



Unveiling the anticancer activity of Fujairah honey via bioactivity-guided fractionation and metabolomics

Eman J. Abuzaid¹, Khawla Mohammed Alyammahi², Attiat Elnaggar^{3,4}, Rania Hamdy^{3,5}, Alshaimaa M. Hamoda^{1,6}, Doha H. Aboubaker^{3,7}, Shaymaa Mohamed^{6,8}, Hamza Mohammad Al-Hroub¹, Nashwa Ahmed Mohamed⁹, Fouad Lamghari², Ali El-Keblawy^{3,10}, Sameh S.M. Soliman^{1,11,*}

¹Research Institute for Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, United Arab Emirates

²Fujairah Research Centre, Fujairah, United Arab Emirates

³Advanced Biotechnology Research Center, Research Institute for Science and Engineering (RISE), University of Sharjah, Sharjah, United Arab Emirates

⁴Department of Botany and Microbiology, Faculty of Science, Alexandria University, Alexandria, Egypt

⁵Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

⁶Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

⁷Medicinal and Aromatic Plants Department, Pharmaceutical and Drug Industries Institute, National Research Centre, Giza, Egypt

⁸Pharmacognosy and Pharmaceutical Chemistry Department, College of Pharmacy, Taibah University, Medina, Saudi Arabia

⁹College of Law, University of Sharjah, Sharjah, United Arab Emirates

¹⁰Faculty of Pharmacy, Al Salam University, Tanta, Egypt

¹¹Department of Medicinal Chemistry, College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates

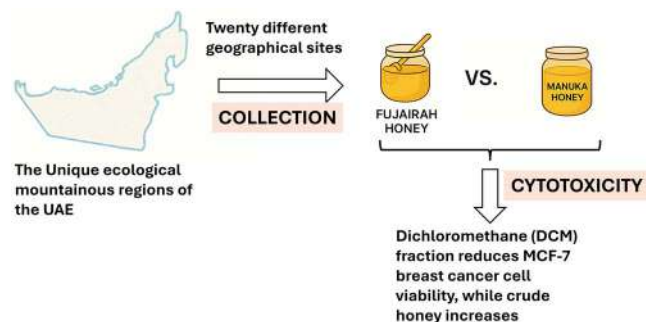
*Corresponding author: Department of Medicinal Chemistry, College of Pharmacy, University of Sharjah, University City Road, Sharjah 27272, United Arab Emirates. Email: ssoliman@sharjah.ac.ae

Abstract

Fujairah honey, collected from the mountainous regions of the United Arab Emirates, represents promising natural sources of functional food and pharmacological potential. This study aimed to characterise the functional food properties of crude Fujairah honey and to employ fractionation approaches to identify constituents with anticancer potential. Twenty Fujairah honey samples (Samar and Sidr) obtained from distinct locations of Fujairah Emirate were evaluated and compared with Manuka honey. The relationship between cytotoxicity, physicochemical properties, and underlying molecular mechanisms including antioxidant capacity, anti-inflammatory, and antimetastatic effects was investigated. Among the samples, Sample 6 (Samar honey derived from *Acacia* species) demonstrated selective cytotoxic activity following fractionation. While the crude honey promoted cell proliferation, its dichloromethane (DCM) fraction induced a 20% reduction in Michigan Cancer Foundation-7 (MCF-7) cell viability. Sample 6 DCM exhibits strong antioxidant activity (92.47% 2,2-diphenyl-1-picrylhydrazyl-hydrate radical scavenging), antimetastatic effects, and significant anti-inflammatory effects through Interleukin-6 (IL-6) downregulation ($p < .0001$) without excessive immune stimulation. Metabolomics profiling revealed elevated levels of fatty acids and monoacylglycerides, and succinic acid (with 28% enhanced cytotoxicity), supporting the unique activity of Samar (particularly Sample 6) honey. Driven by Fujairah's arid climate and unique flora, Fujairah honey emerges as a promising source of novel pharmaceutical and nutritional applications, offering distinctive anticancer and immunomodulatory properties.

Keywords Fujairah honey, honey fractionations, *Acacia* species, arid climate, honey cytotoxicity, honey antioxidant activity, honey metabolomics

Graphical abstract



Introduction

The medicinal and nutritional values of honey have been known for over 8,000 years by ancient Egyptians, Greeks, Romans, and Chinese (Chambó & Alencar Arnaut de Toledo, 2020; Khalil et al., 2023; Qamar & Rehman, 2020). Honey remains widely used for biological properties such as wound-healing, immunomodulatory, anti-inflammatory, antioxidant, and anticancer properties (Aga et al., 2023; Chan-Zapata & Segura-Campos, 2021; Khalil et al., 2023; Tomasin et al., 2024).

Honey exhibits cytotoxic activity, primarily by triggering apoptotic pathways in cancer cells. Studies on colon cancer cells showed that honey upregulates pro-apoptotic markers such as BCL-2-Associated X protein, caspase-3, and p53, while downregulating anti-apoptotic proteins like B-cell lymphoma 2 (Bcl-2) (Aga et al., 2023; Chambó & Alencar Arnaut de Toledo, 2020). The anticancer effects of honey have been attributed to its active constituents, particularly the phenolic contents. *Ziziphus* honey demonstrated anticancer effects against colon, breast, and liver cancers via its polyphenol contents (Chambó & Alencar Arnaut de Toledo, 2020). Research also highlights honey's potential in immune-based cancer therapies (Tomasin et al., 2024). Certain honey types, such as coriander honey, have been found to enhance phagocytosis and increase serum immunoglobulin levels (Hegazi et al., 2015). Honey demonstrated remarkable immunomodulatory effects by reducing the formation of reactive oxygen species and regulation of proinflammatory cytokines, such as IL-1 β , IL-6, and tumour necrosis factor-alpha (Gasparrini et al., 2018; Ghramh et al., 2020). Manuka honey and other varieties were found to suppress excessive inflammatory responses, while other studies showed that honey can stimulate cytokine secretion (Gasparrini et al., 2018; Ghramh et al., 2020). While Manuka honey has been well studied for its anticancer effects, including breast cancer cell inhibition, apoptosis induction, and enhanced tumour suppression in combination with chemotherapy (Fernandez-Cabezudo et al., 2013; Márquez-Garbán et al., 2024), mechanistic research on medicinal honeys from the Gulf Cooperation Council (GCC) region remains limited. *Ziziphus*-derived honeys, such as Saudi Sidr, have shown dose-dependent cytotoxic and antioxidant activity, but their antimetastatic and immunomodulatory effects remain largely unexplored (Bouali et al., 2022; Qanash et al., 2023).

Honey contains several natural components that influence its consistency and activity (Aga et al., 2023; Cianciosi et al., 2018; Qamar & Rehman, 2020). Carbohydrates are the primary compounds, comprising ~75% to 90%, with fructose and glucose being the predominant sugars (Aga et al., 2023; Qamar & Rehman, 2020), while sucrose

presents in smaller amounts. The remaining 18%–20% consists of water and bioactive compounds such as amino acids, vitamins, minerals, enzymes, organic acids, flavonoids, phenolic compounds, and proteins (Aga et al., 2023).

There are over 300 different varieties of honey worldwide, each distinguished by its botanical origin and floral source (Qamar & Rehman, 2020). Honeybees collect nectar from either a single plant species, producing unifloral honey or multiple floral sources, resulting in multifloral honey (Ghramh et al., 2020). The classification and composition of honey are influenced by various factors, including nectar source, storage conditions, and environmental characteristics (Chambó & Alencar Arnaut de Toledo, 2020; Chan-Zapata & Segura-Campos, 2021; Khalil et al., 2023). Geographical origin plays a significant role in determining honey's chemical profile (Aga et al., 2023; Lim et al., 2022). For instance, honey from arid regions typically contains higher levels of polyphenols compared to honey from humid or rainy regions (Aga et al., 2023). Furthermore, its colour, which can range from nearly colourless to dark amber, is influenced by floral sources and harvesting season (Aga et al., 2023; Lim et al., 2022; Chambó & Alencar Arnaut de Toledo, 2020). These variations contribute to the unique nutritional and medicinal values of different honey types (Chan-Zapata & Segura-Campos, 2021; Khalil et al., 2023). Recent studies also show that honeys from the same species can vary significantly in antioxidant capacity and chemical composition, depending on the geographical location, microclimate, and harvest period (Awolu et al., 2025).

In the GCC region, a wide variety of honey is available with Sidr honey being one of the most highly valued (Ghramh et al., 2020). This unifloral honey, native to the desert regions, is widely recognised for its medicinal benefits (Al-Waili et al., 2011; Ghramh et al., 2020). Similarly, Fujairah honey, harvested from the UAE's mountainous and coastal regions, has gained increasing interest for its unique geographical location and hence bioactive composition and potential biomedical applications (Salome et al., 2022). The distinct environmental conditions in these regions influence the chemical profile of honey, contributing to its therapeutic effects. This study aims to investigate the influence of geographical location on the biological activity and chemical composition of honey collected from Fujairah. The study also explores honey functional food characteristics and employs bioactivity-guided fractionation and metabolomics in comparison to commercially available Manuka honey. To our knowledge, this is the first study to examine the anti-inflammatory and antimetastatic properties of Fujairah Samar honey, integrating antioxidant, cytotoxic, and mechanistic assays alongside bioactivity-guided

Table 1 Honey sample code.

Code	Honey year	Apiary number	Apiary location
1	Samar-2022	AP 21	Al Hyle–Rat Farm
2	Samar-2022	AP 05	Tuwiyaïn
3	Samar-2022	AP 08	Ohala
4	Samar-2022	AP 12	Dibba
5	Samar-2022	AP 17	Tuwiyaïn
6	Samar-2023	AP 21	Al Hyle–Rat Farm
7	Samar-2023	AP 05	Tuwiyaïn
8	Samar-2023	AP 08	Ohala
9	Samar-2023	AP 12	Dibba
10	Samar-2023	AP 17	Tuwiyaïn
11	Sidr-2022	AP 02	Fujairah
12	Sidr-2022	AP 12	Dibba
13	Sidr-2022	AP 13	Al Far far
14	Sidr-2022	AP 16	Tuwiyaïn
15	Sidr-2022	AP 17	Tuwiyaïn
16	Sidr-2023	AP 02	Fujairah
17	Sidr-2023	AP 12	Dibba
18	Sidr-2023	AP 13	Al Far far
19	Sidr-2023	AP 16	Tuwiyaïn
20	Sidr-2023	AP 17	Tuwiyaïn

fractionation and metabolomics. This assists in quality authentication, establishes benchmarking, and supports the development of honey-based therapeutics.

Material and methods

Honey sample collection

The study involved the collection of 20 honey samples from different apiary locations across the Fujairah Emirate (UAE), categorised into two primary honey types: Samar honey and Sidr honey. For each of the 20 honey samples, three independent biological replicates were used. These honey samples varied in altitude, main plant types, temperature, precipitation, and wind speed, as recorded by the Fujairah Research Centre. Australian Manuka honey was purchased in October 2022 from Life Pharmacy, UAE, and used as a high-standard commercial control. A total of 10 Samar honey samples, primarily sourced from *Acacia* species, were collected between mid-May and mid-June in both 2022 and 2023. The apiary locations for these samples included Tuwiyaïn, Ohala, Dibba, and Al Hyle–Rat Farm. Similarly, 10 Sidr honey samples, derived from *Ziziphus* species, were collected between early October and late November in both 2022 and 2023 (Table 1). The Sidr honey samples were sourced from Fujairah, Dibba, Al Farfar, and Tuwiyaïn locations. The selected various collection sites ensured a diverse representation of the floral nectar sources, influencing the physicochemical properties and composition of the honey.

Honey extraction and fractionation

Honey samples (10 g) were dissolved in 10 ml of Milli-Q water and mixed until fully dissolved. Liquid–liquid extraction was performed sequentially using hexane, dichloromethane (DCM), and ethyl acetate, each added at 10 ml and repeated three times. After phase separation, the combined organic layers were dried with anhydrous sodium sulphate (Na_2SO_4), filtered, and allowed to evaporate under ambient conditions. The dried extracts were weighed and reconstituted in

dimethyl sulfoxide (DMSO) to a final concentration of 1 mg/ml (final DMSO concentration < 1%).

Physicochemical properties of honey

Determination of colour (Pfund)

Honey samples were weighed and diluted to a concentration of 50% (wt/vol) using Milli-Q water, then heated up to 40 °C in a water bath. The colour was determined at 635 nm using a spectrophotometer (Tecan Austria GmbH, INFINITE 200 PRO, Austria) according to the method by White and Collaborators (1984). The Pfund scale was calculated according to Sereia et al. (2017) using the following equation to determine the colour of each sample.

$$\text{Pfund} = -38.70 + (371.39 \times \text{Absorbance})$$

Determination of colour intensity

Honey samples were weighed and diluted with Milli-Q water to a concentration of 50% (wt/vol) followed by filtration using a 0.45 µm syringe filter. The absorbance was measured using a spectrophotometer (Tecan Austria GmbH, INFINITE 200 PRO, Austria) at two different wavelengths, 450 and 720 nm, to display the colour intensity of the honey samples. The difference in absorbance readings at 450 and 720 nm was calculated and recorded as Absorbance Units (Beretta et al., 2005).

Determination of pH

The honey samples were weighed and diluted with Milli-Q water to a concentration of 10% (wt/vol). pH was then measured using a pH meter (JENWAY-3510, Bibby Scientific Ltd., UK) according to Moniruzzaman et al. (2013).

Determination of electrical conductivity

Honey samples were weighed and diluted with Milli-Q water to achieve a concentration of 20% (wt/vol) (Bogdanov et al., 1997; Moniruzzaman et al., 2013). The electrical conductivity of honey was measured using a conductivity meter (PH-950, Biobase Biotech Co., Ltd., China).

Determination of moisture content

For the evaluation of moisture content, 5 g of each honey sample was placed in porcelain crucibles and heated up for 24 hr in a drying oven at 70 °C until constant weight. The dried samples were then placed in a desiccator until they reached room temperature. The samples were weighed using an analytical balance (Kern, ABT100-5NM, Kern & Sohn GmbH, Germany). The Moisture content was then calculated according to the following equation (Berhe et al., 2018; Lim et al., 2022).

$$\text{Moisture content (\%)} = ((W2 - W3)/(W2 - W1)) \times 100$$

where W1 = weight of porcelain crucible, W2 = weight of porcelain crucible and sample, W3 = weight of porcelain crucible and dried sample, and (W2–W3) = weight of water in the sample.

Determination of ash content

Honey samples (5 g) were weighed and placed in porcelain crucibles and heated for 24 hr in a dry oven (Scichem Tech, Model: SCT-convect-4) at 100 °C, followed by calcination in a Muffle furnace (LEF-103S-1, LabTech, Italy) at 550 °C to constant weight. The samples were cooled in a desiccator and weighed following the incubation using an analytical balance (Kern, ABT100-5NM, Kern & Sohn GmbH, Germany). The

ash content was calculated according to the following equation (Berhe et al., 2018; Lim et al., 2022).

$$\text{Total Ash \%} = ((W3 - W1)/(W2 - W1)) \times 100$$

where: W1 = weight of the porcelain crucible, W2 = weight of porcelain crucible and the honey sample, W3 = weight of crucible and dried honey sample, (W2 - W1) = initial honey sample weight, and (W3 - W1) = weight of ash.

Cell culture and cytotoxicity assay

MCF-7 human breast cancer cell line was cultured using Dulbecco's Modified Eagle Medium (Cat#: D6429, Merck, Germany) supplemented with 10% fetal bovine serum and 1.5% streptomycin/penicillin. The cells were maintained at 37 °C in a humidified atmosphere of 5% CO₂. The cytotoxic effects of pure honey and its fractions were evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay according to a previously published method (Almehdi et al., 2023). MCF-7 cells (4×10^4 cells/well) were seeded in 96-well plates with 100 μ l of Dulbecco's Modified Eagle Medium and incubated for 24 hr to allow adhesion. The cells were then treated with 1 mg/ml of the tested honey samples for 24 hr. Following incubation, 20 μ l of 5 mg/ml 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reagent (Cat#: M2128, Sigma-Aldrich, Saint Louis, MO, USA) was added to each well and incubated for 4 hr. After incubation, the liquid was aspirated, and 100 μ l of DMSO was added to each well to dissolve the formazan crystals, followed by 30-min incubation. Absorbance was measured at 570 nm using a Multiskan Go spectrophotometer. Wells containing only media served as negative controls, while empty wells were used as blanks. Each experiment was independently repeated six times to ensure reproducibility. Percentage cell viability was calculated as follows:

$$\text{Cell viability (\%)} = [(\text{optical density (OD) treated} - \text{OD blank}) \div (\text{OD untreated} - \text{OD blank})] \times 100.$$

DPPH assay

Using a modified protocol from Al-Nablsi et al. (2022) and Hamdy et al. (2025), 2,2-diphenyl-1-picrylhydrazyl-hydrate (DPPH) radical scavenging assay was employed to evaluate the free radical scavenging ability of all honey samples at 25 mg/ml. The positive control was butylated hydroxytoluene, while the DPPH reagent was dissolved in methanol at a concentration of 0.08 mg/ml. Each sample was tested in triplicate using a 96-well plate, where 50 μ l of the sample was mixed with 50 μ l of the DPPH reagent. A negative control consisting of DPPH in methanol was also included. The plate was incubated in the dark at room temperature for 60 min. Colour changes in the DPPH reagent from dark violet to light yellow indicated the reduction of free radicals by the antioxidants present in the samples. Absorbance (Abs) was recorded at 515 nm using an Epoch 2 Microplate Spectrophotometer (BioTek Instruments, Inc., Winooski, VT, USA). The resulting data were analysed in Excel to calculate the percentage of free radical scavenging activity based on the reduction in DPPH absorbance using the following standard formula:

$$\text{Scavenging \%} = [(\text{Abs negative control} - \text{Abs sample})/\text{Abs negative control}] \times 100.$$

Preparation of peripheral blood monocyte-derived macrophages

Blood collection was approved by the University of Sharjah ethics committee (REC-24-03-25-01-S), and healthy donors signed a written

consent form. Peripheral blood monocyte-derived macrophages (PBMCs) were prepared according to our previous method (Ismail et al., 2024; Mohammad et al., 2023). Samples were collected in ethylenediaminetetraacetic acid (EDTA)-treated tubes and pooled in 50 ml falcon tubes. To separate the peripheral blood mononuclear cells (PBMCs), 12.5 ml pooled blood was overlaid onto 10 ml Histopaque-1077 (Sigma, St. Louis, MO, USA), followed by centrifugation at $400 \times g$ for 20 min at room temperature, with brakes turned off. PBMCs in the interface were aspirated and washed with warm PBS. The pellets were suspended in 1 ml red blood cells lysis buffer Hybri-Max (Sigma, USA), centrifuged, and the pellet was resuspended using Roswell Park Memorial Institute (RPMI) media, and the viable cells were counted using Trypan blue vital dye. Cells (3×10^5 cells/ml) were seeded in 12-well plates with RPMI-1640 (10% fetal bovine serum, 1% Penicillin/Streptomycin, Sigma, USA) and incubated for 24 hr at 37 °C, 5% CO₂.

Quantitative real-time PCR for PBMCs treated with honey samples

Total RNA was extracted from PBMCs treated with 1 mg/ml DCM fractions from selected honey samples compared to Manuka, employed as a control, using Invitrogen PureLink RNA Mini Kit, following the manufacturer's protocol and according to our previous method (Shakartalla et al., 2024). Complementary DNA (cDNA) synthesis was performed using the SensiFAST cDNA Synthesis Kit. Primers (Macrogen, Korea) are listed in Table 2. Quantitative real-time PCR was conducted on a QuantStudio 3 (Thermo Scientific) using the SensiFAST SYBR Hi-ROX kit, with all samples run in triplicate. The average threshold cycle values for the genes were obtained from each reaction, and the expression was quantified using the $2^{(-\Delta\Delta C_T)}$ relative method (Shakartalla et al., 2024).

Wound healing effect on cancer cells

To investigate the antimetastatic effect of DCM fractions on MCF-7 and MDA-MB-231 cells, a wound healing assay was performed according to a previous method with some modifications (Salih et al., 2023). In brief, 5×10^5 breast cancer cells were seeded per well in a 12-well plate. After 24 hr, a linear wound was developed by scratching the cell monolayer using a 10 μ l tip, followed by two phosphate-buffered saline (PBS) washes. Fresh media containing 1 mg/ml of the honey DCM fractions were added to the wells. Photos were captured at different time points (0, 24, and 48 hr) using an Olympus IX53 inverted microscope (Olympus, Tokyo, Japan) connected to an Olympus DP22 Microscope Digital Camera. The photos were processed using ImageJ 1.52a software (National Institutes of Health, USA). The migration distance was calculated as: Migration distance (μ m) = Wound Width at 0 hr - Wound Width at 24 or 48 hr.

Metabolomics analysis

Dichloromethane fractions of the honey samples were treated with 20 μ l of methoxyamine (20 mg/ml in pyridine) along with 50 μ l hexane. The mixture was vortexed and incubated in a water bath at 37 °C for 1.5 hr (Rontani, 2022; Tsikas & Zoerner, 2014). Following this, 90 μ l of *N*-trimethylsilyl-*N*-methyl trifluoroacetamide with 1% trimethylchlorosilane (MSTFA + 1% TMS) was added, vortexed for 30 s, and further incubated at 37 °C for 1 hr (Semreen et al., 2019; Soliman et al., 2020). The resulting solution was filtered using 0.45 μ m nylon syringe filters (Membrane Solutions, Auburn, WA, USA) and analysed using GC-MS in V3 mass spectrometry scan mode (Hamoda

Table 2 Primers employed in the study.

Gene name	Forward primer	Reverse primer	Reference
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	GTCTCCTCTGACTTCAACAGCG	ACCACCCTGTTGCTGTAGCCAA	Nabokina et al. (2014)
IL-1 α	CGCCAATGACTCAGAGGAAGA	AGGGCGTCATTGAGGATGAA	Jin et al. (2010)
IL-6	AGACAGCCACTCACCTCTTCAG	TTCTGCCAGTGCCTCTTTGCTG	Balint et al. (2019)
IL-10	CCTAACATGCTTCGAGATCTCC	CTCCAGCAAGGACTCCTTTAAC	Altaie et al. (2021)
IL-17A	CCCAGTTGATTGGAAGAAA	TTCGTGGGATTGTGATTCC	Schindler et al. (2017)

et al., 2023). GC–MS analysis was performed using a Shimadzu QP2010 GC-2010 system coupled with a GC–MS QP-2010 Ultra and equipped with an AOC-20i+s auto-sampler. A Restek Rtx-5ms column (thick 30 m, diameter 0.25 mm, and length 0.25 μ m) was used, with helium as the carrier gas at a flow rate of 17.5 ml/min. The initial temperature was set at 35 °C for 2 min, then increased at a rate of 10 °C/min until reaching 250 °C, followed by a rise of 20 °C/min until 320 °C, where it was held for 23 min. The injection volume was 1 μ l, with an injection temperature of 250 °C in splitless mode. The mass spectrometer operated in electron impact mode with an electron energy of 70 eV, an ion source temperature of 240 °C, and an interface temperature of 250 °C. The MS mode was set to scan 50–650 m/z at a scan speed of 2,500. Spectral data were interpreted using NIST 14 Mass Spectral Library (Hamoda et al., 2023).

The identified metabolites were imported into MetaboAnalyst V.6.0 (<https://www.metaboanalyst.ca/home.xhtml>). For multivariate statistical analysis, hierarchical cluster analysis was performed to assess the similarity and grouping of samples based on their metabolic profiles. Principal component analysis was conducted to enhance classification and identify key discriminative features. Variable importance in projection (VIP) scores were calculated to rank the metabolites based on their contribution to group separation. A dendrogram was also generated from hierarchical cluster analysis to visualise the clustering relationships among the honey samples (Xia & Wishart, 2011).

Succinic acid isolation and elucidation

Succinic acid crystals were precipitated following the addition of methanol to crude honey sample and analysed by thin-layer chromatography (TLC) using a solvent system (butanol, acetic acid, and water) in a 4:2:1 ratio. The crystals were dissolved in deuterated methanol (CD₃OD) for analysis using proton and carbon nuclear magnetic resonance on a Bruker Ascend Aeon-500 MHz spectrophotometer with an Avance III HD console, operating at 500 MHz for proton nuclear magnetic resonance and 125 megahertz (MHz) for carbon-13 nuclear magnetic resonance. Tetramethylsilane served as internal reference. Mass spectrometry was conducted using Xevo TQD ACQUITY mass spectrometer (Waters, UK).

Statistical analysis

All statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software, La Jolla, CA, USA). One-way analysis of variance was employed to evaluate the antioxidant and cytotoxic activities (Bonferroni's multiple comparisons test). Each experiment was conducted in at least three independent replicates, and the results were expressed as $M \pm SE$ of the mean. Statistical significance was set at $p < .05$.

Results

Geographical variability and environmental impact on Fujairah honey

As illustrated on the Fujairah map, the spatial distribution of apiaries in Fujairah highlights the varied landscapes ranging from coastal zones near the Gulf of Oman to the mountainous regions of the Hajar Mountains (Figure 1). This geographical and seasonal variation plays a crucial role in shaping the floral nectar sources available to bees, directly influencing the composition, taste, and quality of the honey produced (da Silva et al., 2016), which is essential for understanding the unique characteristics of Fujairah honey. Honey, derived from the Samar (*Acacia*) plant species, thrives in hot and arid conditions (Alqarni et al., 2015). During the flowering season, temperatures ranged from 26 to 38 °C in 2022 and 25 to 40 °C in 2023, particularly in Dibba, where temperatures peaked at 40 °C. The low humidity levels ranged from 60% to 65% in 2022 and 55% to 65% in 2023, and the minimal rainfall ranged from 0 mm in 2022 to <5 mm in 2023. In contrast, Sidr honey (*Ziziphus*) flourishes in moderate temperatures of 23–33 °C in 2022 and 26–36 °C in 2023, with higher humidity levels (60%–65%). Increased precipitation ranged from 2.8–3.5 mm in 2022 to 3.0–3.2 mm in 2023. These climatic and botanical differences significantly influence the quality and characteristics of Fujairah honey (Table 3).

Honey samples showed significant variation in physicochemical properties

The physicochemical analysis of 20 honey samples, including Samar and Sidr, in addition to the Australian Manuka (as a control), revealed significant variations in colour, pH, electrical conductivity, water, and ash contents (details are shown in Supplementary Materials and Supplementary Table 1). Samar honey, particularly Sample 3 from Ohala, consistently exhibited the highest Pfund colour values, colour intensity, electrical conductivity, water, and ash content, suggesting it is compositionally richer and more bioactive than Sidr and Manuka honeys. These characteristics, especially higher mineral content (ash), acidity (lower pH), and darker colour, are strongly associated with enhanced antioxidant and potential anticancer properties. The bioactive richness of darker, more mineral-dense honeys like Samar may correlate with greater efficacy in inhibiting cancer cell proliferation, supporting their values as functional supplements in oncological contexts. On the other hand, Sample 6 displayed notable physicochemical characteristics, suggesting a moderate bioactive profile among the tested Fujairah honeys. Sample 6, likely a Samar honey, presents a well-balanced profile with strong mineral content, moderate antioxidant indicators, and acceptable acidity. These features suggest a potential therapeutic use, including antioxidant and possibly

Table 3 Comparative climate data for Samar and Sidr honey samples (2022–2023).

Season	Year	Temperature (°C)	Avg. humidity (%)	Precipitation (mm)	Wind speed (km/hr)
Samar	2022	26–38	60–65	0	11–13
Samar	2023	25–40	55–65	<5	11–15
Sidr	2022	23–33	60–65	2.8–3.5	11–13
Sidr	2023	26–36	60–65	3.0–3.2	11–13

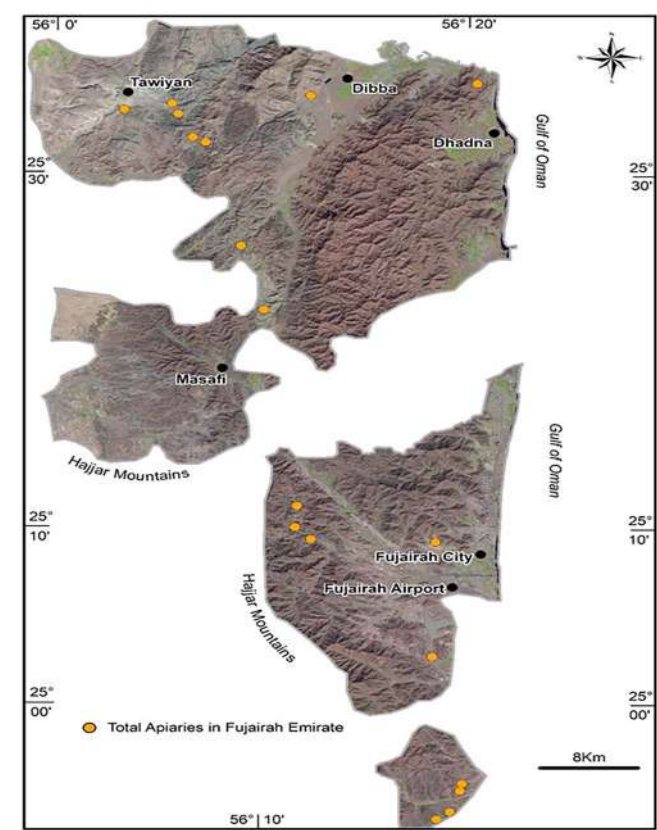


Figure 1 Apiary distribution map in different locations of Fujairah emirate. The map shows apiary distribution across Dibba, Tawiyah, and Fujairah City, with scattered apiaries influenced by diverse climate, geography region, and seasonal flora.

anticancer support, though not as pronounced as the top-performing Sample 3.

Fujairah honey samples exhibited significant increase in cell viability and antioxidant activity

Unexpectedly, some honey samples enhanced cancer cell growth, while others showed no different activity compared to the negative control (Figure 2A). Specifically, Samples 6, 15, 19, and 20 demonstrated a highly significant increase in cell viability with a p -value of $<.0001$, showing percentage increases of 34%, 32%, 42%, and 33%, respectively. Samples 9 and 18 also showed a significant increase with a p -value of $<.001$ and percentage increases of 28%. Additionally, Samples 3 and 12 exhibited a notable increase in cell viability with a p -value of $<.01$, showing percentage increases of 25% (Figure 2A). Importantly, no significant increase or decrease in the viability was

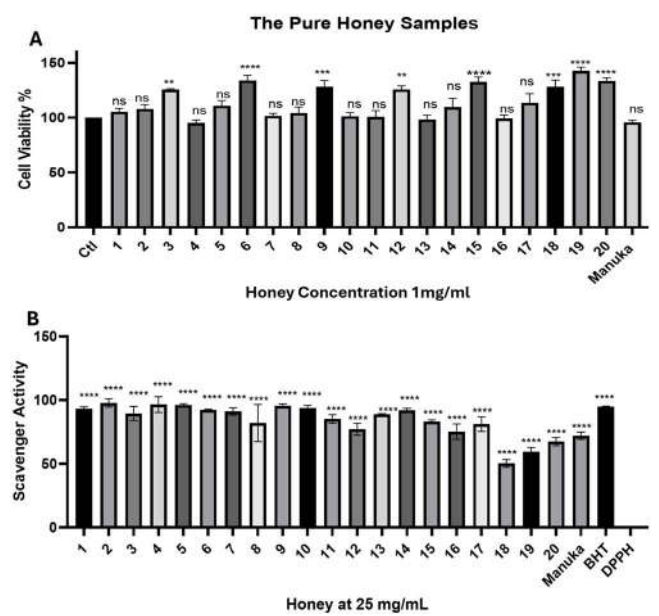


Figure 2 Cytotoxic and antioxidant activity of different Fujairah honey samples. (A) Cytotoxic effect of honey samples obtained from different Fujairah geographical regions at 1 mg/ml on MCF-7 breast cancer cells. (B) Antioxidant activity of the honey samples obtained from different Fujairah geographical regions using DPPH assay. Data were presented as mean $\pm$ SEM ($n = 3$). The data were analysed using one-way ANOVA, and statistical significance was calculated with Bonferroni's multiple comparisons test. The statistical significance was determined at p -value of $\leq .0001$. Significance level was indicated by asterisks (* $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .0001$). ANOVA = analysis of variance; DPPH = % 2,2-diphenyl-1-picrylhydrazyl-hydrate; SEM = standard error of the mean.

observed with the other samples. Although the results indicate the safety of the samples on cells, they showed negative cytotoxic results.

Fujairah honey samples demonstrated significant differences in radical scavenging activity, as shown by DPPH assay ($p < .0001$) (Figure 2B). Honey samples 2, 4, 5, 9, 10, 1, 6, 14, and 7 exhibited the highest scavenging activities, with percentages of 97.85%, 96.51%, 96.24%, 95.43%, 93.82%, 93.01%, 92.47%, 91.94%, and 91.13%, respectively (Figure 2B). Honey samples 3, 13, 11, 15, 8, and 17 displayed lower scavenging activities of 89.52%, 88.98%, 85.22%, 83.06%, 81.99%, and 81.18%, respectively. Honey samples 12, 16, Manuka, 20, 19, and 18 showed the lowest scavenging activities, with percentages of 77.15%, 75.27%, 72.04%, 67.47%, 59.41%, and 50.27%, respectively. Among all the samples, Sample 2 exhibited the highest scavenging activity, whereas Sample 18 had the lowest (Figure 2B). Importantly, no link between antioxidant and anticancer activity of the honey samples was observed.

Collectively, screening of 20 honey samples from distinct Fujairah regions revealed that several samples significantly enhanced cell viability, indicating their safety and potential nutritive effects on normal cells. However, the lack of cytotoxicity suggests these samples do not possess anticancer activity when employed as crude samples. Furthermore, the samples showed significant variation in antioxidant activity. Sample 6 exhibited enhanced cell viability, while showed high antioxidant activity with DPPH scavenging capacity of 92.47%. This suggests that Sample 6 is rich in antioxidant compounds, which may contribute to cellular protection, though it does not correlate with anticancer activity, as indicated by the overall study findings. Considering this variable activity of Sample 6, it was selected for further fractionation-based investigation.

Fractionations of honey Sample 6 showed variable activity, with superiority to DCM fraction

Fractionation of honey Sample 6 reveals a diverse range of biological activities based on its chemical composition. The unfractionated honey increased MCF-7 cell viability by 21%, indicating a proliferative stimulating effect. However, the DCM fraction significantly reduced cell viability by 20%, suggesting the presence of potent anticancer compounds within this fraction (Figure 3A). Similarly, DCM extracts of other honey samples demonstrated significant cytotoxic effects (Figure 3B). DCM fractions of Samples 20, 19, 15, 18, and 2 exhibited the highest inhibition at 39.76%, 39.38%, 36.98%, 35.74%, and 32.99%, respectively, while Sample 14 DCM showed notable inhibition at 31.24%. These findings highlight the potential of DCM fractions of honey samples as potent cytotoxic agents for further investigation as anticancer supplement.

Antioxidant activity of DCM fractions demonstrated significant differences in their scavenging activity, as shown by DPPH assay ($p < .0001$) (Figure 3C). Honey samples 9, 6, 19, 17, and 7 exhibited the highest scavenging activities, with percentages of 93.64%, 92.81%, 92.78%, 91.23%, and 90.62%, respectively. Methanol fraction reduced cell viability by 18%. Water fraction, left after DCM extraction, showed higher cell viability by 27% (Figure 3A), possibly due to the cell-promoting compounds concentrated after DCM extraction.

Pearson correlation indicates a positive correlation between cytotoxicity and antioxidant activity of DCM fractions but not the crude honey

The Pearson correlation matrix indicates a significant negative relationship between the cytotoxicity of DCM extract and crude honey ($r = -0.186$, $p \leq .05$). In contrast, a significant positive relationship was found between the cytotoxicity of DCM extract and antioxidant activity of different honey samples ($r = 0.581$, $p \leq .001$) (Table 4). Additionally, the cytotoxicity of crude honey showed a significant negative relationship with antioxidant activity ($r = -0.277$, $p \leq .05$). Furthermore, the cytotoxicity and antioxidant activity of DCM fractions are not correlated. Interestingly, samples 9, 6, and 19 DCM fractions showed aligned cytotoxicity and antioxidant activities (Figure 3).

Samples 6, 10, 19, and 20 were selected for further analysis due to their combined significant antioxidant and anticancer activities, particularly the DCM fractions.

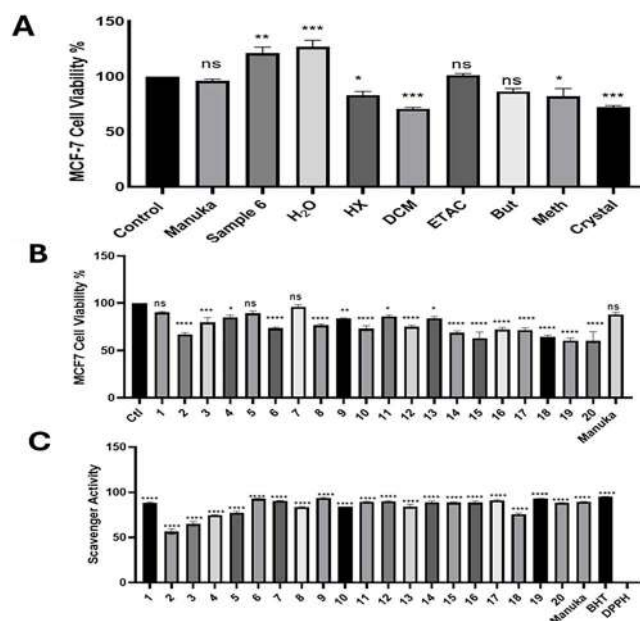


Figure 3 Cytotoxicity and antioxidant of honey sample fractions. (A) Cytotoxic effect of honey Sample 6 vs. its fractions at 1 mg/ml against MCF-7 breast cancer cell line. Where HX = hexane; DCM = dichloromethane; ETAC = ethyl acetate; But = butanol; Meth = methanol. (B) Cytotoxic activity of the honey samples DCM fractions at 1 mg/ml against MCF-7 breast cancer cell line. (C) Antioxidant activity of honey samples DCM fractions. Data were presented as mean $\pm$ SEM ($n = 3$). Statistical analysis was performed using one-way ANOVA, and statistical significance was calculated with Bonferroni's multiple comparisons test. The significance level was indicated by asterisks (* $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .0001$). ANOVA = analysis of variance; SEM = standard error of the mean.

DCM fraction from honey Sample 6 exhibits superior anti-inflammatory and notable antimetastatic activities with minimal immunostimulatory side effects

Wound healing assay revealed that DCM fractions from honey samples 6, 10, 19, 20, and Manuka significantly ($p < .05$) inhibited cell migration of MCF-7 cells (Figure 4A and C), indicating a notable antimetastatic activity, particularly for Samples 6 and 10. Similarly, Samples 6 and 10 showed minimal effect on the migration of the highly metastatic MDA-MB-231 cell line (Figure 4B and D).

Cytokine expression analysis revealed a significant downregulation of IL-1 α across all treated groups compared to control ($p < .0001$) (Figure 5A), with the highest reduction observed in Manuka-treated samples ($p < .0001$). IL-6 gene expression levels were also significantly decreased by samples 6, 10, and 19 ($p < .0001$), while Sample 20 showed the lowest reduction ($p < .05$). On the contrary, Manuka caused the highest gene expression ($p < .0001$) (Figure 5B). IL-10 gene expression was significantly increased by Sample 20 ($p < .01$) and Manuka ($p < .001$) treatments, with insignificant increase or decrease due to treatment by Samples 6 and 19 or 10 (Figure 5C). IL-17 gene expression was significantly elevated in all samples except Sample 10. The highest expression was observed in Sample 20 ($p < .0001$), followed by Sample 19 ($p < .0001$) (Figure 5D). Sample 6 demonstrated strong anti-inflammatory potential, significantly downregulating IL-6 gene expression ($p < .0001$), a key proinflammatory cytokine. While it did not significantly affect IL-10 (an anti-inflammatory marker) and

Table 4 Pearson correlation matrix between cytotoxicity and antioxidant activities of crude honey and DCM fractions.

		Cytotoxicity		Antioxidant activity	
		DCM	Crude	Crude	DCM
Cytotoxicity	DCM	1.000			
	Crude	−0.186*	1.000		
Antioxidant activity	Crude	0.581***	−0.277*	1.000	
	DCM	0.081	0.171	−0.196	1.000

p* ≤ .05. *p* ≤ .01. ****p* ≤ .001. Note. DCM = dichloromethane.

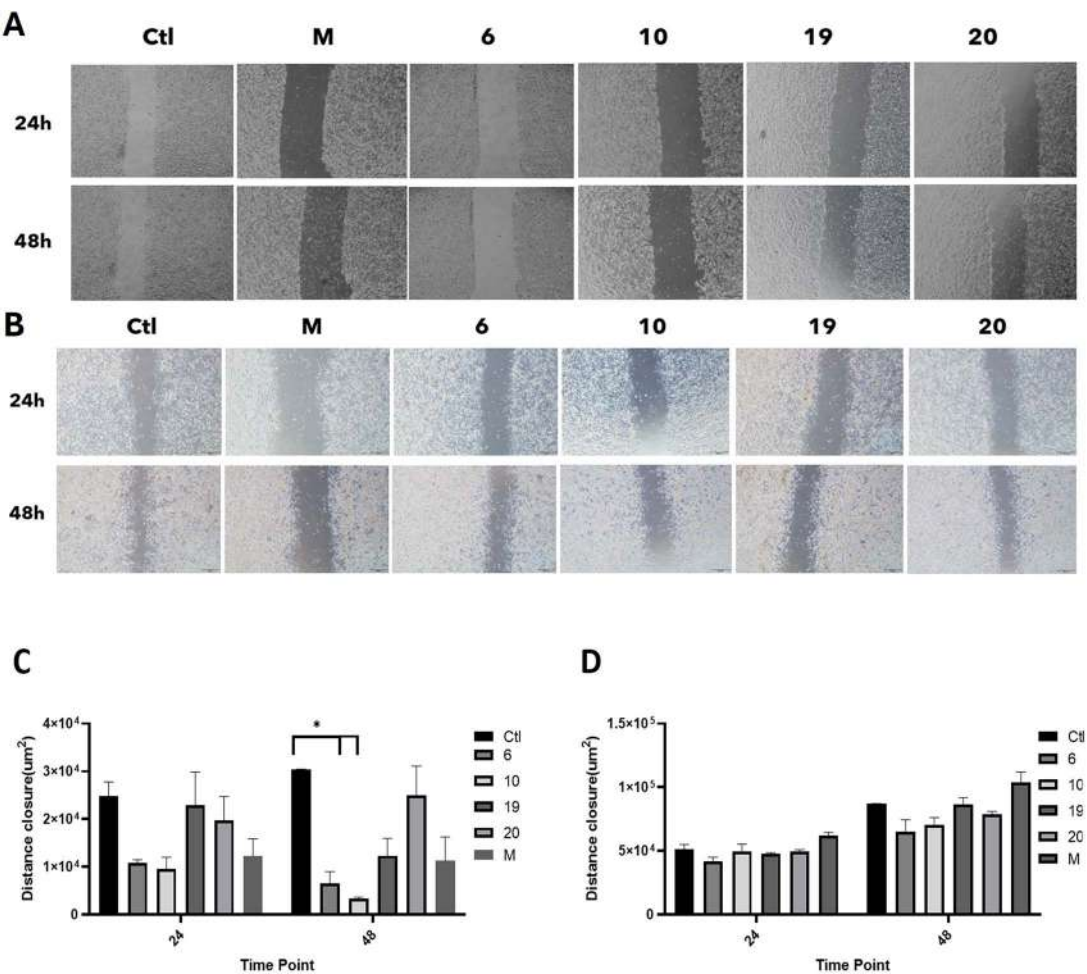


Figure 4 Wound healing assay quantifying the distance closure of MCF-7 and MDA-MB-231 cells. (A and C) Pictures under microscope using Olympus IX73 inverted microscope connected to Olympus DP22 microscope digital camera. (B and D) Quantification of wound closure (μm^2) measured at 24- and 48-hr treatment with DCM fractions, extracted from honey samples 6, 10, 19, 20, and Manuka. Data were presented as mean $\pm$ SEM ($n = 3$). The statistical analysis was performed using two-way analysis of variance (ANOVA) and Tukey's multiple comparison test. **p*-value $\leq .05$ was considered significant, ***p*-value $< .01$. *** reveals that *p*-value $< .001$. **** reveals that *p*-value $< .0001$. DCM = dichloromethane; SEM = standard error of the mean.

showed no increase in IL-17 expression, its profile suggests a selective and balanced immunomodulatory effect, particularly by suppressing inflammatory mediators without excessively stimulating others.

While it did not perform as broadly as Manuka honey in all cytokine categories, Sample 6 selectively suppressed inflammatory mediators (like IL-6) without overstimulating other immune responses. This suggests a balanced immunomodulatory effect, potentially making it beneficial in therapeutic contexts requiring inflammation control, such as cancer or autoimmune-related inflammation.

Distinct metabolomics profiles differentiate Fujairah honey samples from Manuka

Metabolomics analysis revealed distinct clustering patterns and varying metabolite concentrations across the 20 honey samples and from Manuka honey (Figure 6A). The analysis highlighted the relative abundance of the top 35 metabolites, uncovering unique distribution trends that may be associated with the botanical origins of the honey sample and highlighting the potential of metabolite-based

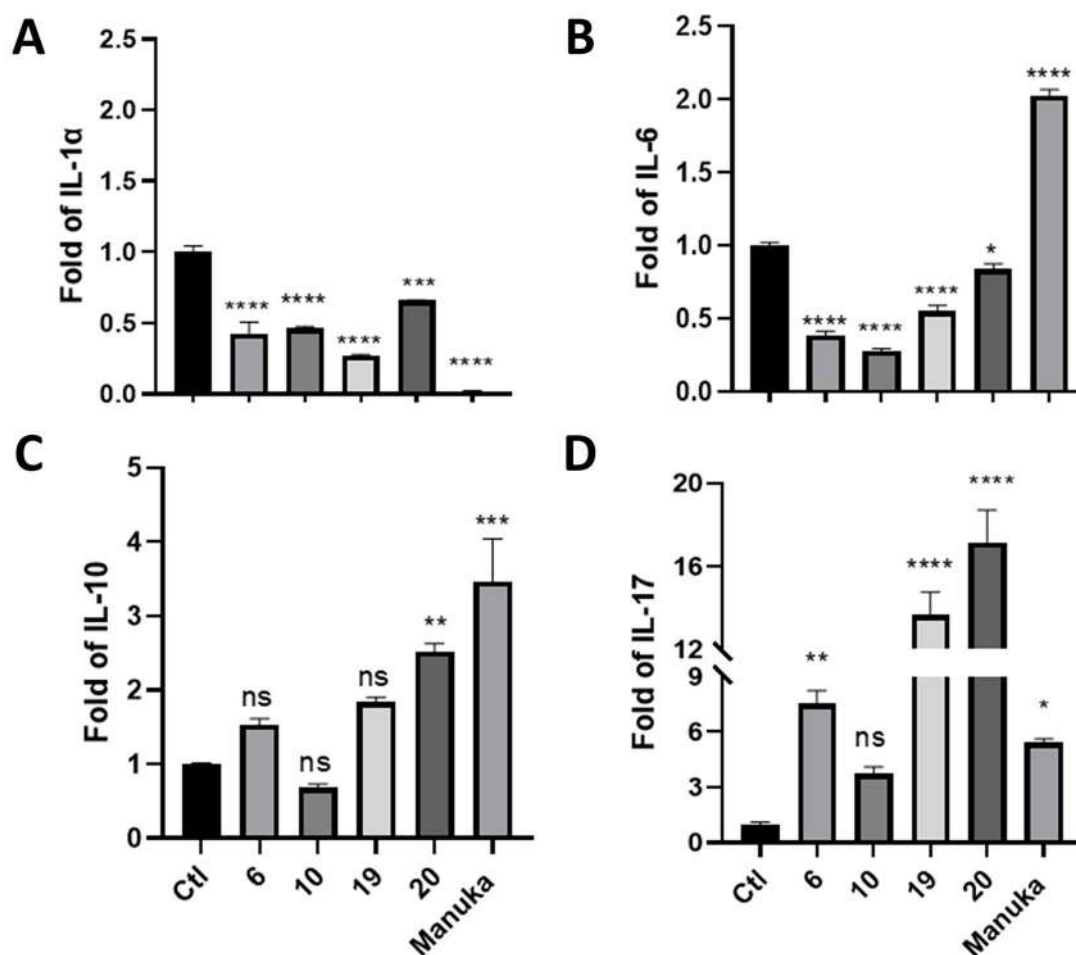


Figure 5 Gene expression analysis of IL-1 α , IL-6, IL-10, and IL-17 for PBMC cells treated with DCM fractions, extracted from honey samples compared to control untreated cells. (A) IL-1 α , (B) IL-6, (C) IL-10, and (D) IL-17 represent different cytokine transcripts. All treatments were performed in triplicates. Data were presented as mean $\pm$ SEM ($n = 3$). The statistical analysis was performed using one-way analysis of variance (ANOVA) and Bonferroni's multiple comparison test. * p -value $\leq .05$ was considered significant, ** p -value $< .01$. *** reveals that p -value $< .001$. **** reveals that p -value $< .0001$. PBMC = peripheral blood monocyte-derived macrophage; SEM = standard error of the mean.

differentiation and authentication of honey. Principal component analysis scores plot also shows partial overlap among honey groups, with some distinct clusters reflecting metabolic variation (Figure 6B). Variable importance in projection score analysis revealed that D-altriose, palmitic acid, and stearic acid are the most influential metabolites with variable importance in projection scores: 16, 10, and 9, respectively (Figure 6C). D-altriose is a rare natural monosaccharide, while palmitic and stearic acids are common long chain saturated fatty acids. Other distinct metabolites with lower variable importance in projection scores include sugar alcohols (D-pinitol, L-sorbopyranose), rare sugars (β -D-allopyranose), monosaccharides (D-fructose, palatinose), aliphatic alcohols and amines (2-hexyl-1-decanol, 2-isopropyl-5-methylheptanol, methylamine), and glyceryl esters (1-monopalmitin, glycerol monostearate) (Figure 6C).

Metabolomics insights reveal the anticancer potential of Fujairah honey, especially Sample 6

Sample 6 was further selected due to its balanced and reproducible bioactivity profile, demonstrating moderate cytotoxicity, strong antioxidant capacity, significant IL-6 downregulation, and

antimigratory effects. The metabolomic profile of Sample 6 demonstrates notable alterations in metabolites involved in lipid metabolism and energy homeostasis (Figure 6C), suggesting potential biological activity. Elevated levels of fatty acids (palmitic and stearic acids), along with monoacylglycerides such as 1-monopalmitin and glycerol monostearate, suggest enhanced bioactive lipid signalling. These metabolites are known to disrupt cell membranes, impair energy metabolism, and trigger apoptosis processes closely linked to anticancer and antioxidant effects (Chauhan et al., 2025). Although a higher sucrose concentration is typical for honey, its presence in the crude extract but not in the DCM fraction may explain differences in observed cell proliferation.

These findings reinforce Sample 6 capacity to modulate cancer-related pathways, making it a promising candidate for complementary cancer therapy.

Isolated crystals from honey Sample 6 exhibited superior activity compared to crude honey

The addition of methanol to crude honey Sample 6 caused the precipitation of needle crystals, which were purified on preparative thin-layer chromatography (Figure 7A) and identified by MS

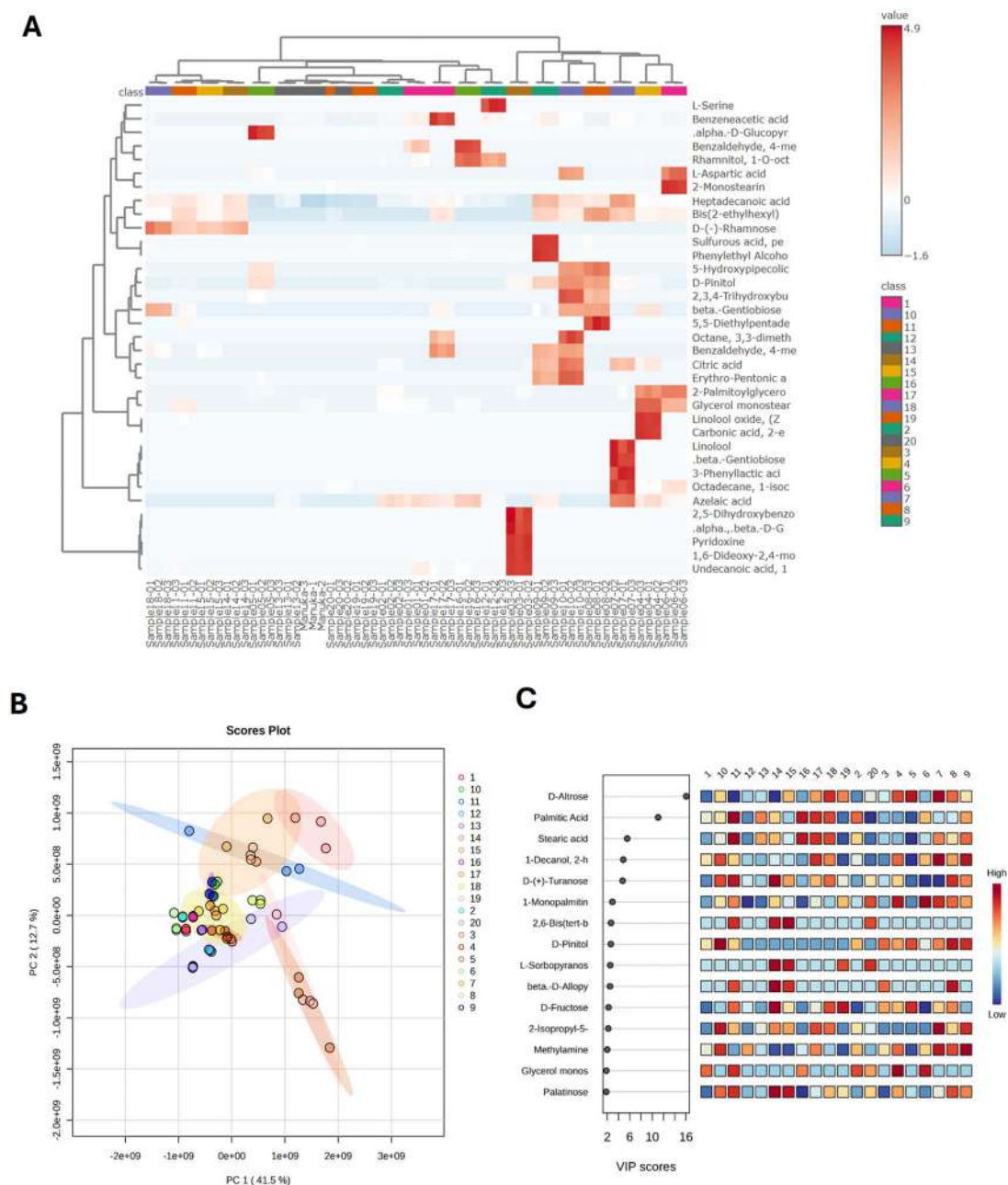


Figure 6 Metabolomics analysis of Fujairah honey samples. (A) Heatmap analysis and hierarchical grouping of the top 35 metabolites of the 20 honey samples compared to manuka. Different colours represent varying levels of metabolite concentration, where red indicates a high concentration, and blue indicates a low concentration. (B) PCA of the 20 honey samples. (C) VIP score plot of the key metabolites for the 20 honey samples. Different colours represent varying levels of metabolite concentration, where red indicates a high concentration, and blue for a low concentration. The data represented as $n = 3$ replicas. PCA = principal component analysis; VIP = Variable importance in projection.

and nuclear magnetic resonance as succinic acid (Figure 7B and Supplementary Figures 1–3). Proton nuclear magnetic resonance spectrum showed a singlet signal of two equivalent methylene protons ($-\text{CH}_2-\text{CH}_2-$) at δ H 2.58 ppm, which is the typical appearance of succinic acid due to its symmetrical structure. Carbon-13 nuclear magnetic resonance showed two different signals, one upfield of the two equivalent methylene carbons signals at δ C 29.8 and another downfield signal of the quaternary carbons at δ C 176.25 linked to the two equivalent acidic carbonyl groups. Heteronuclear multiple bond correlation (HMBC) between the methylene protons at δ H 2.58 and

the methylene carbon at δ C 29.8, as well as the carbonyl carbon at δ C 176.25 (Supplementary Figure 3), further confirmed the structure of succinic acid.

The isolated crystals caused a marked decrease in MCF-7 cell viability ($p < .001$) by 28% (Figure 7C).

Discussion

The investigation of Fujairah honey unveils its potential in cancer therapy. The physicochemical analysis revealed that Samar honey,

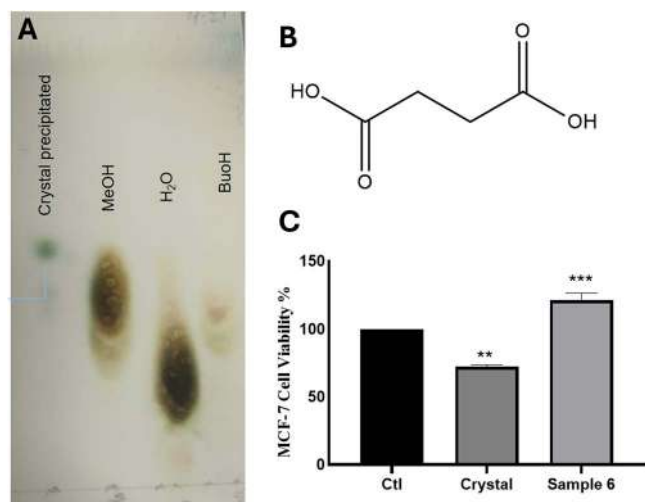


Figure 7 Sample 6 succinic acid crystals isolation and activity. (A) TLC of the fractions alongside the isolated succinic acid using (butanol, acetic acid, and water in a 4:2:1) solvent system. The TLC was detected using ultraviolet (UV) light and visualised with para-anisaldehyde reagent. (B) Structure of isolated succinic acid crystals ($C_4H_6O_4$) from Fujairah honey Sample 6. (C) Activity of honey Sample 6 and its isolated crystals at 1 mg/ml on MCF-7 breast cancer cell line. Values are means $\pm$ SEM ($n = 3$). Statistical analysis was performed using one-way ANOVA, and statistical significance was calculated with Bonferroni's multiple comparisons test. The significance level was indicated by asterisks (* $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .0001$). ANOVA = analysis of variance; SEM = standard error of the mean; TLC = thin-layer chromatography.

especially Sample 6, possesses a rich mineral content, darker colour, and lower pH. Consistent with previous studies, these characteristics are associated with elevated polyphenol and flavonoid levels, known for their antioxidant and anticancer properties (Chambó & Alencar Arnaut de Toledo, 2020; Tomasin et al., 2024). For instance, the high antioxidant activity observed in Sample 6 (92.47% DPPH scavenging) aligns with previous studies linking polyphenol-rich honeys to free radical scavenging and cellular protection (Badolato et al., 2017; Chan-Zapata & Segura-Campos, 2021). However, the correlation between the antioxidant and cytotoxic activities of crude honey samples is lacking, suggesting that specific bioactive compounds, concentrated in fractions like DCM, are responsible for anticancer effects. These findings support the growing research that antioxidant capacity alone is not predictive of anticancer efficacy, and that cytotoxicity often arises from specific low-molecular-weight compounds or synergistic interactions that can be revealed through bioactivity-guided fractionation (Gheldof et al., 2002).

The DCM fraction of Sample 6 significantly reduced MCF-7 breast cancer cell viability in vitro by 20%, contrasting with the proliferative effect of crude honey (21% increase). This underscores the importance of fractionation to highlight cytotoxic compounds, such as fatty acids (palmitic and stearic acids) and monoacylglycerides (1-monopalmitin, glycerol monostearate), identified via metabolomic analysis. These metabolites are known to disrupt cancer cell membranes and energy homeostasis (Gasparrini et al., 2018; Tretter et al., 2016). For example, monoacylglycerides such as 1-monopalmitin have been reported to inhibit tumour growth and induce apoptosis in non-small cell lung cancer by suppressing proliferation and apoptosis-inhibitor proteins (Niu et al., 2023), while glycerol monostearate has shown antioxidant and anticancer effects when incorporated into lipid-based delivery

systems (Chauhan et al., 2025). Phenolic compounds, including ferulic acid, gentisic acid, and 4-hydroxybenzoic acid, are well known for modulating key oncogenic and inflammatory pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and phosphoinositide 3-kinase / Protein Kinase B / mammalian target of rapamycin (PI3K/Akt/mTOR) signalling, alongside strong antioxidant and antimetastatic effects (Feng et al., 2024; Rauf et al., 2025; Wang et al., 2018). We acknowledge that the mechanistic roles of these compounds in driving cytotoxicity remain exploratory and are inferred from literature-based evidence rather than direct experimental confirmation in this study.

The isolation of succinic acid, which further reduced MCF-7 viability by 28% ($p < .001$), suggests its potential as a lead compound in cancer research, which needs further experimental validation. Succinic acid, a natural intermediate of the Krebs cycle (Salih et al., 2023), is known to stabilise hypoxia-inducible factor-1 α (HIF-1 α) but, when accumulated, promotes oxidative stress and metastasis via SUCNR1 signalling (Kuo et al., 2022). It disrupts lysosomal and mitochondrial membranes, triggering apoptosis (Chang et al., 2025). It also inhibits T-cell acute lymphoblastic leukemia (T-ALL) cell lines without harming normal cells (Chang et al., 2025) and reduces liver cancer cell growth (Chang et al., 2025). Its role in modulating mitochondrial function and inducing apoptosis is well documented (Salih et al., 2023). These findings support succinic acid as a promising candidate for further exploration in mitochondria-targeted anticancer therapies.

These findings highlight the importance of combining metabolomics with functional assays to uncover new therapeutic candidates in natural products. While the tested concentrations exceed typical dietary exposure, the active metabolites in the DCM fraction may hold promise for targeted delivery via nanocarriers, warranting further in vivo evaluation.

The anti-inflammatory profile of Sample 6, characterised by significant downregulation of IL-6 ($p < .0001$) without excessive IL-10 or IL-17 stimulation, indicates a selective immunomodulatory effect. This balance is critical for nutritional and pharmaceutical applications, as excessive immune stimulation can exacerbate tumour progression (Cianciosi et al., 2018). The antimetastatic activity of Fujairah honey especially Sample 6 further supports its potential in preventing cancer spread, a key challenge in breast cancer management (Soliman et al., 2020). These properties align with the growing interest in natural products as adjuvants in cancer therapy, offering reduced toxicity compared to conventional chemotherapeutics (Tomasin et al., 2024). This also aligns with previous studies suggesting that some honeys can selectively modulate immune pathways depending on their phenolic profile and sugar matrix, reinforcing their suitability as complementary therapeutics (Ranneh et al., 2021). Sample 6, sourced from *Acacia* species (Samar honey), was collected from apiaries in Fujairah, such as Tuwiyain, Ohala, Dibba, or Al Hyle Farm, between mid-May and mid-June in 2022 and 2023 (Table 1). The *Acacia* floral source contributes to the unique chemical profile, including high levels of bioactive lipids and organic acids (Chan-Zapata & Segura-Campos, 2021). The collection sites feature hot, arid conditions with temperatures ranging from 25 to 40 °C, low humidity (55%–65%), and minimal rainfall (0 to <5 mm) during the flowering season (Table 3). Arid regions like Fujairah produce honeys with higher polyphenol content than humid regions. The arid Fujairah environment and the *Acacia* source ensure a unique blend of bioactive compounds, making Sample 6's chemical profile distinct from Sidr or Manuka honeys (Al-Waili et al., 2011).

The study highlighted that climatic differences significantly influence the quality and characteristics of Fujairah honey, with Samar honey thriving in arid conditions (Table 3). The hot, arid climate and low precipitation in Fujairah's Samar honey collection sites promote concentrated nectar sources, leading to a richer bioactive composition. The harsh environmental conditions stress plants, increasing the production of secondary metabolites, which are transferred to the honey and enhance its anticancer potential (Ghramh et al., 2020; Lim et al., 2022). This is consistent with environmental metabolomics studies showing that honey produced under abiotic stress conditions, such as drought or heat, often exhibits superior bioactivity due to elevated concentrations of stress-induced secondary metabolites (Mida et al., 2021).

From a nutritional and pharmaceutical perspective, Fujairah honey could be developed into various formulations to leverage its antioxidant, anti-inflammatory, and anticancer properties. Interestingly, crude honey samples in this study exhibited a proliferative effect on MCF-7 cells, likely due to their high sugar content and nutritional composition, which can enhance cellular metabolism and promote growth in vitro. The DCM fraction and succinic acid could be incorporated into nanocarrier systems to enhance bioavailability and cancer targeting (Blagojevic & Kamaly, 2025). This highlights the dual role of honey as a nutritive agent and a source of therapeutic compounds underscoring the complexity of interpreting its biological effects. While natural sugars and micronutrients may support cell viability, bioactivity-guided fractionation allows for the isolation of specific compounds, such as those found in the DCM fraction, with demonstrated anticancer, antioxidant, and anti-inflammatory potential.

As international regulations governing the importation/exportation and health claims of nutraceuticals continue to tighten, challenges related to cross-border product classification and intellectual property protection become increasingly relevant. In particular, the distinct chemical fingerprint and observed therapeutic potential of Sample 6 may necessitate compliance with regulatory frameworks to enable its safe commercialisation and global distribution. With the rigorous quality control measures conducted in this study encompassing physicochemical characterisation, metabolic profiling, and geographic authentication, Fujairah honey can achieve consistent nutritional and therapeutic standards under the UAE.S GSO 147:2017. The UAE.S GSO 147:2017 standard defines the essential quality and safety criteria for natural honey distributed and marketed within the UAE and other GCC countries, including benchmarking (Osaili et al., 2023; UAE.S 147:2017, 2017). Adhering to these standards not only aligns with the analytical parameters assessed in our study but also reinforces the authenticity, consumer protection, and regional trade harmonisation of Fujairah honey under a blockchain framework (Almiani et al., 2025).

Limitations and future directions

This study provides the first characterisation of the biological properties of Fujairah honey; however, several limitations remain to be investigated. Cytotoxicity was assessed only in MCF-7 cells, and additional cancer cell panel and non-cancerous cells are required to validate the findings. As the study is based on in vitro assays, results may not directly translate to in vivo settings. Mechanistic markers, such as caspase-3, were not evaluated and should be explored in future studies. The DCM fraction showed promising bioactivity, and its identified metabolites may serve as candidates for targeted delivery

using nanoparticle-based strategies. However, a key limitation of this study is the lack of direct mechanistic validation linking individual metabolites to the observed cytotoxic effects, which warrants further targeted investigation. Future comparison study will focus on comprehensive LC–MS profiling and the detection of established Manuka honey markers (e.g., Unique Mānuka Factor (UMF) and methylglyoxal (MGO)) to enable more accurate comparisons and quality benchmarking. Finally, cytokine analysis was limited to mRNA expression; future studies will include protein expression and proteomic validation.

Conclusion

The uniqueness of Fujairah honey, particularly Sample 6, lies in its exceptional bioactive profile, shaped by the UAE's arid environment and *Acacia*-derived nectar sources. Unlike Manuka or Sidr honeys, Sample 6's DCM fraction exhibits selective cytotoxicity against MCF-7 breast cancer cells, driven by elevated fatty acids and monoacylglycerides, known to disrupt cancer cell energy metabolism and apoptosis. The isolation of succinic acid, reducing MCF-7 viability by 28% ($p < .001$), further underscores its potential as a lead compound for targeted cancer therapies. The honey's balanced immunomodulatory effects, significantly downregulating IL-6 ($p < .0001$) without excessive immune stimulation, align with the need for therapies that control inflammation without promoting tumour progression. Fujairah's hot, low-humidity climate (25–40 °C, 55%–65% humidity) has been associated in previous studies with increased polyphenol and flavonoid content in honey, which may contribute to the high antioxidant activity observed in Sample 6 (92.47% DPPH scavenging). These characteristics, distinct from other regional honeys, highlight Fujairah honey's potential for developing innovative, natural product-based adjuvants for breast cancer treatment, warranting further standardisation and mechanistic studies. Future work should prioritise fractionation-guided compound isolation, multi-omics validation of anticancer pathways, and in vivo modelling to substantiate efficacy. Moreover, regulatory alignment and global nutraceutical classification are critical for translating this regional bioresource into a globally accepted therapeutic or dietary supplement.

Supplementary material

Supplementary material is available at *International Journal of Food Science and Technology* online.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Author contributions

Eman J. Abuzaid (Investigation, Methodology, Writing—original draft), Khawla Mohammed Alyammahi (Supervision, Writing—original draft), Attiat Elnaggar (Investigation, Methodology, Writing—original draft), Rania Hamdy (Investigation, Methodology, Validation, Visualization, Writing—original draft), Alshaimaa M. Hamoda (Investigation, Writing—original draft), Doha H. Aboubaker (Methodology), Shaymaa Mohamed (Methodology), Hamza Mohammad Al-Hroub (Methodology), Nashwa Ahmed Mohamed (Formal analysis,

Investigation, Methodology, Writing—original draft), Fouad Lamghari (Funding acquisition, Supervision), Ali El-Keblawy (Supervision, Writing—original draft), and Sameh S.M. Soliman (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing)

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Conflicts of interest

The authors declare no conflicts of interest.

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