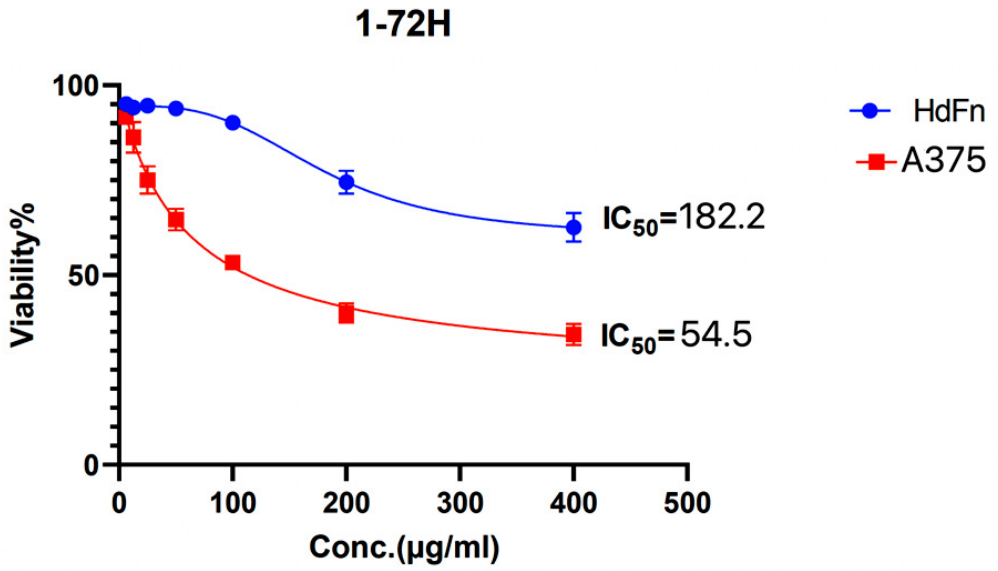

Fig. 9. IC_{50} of Syringic acid on A375 cell line

indications of the presence of functional groups that characterize the apigenin compound, as the peak (3381–3000 cm{ ¹) for O-H group, (2904–2620 cm{ ¹)for C-H group, (1650–1512 cm{ ¹) for C=O group formed the chemical structure of the isolated apigenin compound. While syringic acid FT-IR spectroscopy showed three major band which 3361cm^{-1} for O-H group ,1710 cm^{-1}for C=O group and 1618 cm^{-1} for C=C group the structural components of this compound. As for the MTT test, it showed a direct correlation between increasing concentration and the percentage decrease in live cancer cells. Apigenin had a clear effect, with a IC_{50} % 40.8 ìg /ml which higher effect than that of syringic acid with IC_{50} 54.5ìg /ml %. This is due to the nature of the compound, as it has a more potent effect in inducing apoptosis than syringic acid, which has a simpler phenolic structure than apigenin with flavonoid structure with four hydroxyl group that have effect on PI3K/Akt and MAPK path way.[32] The results also showed that both compounds had low activity against normal cells, exhibiting selective properties against cancer cells and being safer against normal cells. There are some limitations to this study. Only one cancer cell line was used, which limits the generalizability of the results to other cancer types. While the two compounds were isolated and characterized, further diagnostic testing is needed to determine their complete structural composition. Therefore, we anticipate conducting more comprehensive future studies to investigate the efficacy of these anticancer compounds.

CONCLUSION

The results indicate that two phenolic compounds isolated from parsley leaves Apigenin and Syringic acid exhibited an anti-cancer effect against A375 cell line that depended on increasing concentration of each compound. Apigenin was the more potent cytotoxic compound than Syringic acid. Both compounds demonstrated a safe and harmless effect on normal cells HdFn. Therefore, further preclinical studies to understand their mechanism of action in killing these cancer cells, with the aim of developing natural anti-cancer treatments.

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Conflict of Interest

The author(s) declares no conflict of interest

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval Informed Consent Statement. This study did not involve human participants, and therefore, informed consent was not required.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not Applicable.

Author contributions

Ashwaq T. Kareem: contributed to data gathering, analysis, practical (follow the procedure), and written parts of the study; Samer khalid Ali gave final approval and agreement for all aspects of the study, supervision, revision, and rearrangement.

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