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Research Article

## The Antioxidant and Anticancer Properties of Khastawi Date Seeds Extracts

Lana Abed Mansur Alnajar <sup>a</sup>, Alaa Hashim AlMoula <sup>a\*</sup>, Andy Neal Saeed Shamaya <sup>b</sup>

<sup>a</sup> Department of Chemistry, College of Education for Pure Sciences, University of Kirkuk, Kirkuk 36001, Iraq

<sup>b</sup> Department of Chemistry, College of Science, University of Baghdad, Baghdad 10070, Iraq

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#### For Correspondence:

Alaa Hashim AlMoula, Department of Chemistry, College of Education for Pure Sciences, University of Kirkuk, Kirkuk 36001, Iraq

### Abstract

**Objective(s):** To characterize the major chemical constituents of Khastawi date seed extract and evaluate its antioxidant activity and selective cytotoxicity against FTC-133 human thyroid cancer cells. **Design:** In vitro experimental study combining GC-MS chemical profiling, DPPH radical-scavenging testing, MTT cell-viability assays, and high-content screening (HCS). **Intervention(s):** Khastawi date seeds were extracted by Soxhlet extraction using the reported mixed-solvent system. FTC-133 cells and normal human dermal fibroblasts (HdFn) were exposed to the crude extract at 25-400 µg/mL for 24, 48, and 72 h. **Main outcome measure(s):** GC-MS library-matched constituents, DPPH inhibition and IC<sub>50</sub>, MTT cell viability and IC<sub>50</sub>, and multiparametric HCS cellular responses. **Results:** GC-MS revealed several bioactive constituents, including fatty-acid-related compounds. DPPH scavenging increased with concentration, and the extract showed an IC<sub>50</sub> of 294.02 ppm compared with 34.22 ppm for ascorbic acid. FTC-133 cells were more sensitive to the extract than HdFn cells. The FTC-133 IC<sub>50</sub> values were 111.5, 90.79, and 83.12 µg/mL at 24, 48, and 72 h, respectively, compared with 265.4, 201.8, and 145.2 µg/mL for HdFn cells. HCS documented changes in multiple cellular-health parameters after extract exposure. **Conclusion:** Khastawi date seed extract demonstrated moderate antioxidant activity and selective in vitro cytotoxicity toward FTC-133 thyroid cancer cells, supporting further investigation of its bioactive constituents.

**Keywords:** Khastawi date seed; GC-MS; DPPH; MTT; high-content screening; antioxidant; anticancer activity.

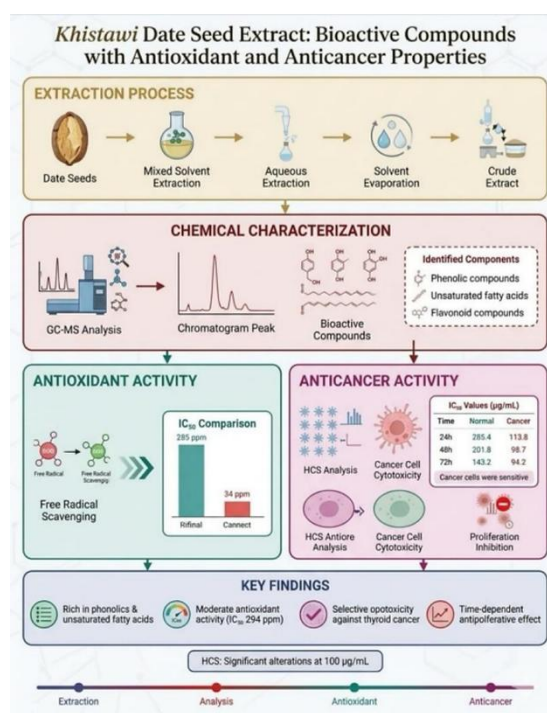


Figure 1. Schematic overview of the extraction, chemical characterization, antioxidant testing, and anticancer evaluation of Khastawi date seed extract.

## INTRODUCTION

Date palm (*Phoenix dactylifera* L.) fruit and seeds are increasingly investigated as functional-food and nutraceutical materials because they contain phenolic compounds, carotenoids, tocopherols, phytosterols, dietary fiber, and other bioactive constituents with antioxidant potential <sup>1,2</sup>. Chemical characterization is important for relating these constituents to measured biological activities, and GC-MS has been successfully applied to profile volatile and lipid-derived components of date palm materials <sup>3</sup>. Date seed extracts have also shown antioxidant and cell-based anticancer activity in previous *in vitro* studies. Polyphenol-rich date seed preparations have reduced viability in breast, hepatic, colorectal, prostate, colon, and lung cancer cell models, although the magnitude of the response depends on cultivar, extraction method, concentration, and exposure time <sup>2,4,5</sup>. The present study focused on Khastawi date seeds collected in Kirkuk, Iraq. Its objective was to characterize the major constituents of the crude extract by GC-MS and to evaluate antioxidant activity, cytotoxicity against FTC-133 human thyroid cancer cells, selectivity relative to normal human dermal fibroblasts (HdFn), and multiparametric cellular responses by high-content screening.

## MATERIALS AND METHODS

### Chemicals

Ethanol was obtained from Sigma-Aldrich Co. A DPPH antioxidant-capacity assay reagent/kit supplied by BioAssay Systems was used for the antioxidant assessment.

### Instrumentation

GC-MS analyses were performed using Agilent instrumentation. Optical density in the MTT assay was measured with an ELISA microplate reader at 575 nm. UV-Vis spectrophotometric measurements were performed using a JASCO V-770 spectrophotometer.

### Sample Preparation and Extraction

Khastawi date seeds (*Phoenix dactylifera* L.) were obtained from the local market in Kirkuk. The seeds were separated from the fruits, thoroughly washed with distilled water to remove adhering material, and dried at room temperature for several days. The dried seeds were ground to powder. A 20 g portion of seed powder was placed in a thimble and extracted using a Soxhlet apparatus. A mixture of solvents with different polarities (ethanol, water, dimethyl sulfoxide [DMSO], acetone, dimethylformamide [DMF], and ethyl acetate) was used to recover bioactive constituents. Extraction was continued for 8 h through repeated Soxhlet cycles. After extraction, the solvent was removed to obtain the crude date seed extract. Soxhlet extraction and solvent-dependent recovery of bioactive compounds from date seeds have been described previously <sup>6,7</sup>.

### GC-MS Analysis

The derivatized sample was analyzed using an Agilent 6890N Network Gas Chromatography system coupled to an Agilent 5973 Network Mass Selective Detector and

equipped with an Agilent 7683 Series Injector (Agilent, CA, USA). A 1  $\mu$ L aliquot of the extract was injected in splitless mode onto a DB-5MS + DG column (J&W 122-5532G; 30 m length, 250  $\mu$ m internal diameter, 0.25  $\mu$ m film thickness, with a built-in 10 m DuraGuard column). Helium was used as the carrier gas at a constant flow rate of 1.2 mL/min, and the injector temperature was set at 250 °C. The oven temperature was initially maintained at 100 °C for 12 min, increased to 140 °C at 5 °C/min and held for 10 min, then increased to 250 °C at 5 °C/min and held for a further 10 min, giving a total analysis time of 62 min. Chromatographic peak integration was performed using Chem Station, while mass spectra were identified using the library of the National Institute of Standards and Technology (NIST) 2014. When no internal standard was used, only similarities index 90 or above was reported.

### DPPH Antioxidant Assay

Free-radical scavenging activity was evaluated using DPPH (2,2-diphenyl-1-picrylhydrazyl) according to a modified DPPH radical-scavenging method <sup>8</sup>. The extract was dissolved in methanol to prepare eight concentrations (800, 400, 200, 100, 50, 25, 12.5, and 6.25 ppm). DPPH was prepared in absolute methanol at a concentration of 50 ppm. Equal volumes of the extract solution and DPPH solution were mixed, protected from light, and incubated for 1 h at 37 °C. Absorbance was then measured at 517 nm using a spectrophotometer. Ascorbic acid was used as the reference antioxidant. DPPH radical-scavenging activity was calculated as follows:

$$\text{Inhibition (\%)} = [(A_{\text{blank}} - A_{\text{sample}}) / A_{\text{blank}}] \times 100$$

### MTT Assay

The cytotoxic effect of the date seed extract on FTC-133 thyroid cancer cells and HdFn normal human dermal fibroblasts was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric viability assay <sup>9</sup>. Cells ( $1 \times 10^4$ - $1 \times 10^6$  cells/mL) were cultured in flat-bottom 96-well microplates containing 200  $\mu$ L of complete culture medium per well. After removal of the medium, the extract was added at concentrations of 25, 50, 100, 200, and 400  $\mu$ g/mL using two-fold serial dilutions. Each concentration and the untreated control were tested in triplicate. Plates were incubated for 24, 48, or 72 h at 37 °C in 5% CO<sub>2</sub>. MTT solution (10  $\mu$ L) was then added to each well, followed by incubation for an additional 4 h under the same conditions. After removal of the medium, 100  $\mu$ L of solubilization solution was added for 5 min, and optical density was measured at 575 nm using an ELISA reader. The optical-density data were analyzed to determine the concentration required to reduce cell viability by 50% (IC<sub>50</sub>) for each cell line.

### High-Content Screening

A multiparametric assessment of cytotoxicity was performed after exposure to date seed extract using high-content screening (HCS), following the general principles of multiparameter cellular toxicity assessment <sup>10</sup>. Five cellular health parameters were

assessed: viable cell count, total nuclear intensity, cell membrane permeability, mitochondrial membrane permeability, and cytochrome c release. After 24 h of exposure to different extract concentrations, cells were stained with mitochondrial membrane potential and permeability dyes for 30 min at 37 °C. The cells were then fixed and permeabilized before incubation with a primary antibody against cytochrome c and a DyLight 649-conjugated anti-mouse IgG secondary antibody for 60 min. Plates were analyzed using an ArrayScan high-content screening system.

## RESULTS AND DISCUSSION

### GC-MS Analysis

GC-MS analysis was used to characterize volatile and semi-volatile constituents of the Khastawi date seed extract. The chromatogram showed multiple peaks corresponding to tentatively identified bioactive

constituents, and the major library-matched compounds are summarized in Table 1 and shown in Figure 2. The detected profile included ester-, aldehyde-, and fatty-acid-related compounds. Date seed oils from other cultivars have likewise been reported to contain substantial proportions of oleic acid together with lauric, myristic, palmitic, stearic, linoleic, and linolenic acids <sup>11-13</sup>. Besbes et al. reported oil contents of approximately 10-13% in two Phoenix dactylifera seed cultivars and identified oleic acid as the major unsaturated fatty acid <sup>11</sup>. Biglar et al. and Harkat et al. also documented cultivar-dependent differences in date seed oil composition <sup>12,13</sup>. Such variation is expected to reflect cultivar, geographic origin, extraction conditions, and analytical methodology. Because the present identifications are based on GC-MS library matching, confirmation with authentic standards would be required for definitive structural assignment of individual peaks.

**Table 1. Major chemical constituents tentatively identified in Khastawi date seed extract by GC-MS library matching.**

| Molecular mass (g/mol) | Chemical formula | Peak area (%) | RT (min) | Class                 | Compound                                   |
|------------------------|------------------|---------------|----------|-----------------------|--------------------------------------------|
| 212.24                 | C14H12O2         | 49.9          | 1.26     | Ester                 | Benzyl benzoate                            |
| <b>238.41</b>          | C16H30O          | 68.007        | 0.12     | Aldehyde              | cis-9-Hexadecenal                          |
| <b>284.48</b>          | C18H36O2         | 62.007        | 6.44     | Fatty carboxylic acid | Stearic acid                               |
| <b>280.45</b>          | C18H32O2         | 62.72         | 13.01    | Fatty carboxylic acid | Linoleic acid                              |
| <b>280.50</b>          | C18H32O2         | 61.863        | 13.01    | Fatty carboxylic acid | Linoleic acid                              |
| <b>282.46</b>          | C18H34O2         | 61.863        | 21.73    | Fatty carboxylic acid | Oleic acid                                 |
| <b>256.42</b>          | C16H32O2         | 56.491        | 36.44    | Fatty carboxylic acid | Palmitic acid                              |
| <b>558.89</b>          | C36H62O4         | 62.063        | 36.44    | Fatty carboxylic acid | Elaidic acid Linoleic + linolenic acid mix |

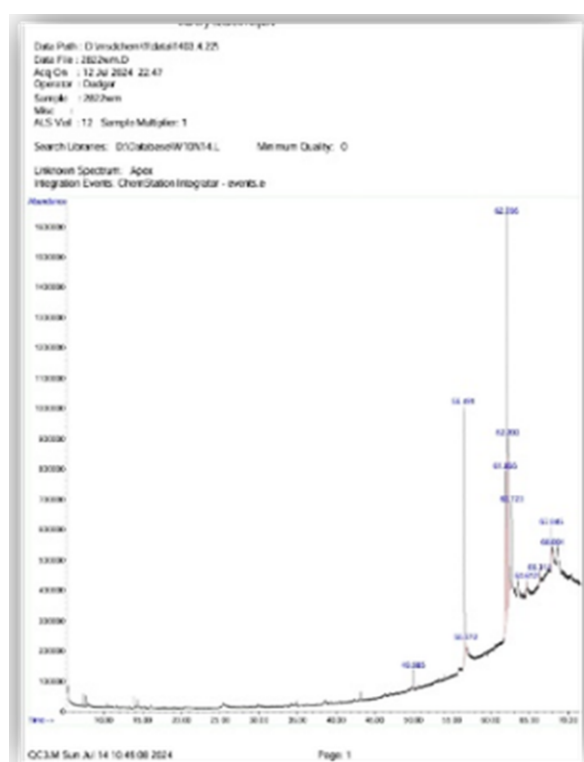


Figure 2. GC-MS chromatogram of Khastawi date seed extract.

### Antioxidant Activity

The antioxidant activity of Iraqi Khastawi date seed extract was evaluated using the DPPH radical-scavenging assay and compared with ascorbic acid. The extract showed a concentration-dependent increase in radical-scavenging activity, from 4.26% inhibition at 6.25 ppm to 90.09% at 800 ppm (Table 2 and Figure 3). The  $IC_{50}$  of the extract was 294.02 ppm, whereas ascorbic acid showed an  $IC_{50}$  of 34.22 ppm and produced 88.23% inhibition at 6.25 ppm and 99.62% inhibition at 800 ppm. Because a lower  $IC_{50}$  indicates stronger radical-scavenging activity, ascorbic acid exhibited greater antioxidant capacity than the date seed extract under the present assay conditions. Previous investigations have shown that date seed antioxidant activity varies with cultivar and extraction solvent and is associated with phenolic-rich fractions<sup>2,7,14</sup>. Shams Ardekani et al. demonstrated marked differences in total phenolic content and antioxidant activity among date seed varieties and solvent systems<sup>14</sup>, while recent comparative work also reported a positive relationship between phenolic content and antioxidant activity in date seed extracts<sup>2</sup>. These results are in agreement with concentration-dependent DPPH

response observed in the present study of Khastawi extract. However, direct numerical comparisons between studies should be made with caution, taking into account differences in extraction and assay conditions.

Table 2. DPPH radical-scavenging activity of Khastawi date seed extract and ascorbic acid.

| Concentration (ppm) | Date Seeds (% Inhibition) | Ascorbic Acid (% Inhibition) |
|---------------------|---------------------------|------------------------------|
| 800                 | 90.09                     | 99.62                        |
| 400                 | 83.81                     | 99.58                        |
| 200                 | 65.34                     | 98.52                        |
| 100                 | 48.21                     | 96.94                        |
| 50                  | 20.82                     | 95.42                        |
| 25                  | 9.58                      | 92.15                        |
| 12.5                | 4.50                      | 91.72                        |
| 6.25                | 4.26                      | 88.23                        |

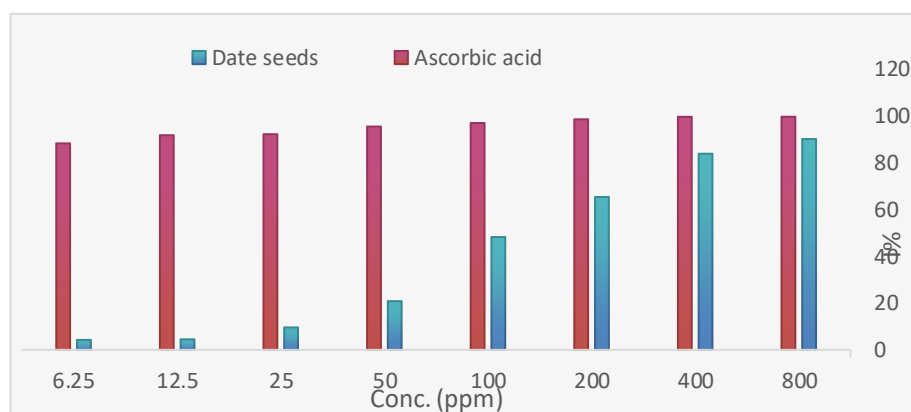


Figure 3. Comparison of DPPH radical-scavenging activity of Khastawi date seed extract and ascorbic acid.

### MTT Assay

The MTT assay demonstrated concentration- and time-dependent reductions in cell viability following exposure to Khastawi date seed extract (Tables 3-5; Figure 4). After 24 h, cell viability at 400  $\mu$ g/mL was 47.033% in FTC-133 cells compared with 78.329% in HdFn cells; at 200  $\mu$ g/mL, the corresponding values were 52.733% and 84.384%, respectively. After 48 h, viability at 400  $\mu$ g/mL decreased to 42.299% in FTC-133 cells and 72.855% in HdFn cells, while at 200  $\mu$ g/mL the values were 49.216% and 79.996%. After 72 h, viability at 400  $\mu$ g/mL was 38.019% in FTC-133 cells and 66.866% in HdFn cells, and at 200  $\mu$ g/mL it was 45.269% and 72.920%, respectively. The  $IC_{50}$  values for HdFn cells were 265.4, 201.8, and 145.2  $\mu$ g/mL at 24,

48, and 72 h, respectively, whereas the corresponding  $IC_{50}$  values for FTC-133 cells were 111.5, 90.79, and 83.12  $\mu$ g/mL. These results indicate greater sensitivity of FTC-133 cells to the extract than normal HdFn cells under the tested conditions. Previous studies have reported reduced viability of several cancer cell lines after exposure to date seed extracts, including breast, hepatic, colorectal, prostate, colon, and lung cancer models<sup>2,4,5</sup>. The present data therefore extend the in vitro evaluation of date seed extract to FTC-133 thyroid cancer cells. However, the study used a crude extract and an in vitro model; compound-specific mechanisms and therapeutic relevance require confirmation using isolated constituents, mechanistic assays, and additional biological models.

Table 3. Cytotoxic effect of Khastawi date seed extract on FTC-133 thyroid cancer cells and HdFn normal fibroblasts after 24 h, measured by the MTT assay.

| Concentration<br>( $\mu\text{g/mL}$ ) | Cell viability (%) |                    | P value                       |
|---------------------------------------|--------------------|--------------------|-------------------------------|
|                                       | HdFn               | FTC-133            |                               |
|                                       | Mean $\pm$ SD      | Mean $\pm$ SD      |                               |
| 400                                   | 78.329 $\pm$ 0.519 | 47.033 $\pm$ 0.910 | **** $\rightarrow p < 0.0001$ |
| 200                                   | 84.384 $\pm$ 1.107 | 52.733 $\pm$ 0.509 | **** $\rightarrow p < 0.0001$ |
| 100                                   | 90.040 $\pm$ 0.633 | 69.382 $\pm$ 0.213 | **** $\rightarrow p < 0.0001$ |
| 50                                    | 93.928 $\pm$ 0.582 | 77.210 $\pm$ 0.846 | **** $\rightarrow p < 0.0001$ |
| 25                                    | 96.535 $\pm$ 0.681 | 86.085 $\pm$ 0.411 | **** $\rightarrow p < 0.0001$ |

Table 4. Cytotoxic effect of Khastawi date seed extract on FTC-133 thyroid cancer cells and HdFn normal fibroblasts after 48 h, measured by the MTT assay.

| Concentration<br>( $\mu\text{g/mL}$ ) | Cell viability (%)  |                    | P value                       |
|---------------------------------------|---------------------|--------------------|-------------------------------|
|                                       | HdFn                | FTC-133            |                               |
|                                       | Mean $\pm$ SD       | Mean $\pm$ SD      |                               |
| 400                                   | 72.855 $\pm$ 0.684  | 42.299 $\pm$ 0.862 | **** $\rightarrow p < 0.0001$ |
| 200                                   | 79.996 $\pm$ 0.656  | 49.216 $\pm$ 1.166 | **** $\rightarrow p < 0.0001$ |
| 100                                   | 87.619 $\pm$ 0.605  | 62.315 $\pm$ 0.865 | **** $\rightarrow p < 0.0001$ |
| 50                                    | 91.696 $\pm$ 0.463  | 70.655 $\pm$ 0.577 | **** $\rightarrow p < 0.0001$ |
| 25                                    | 94.3315 $\pm$ 0.874 | 81.064 $\pm$ 0.654 | **** $\rightarrow p < 0.0001$ |

Table 5. Cytotoxic effect of Khastawi date seed extract on FTC-133 thyroid cancer cells and HdFn normal fibroblasts after 72 h, measured by the MTT assay.

| Concentration<br>( $\mu\text{g/mL}$ ) | Cell viability (%) |                    | P value                       |
|---------------------------------------|--------------------|--------------------|-------------------------------|
|                                       | HdFn               | FTC-133            |                               |
|                                       | Mean $\pm$ SD      | Mean $\pm$ SD      |                               |
| 400                                   | 66.866 $\pm$ 0.514 | 38.019 $\pm$ 0.798 | **** $\rightarrow p < 0.0001$ |
| 200                                   | 72.920 $\pm$ 0.263 | 45.269 $\pm$ 0.924 | *** $\rightarrow p < 0.001$   |
| 100                                   | 79.596 $\pm$ 0.641 | 53.427 $\pm$ 0.958 | **** $\rightarrow p < 0.0001$ |
| 50                                    | 85.627 $\pm$ 0.818 | 66.315 $\pm$ 0.996 | **** $\rightarrow p < 0.0001$ |
| 25                                    | 89.395 $\pm$ 0.135 | 73.648 $\pm$ 0.574 | *** $\rightarrow p < 0.001$   |

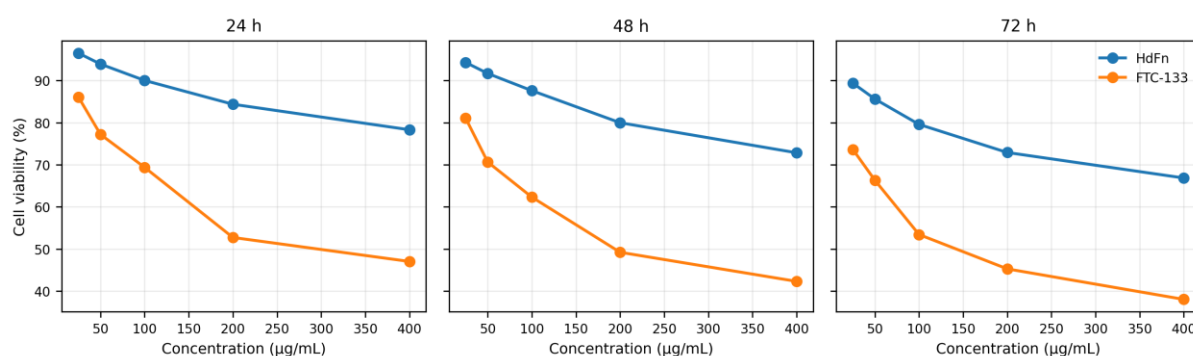


Figure 4. Effect of Khastawi date seed extract on the viability of FTC-133 thyroid cancer cells and HdFn normal fibroblasts after 24, 48, and 72 h.

## High-Content Screening

High-content screening provided a multiparametric description of cellular responses to the date seed extract after 24 h (Table 6). The analysis included viable cell count, total nuclear intensity, cell membrane permeability, mitochondrial membrane permeability, and cytochrome c release across concentrations from 6.25 to 100 µg/mL. At 100 µg/mL, the recorded values were  $2601.25 \pm 190.8$  for viable cell count,  $466.5 \pm 16.7$  for total nuclear intensity,  $102.5 \pm 1.3$  for cell membrane permeability,  $217.5 \pm 14.4$  for mitochondrial membrane

permeability, and  $588 \pm 39.9$  for cytochrome c release. The corresponding untreated-control values were  $2785.5 \pm 116$ ,  $462.5 \pm 10.1$ ,  $106.5 \pm 0.83$ ,  $239 \pm 8.7$ , and  $587.5 \pm 24.2$ , respectively. These measurements complement the MTT viability data by documenting multiple cellular parameters after exposure to the extract. Because the parameters do not all change monotonically with concentration, the HCS findings should be interpreted as supportive multiparametric observations rather than as evidence of a single defined mechanism of action.

Table 6. Multiparametric cellular effects of Khastawi date seed extract on FTC-133 cells assessed using ArrayScan high-content screening.

| Concentration (µg/mL) | Viable cell count            | Total nuclear intensity   | Cell membrane permeability | Mitochondrial membrane permeability | Cytochrome c release      |
|-----------------------|------------------------------|---------------------------|----------------------------|-------------------------------------|---------------------------|
| Untreated control     | $2785.5 \pm 116^a$<br>68.3%  | $462.5 \pm 10.1^b$<br>65% | $106.5 \pm 0.83^a$<br>66%  | $239 \pm 8.7^a$<br>64%              | $587.5 \pm 24.2^b$<br>65% |
| 100                   | $2601.25 \pm 190.8^b$<br>90% | $466.5 \pm 16.7^a$<br>86% | $102.5 \pm 1.3^a$<br>82%   | $217.5 \pm 14.4^b$<br>80%           | $588 \pm 39.9^a$<br>85%   |
| 50                    | $3114.1 \pm 227^a$<br>95%    | $416.5 \pm 19.9^b$<br>90% | $104.25 \pm 1.6^a$<br>90%  | $277 \pm 17.2^a$<br>85%             | $654.5 \pm 47.5^a$<br>90% |
| 25                    | $3240.5 \pm 298^a$<br>99%    | $411 \pm 26.2^b$<br>95%   | $103.5 \pm 2.1^a$<br>93%   | $275 \pm 22.6^a$<br>90%             | $555 \pm 62.5^b$<br>92%   |
| 12.5                  | $3392 \pm 381^a$<br>99.9%    | $414 \pm 33.5^b$<br>97%   | $106 \pm 2.7^a$<br>94%     | $270 \pm 28.8^a$<br>92%             | $488.5 \pm 79.8^b$<br>90% |
| 6.25                  | $3291 \pm 451^a$<br>99.99%   | $406.5 \pm 39.6^b$<br>99% | $100.5 \pm 3.2^a$<br>97%   | $253.5 \pm 34.1^a$<br>96%           | $485.1 \pm 94.4^b$<br>95% |

Values are presented as reported in the original dataset. Different superscript letters (a and b) indicate significant differences, whereas identical letters indicate no significant difference.

## CONCLUSION

The date seed extract of Khastawi revealed several GC-MS library matched bioactive constituents including fatty acid related compounds. The extract showed moderate concentration dependent antioxidant activity and higher cytotoxic activity against FTC-133 thyroid cancer cells than normal HdFn fibroblasts under the tested conditions. The lower IC<sub>50</sub> values in FTC-133 cells at all exposure times indicate selective in vitro cytotoxicity in this experimental system. Further investigation of Khastawi date seed constituents, including confirmation of individual GC-MS identifications, isolation of active compounds and mechanistic evaluation in additional cell and biological models is warranted by these findings.

**Supplementary Information:** No supplementary information file was submitted.

**Data Availability Statement:** All data generated and analyzed in this study are included in the manuscript and presented in the tables and figures.

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**Author Contributions:** All authors contributed to the experimental work and preparation of the manuscript.

**Ethics Approval and Consent to Participate:** Not applicable.

**Consent for Publication:** Not applicable.

**Conflict of Interest:** The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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