



Extracts of Jordanian Date Palm Fruit (*Phoenix Dactylifera L.*) Inhibit Human Mammary Adenocarcinoma (MCF-7) Cells *In Vitro* by Inducing Cell Viability

HIBA F. AL-SAYYED^{1*}, LUAY F. ABU-QATOUSEH², MOHAMMED MALKAWY,
SUZAN AL-WAWI², and MOHAMMAD ALKAFWEEN³

¹Department of Nutrition, Faculty of Pharmacy and Medical Sciences,
University of Petra, Amman, Jordan.

²Department of Pharmacology and Biomedical Sciences, University of Petra, Amman, Jordan.

³Faculty of Pharmacy, Department of Pharmacy, Al-Zaytoonah University of Jordan, Amman, Jordan.

Abstract

World wide, and in Jordan specifically, date palm fruit production has been steadily increasing. Recently, various dates extracts have been used functionally as antioxidants or anticancer agents. In addition, Jordanian date palm fruit of Barhi variety at two maturity stages (*Rutab*) and (*Tamr*) inhibited chemically-induced mammary cancer in animal model. The aim of this study is to strengthen the scientific evidence on the effect of dates on mammary cancer via assessing the effect of different concentrations of water extracts of three varieties of dates grown in Jordan (*Barhi*, *Belle Huwaimil*, and *Medjool*) at two maturity stages (*Rutab* and *Tamr*) on the viability of MCF-7 breast cancer cell line. The effects of different extracts on MCF7 inhibition/proliferation was analyzed using MTT assay. Percentage of inhibition was calculated. The most effective concentration was 100 mg/ml for all varieties. At this concentration, *Medjool* variety at the *Tamr* stage exhibited the highest inhibition. At the 12.5 and 25 mg/ml concentrations of the extracts, the most effective date palm fruit varieties were *Belle Huwaimil* and *Barhi* at the *Tamr* stage respectively. At lower concentrations (3.125 and 6.25 mg/ml), *Medjool* at the *Tamr* stage and *Belle Huwaimil* respectively were the most effective extracts were *Barhi* at the *Tamr* and *Rutab* stages were the least effective (P=0.000**). It is concluded that water extract of palm fruit reduced MCF-7 cell viability.



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CONTACT Hiba F. Al-Sayyed ✉ halsayyed@uop.edu.jo 📍 Department of Nutrition, Faculty of Pharmacy and Medical Sciences, University of Petra, Amman, Jordan.



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Introduction

The relationship between food consumption and cancer has been extensively studied. Specifically, the consumption of fruits and vegetables was found to be protective against different types of cancers¹ specially mammary cancer.² By virtue of dietary fiber³ and antioxidants, fruits and vegetables are thought to improve immunity⁴ and inhibit cancerous cell growth.⁴

The date palm (*Phoenix dactylifera* L.) is a monocotyledon of *Palmae* family growing annually.⁵ Worldwide, date palm fruit production has been steadily increasing over the last 30 years. Most of the worldwide production of the fruit is in the Arab countries.⁶ The last decade showed rapid increase in Jordanian areas cultivated with this plant because it tolerates desert climatic conditions of the Jordanian areas where it is cultivated.⁷

Historically, the plant was used for medicinal purposes such as fever, throat soars, toothaches, liver, abdominal,⁸ eye, and respiratory problems.⁹ Additionally, it has been mentioned that the fruit contains stimulants that strengthen uterus muscles,¹⁰ and is recommended for breast milk production.^{9,10} Recently, various fruit extracts have been used functionally as antioxidants,¹¹⁻¹³ and anticancer agents.¹⁴

The consumption of date palm fruit is related to Islamic values. The fruit consumption reaches the highest levels during the month of *Ramadan* since eating this fruit is a custom favored by Prophet Mohammad (peace be upon him).¹⁵ Date palm fruit has hundreds of varieties sharing three maturity stages: *Khalal*, *Rutab*, and *Tamr*.

Cancer is a risk factor for mortality; the World Health Organization (WHO) reported 9.5 million deaths from cancer in 2018. Mammary cancer caused 1.5% deaths in 2018. Deaths from cancer worldwide are expected to rise to 11 million in 2030. Breast, and liver cancers cause the most cancer deaths each year.¹⁶ Breast cancer is the second risk factor for cancer deaths in Jordan accounting for 11.3 % of total deaths of cancer in 2018.¹⁷ MCF-7 mammary cancer cell line represents the in vitro model for estrogen receptor-positive breast cancer.¹⁸

Jordanian date palm fruit of *Barhi* variety at the *Rutab* and *Tamr* maturity stages was found to reduce chemically-induced mammary cancer tumor multiplicity, size, and increase tumor latency¹⁹ by inducing the hormone 17- β -estradiol²⁰ and modulating the glutathione-S-transferase enzyme activity.²¹ In addition, the water extracts of the fruit were found to be rich in polyphenols and flavonoids and a potential for antioxidant activity.¹²

In the current study, we attempted to evaluate the effect of several concentrations of water extracts of three varieties of date palm fruit grown in Jordan (*Barhi*, *Belle Huwaimil*, and *Medjool*) at two maturity stages (*Rutab* and *Tamr*) on the viability of MCF-7 breast cancer cell line.

Materials and Methods

Fruit and Extract Preparation

Locally grown date palm fruits were provided thankfully by *Wardat ElRaml* shop. In this study, three fruit varieties were tested: *Barhi*, *Belle Huwaimil*, and *Medjool*. The tested fruits were at the two maturity stages *Rutab* (*Barhi*) and *Tamr* (*Barhi*, *Belle Huwaimil*, and *Medjool* varieties). Then, the water extracts were prepared with deionized water (1:10). Subsequently, serial decimal dilution series of 200, 100, 50, 25, 12.5, 6.25, 3.125 and 1.563 mg/ml were performed using Dulbecco's minimal essential medium (DMEM) enriched with 10% fetal bovine serum (FBS).

Cell Line and Culture Conditions

The human breast adenocarcinoma cell line (MCF7) was purchased from American Type Culture Collection (MCF7 ATCC® HTB-22). The MCF7 cells were maintained DMEM, DMEM High Glucose (4.5 g/l), with L-Glutamine supplemented with 10% FBS, 1% penicillin-streptomycin and 0.25 mg/ml amphotericin B (Capricorn-scientific, Germany) at 37°C in a humidified atmosphere of 95% air and 5% CO₂.¹⁸ The cell line that has been used in this assay was sourced from the ATCC and all the STR profile and data are available on the ATCC website. The authors would like to mention that cell lines in our labs are regularly checked for any microbial contamination and strict rules has been followed to discard any cell line or flask with possible contamination.

Cell Proliferation and Viability Assay

Different extract effects on MCF7 proliferation/inhibition was analyzed by MTT assay cell proliferation and viability after 24-hour incubation. Initially, 2×10^4 cells/well were transferred into 96-well plates and let to attach overnight. Initially, 20000 cells/well were seeded into 96-well plates and let to attach overnight. After that, the cells were treated with different concentrations (100 mg/mL, 50 mg/mL, 25 mg/mL, 12.5 mg/mL, 6.25 mg/mL, 3.125 mg/mL or 1.56 mg/mL) of each fruit extract and incubated for 24 hours with 5% CO₂ at 37°C in a humidified atmosphere. The wells with cells only was used as a positive control. After this treatment, MTT reagent (5 mg/ml) in 100 µl of fresh culture medium was added to each well for 4-hour incubation. The formazan crystals formed with MTT treatment were solubilized with acidic isopropanol and the optical density was then measured at 570 nm wavelength using a microplate reader (GloMax, promega). The assay controls were used to specify the cytotoxicity of the extract and to exclude the effect of the vehicle. In addition, water was used in different dilutions to exclude the effect of vehicle too. Further, DMSO was used as a positive control and the cell with media to mimic normal cell line growth. Percentage of inhibition was calculated by the following formula; $(\text{Average viability/ control})$ and $\text{inhibition (\%)} = 100 - \text{viability}$. Furthermore, IC50 was estimated using

Prism software.^{22,23} The procedure was performed in triplicate.

Statistical Analysis

To detect the interaction effect of date palm fruit variety (factor 1), maturity stage (factor 2), as well as concentration (factor 3), data of the duplicate readings of percentage inhibition as well as percentage of viable cells were analyzed by multivariate analysis of variance (MANOVA) using the statistical package for social sciences (SPSS) analysis system. Data in the figures was extracted from mean \pm standard deviation values for the inhibition and viable cell percentages²⁴ $P < 0.05$ was set for significance.

Results

Results of inhibition of cell line are shown in Figure 1. All of date palm fruit concentrations showed inhibition effect on cell line (Figures 1 and 2). The statistical analysis of data showed that there is no interaction effect between date palm fruit variety, maturity stage, and extract concentration in terms of inhibition percentage, neither viable cell percentage ($P > 0.05$). However, there are significant ($P < 0.01$) differences between different extracts in terms of the interaction effect between date palm variety and extract concentration.

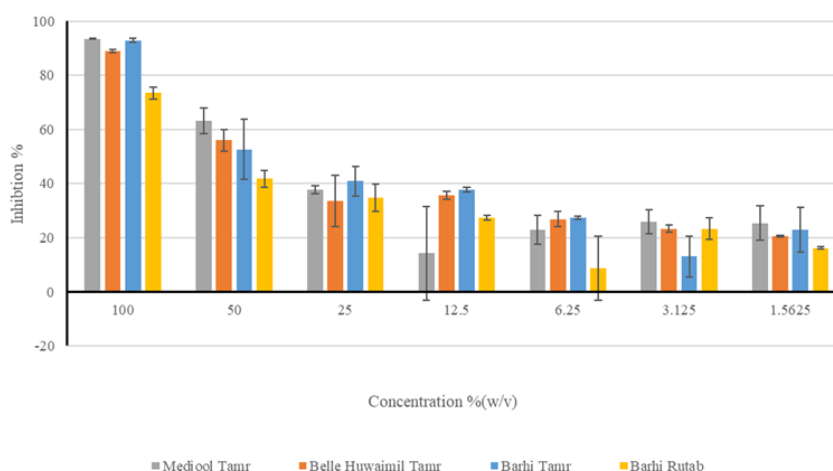


Fig.1: Inhibition percentage of different concentrations of the studied dates varieties

Results show that the inhibition percentage is dose-dependent. The effect of the tested concentrations (1.563 to 100 mg of dates extract (dry)/mL) on

the viability of MCF-7 cells. There is insignificant ($P > 0.05$) inhibition of the growth of cells observed at (1.563-100 mg/mL). However, results showed

that the cytotoxic effect appeared at higher concentrations (50 and 100 mg/mL) where cell viability reduced by ~44% and 78%, respectively (Figure 2). MCF-7 cells growth inhibition as well as cytotoxicity were not significant until a concentration

of 25 mg/mL (80% of cell viability). Interestingly, after 24 hours of treatment with date palm fruit extracts, MCF-7 cell viability decreased sharply and dose-dependently with IC₅₀ values of 12 ± 0.02 mg/mL ($P < 0.01$) (Figure 2).

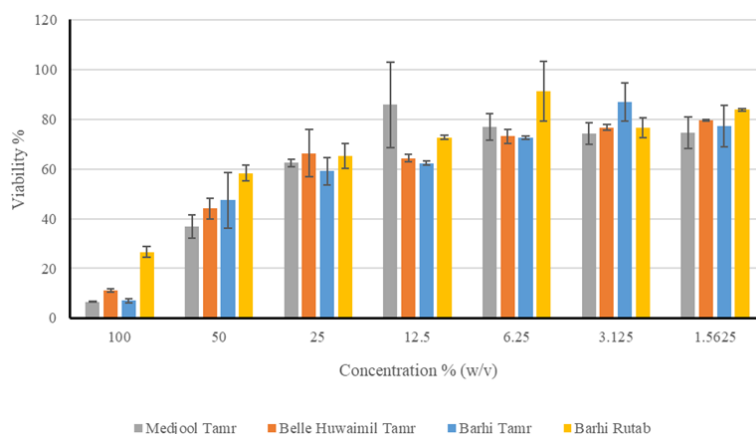


Fig. 2: Effect of the date palm fruit extracts on MCF-7 cancer cell lines viability at 24 hours

The most effective concentration was 100 mg/ml for all varieties. At this concentration, *Tamr of Medjool* variety exhibited the highest inhibition, followed by *Belle Huwaimil* variety at the *Tamr* stage, *Barhi* at the *Rutab* stage, and *Barhi* at the *Tamr* stage respectively ($P=0.000^{**}$) and results were similar at 50 mg/ml concentration extracts. At the medium concentrations of the extracts (12.5 and 25 mg/ml), the most effective fruit varieties were *Belle Huwaimil* and *Barhi* at the *Rutab* stage respectively. At these concentrations, *Medjool* and *Belle Huwaimil* at the *Tamr* stage were the least effective ($P=0.000^{**}$). At lower concentrations (3.125 and 6.25 mg/ml), *Medjool* at the *Tamr* stage and *Belle Huwaimil* respectively were the most effective extracts where *Barhi* at the *Tamr* and *Rutab* stages were the least effective ($P=0.000^{**}$).

Discussion

The insignificant effect of maturity stage ($P > 0.05$) is not surprising since all the fruit varieties were tested at the *Tamr* maturity stage and one variety only (i.e. *Barhi*) was tested at the *Rutab* maturity stage. Thus, probably, there was insufficient data for statistical comparison. On the other hand, the sole effect of variety as well as concentration on the inhibition and cell viability percentages was significant ($P=0.001$).

Our results are concomitant with result found by.^{15,25,26} This result suggests that the cell viability inhibition is probably related to the proliferation suppression neither to any cytotoxic nor cytolytic effects. This activity might be due to the presence of certain compounds within the fruit, such as quercetin (a flavonoids glucosides which known for anticancer effect).²⁷ Previous studies revealed that polyphenol compounds reduce cancer cell growth by inducing apoptosis in many cell lines of mammary cancer.²⁸ A study by Salomón-Torres *et al.* (2019)²⁹ showed that water extracts of *Medjool* variety inhibited MCF-7 breast cancer cell line and the author mentioned that 100 µg/ml extracts was not effective and that is in disagreement with our study.

A previous study showed the 51% percentage of inhibition of cell line after incubation of MCF-7 with 100 mg/ml methanolic extracts.³⁰ The current study revealed that the percentage of inhibition of cell lines was between 14% to 93% after incubation for 24 hours with *Medjool* variety at *Tamr* stage. The variety of *Medjool* contains antioxidants such as ascorbic acid, phenolic compounds,¹² gallic acid,²⁹ p-hydroxybenzoic acid, vanillic, caffeic, synergic, and ferulic acids. Furthermore, this variety of date palm fruit exerted antioxidant activity.^{14,31}

Date water extracts (1.5625, 3.125, 6.25, 12.5, 25, 50, 100 mg/ml)

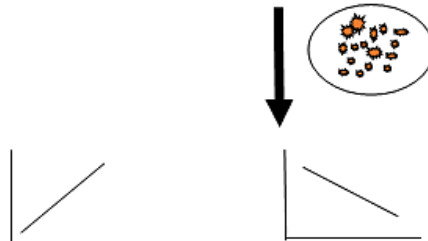
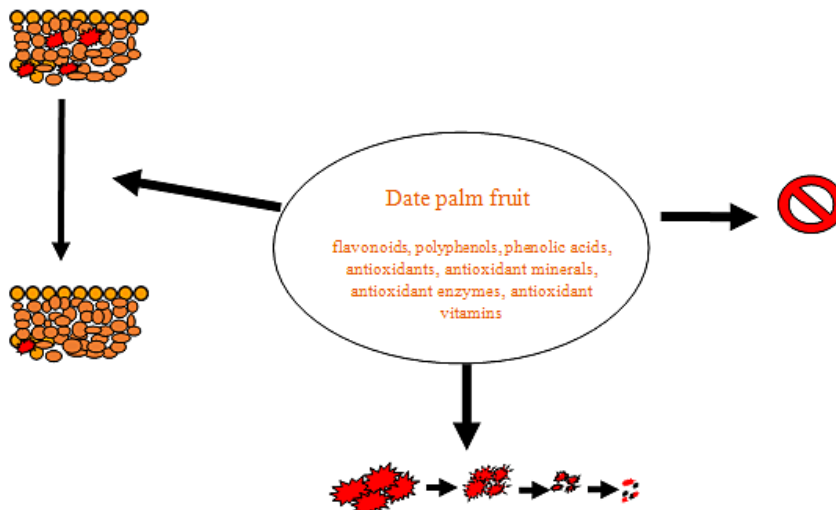
*Barhi (Rutab, Tamr)**Belle Huwaimil, Medjool (Tamr)***a. Summary of the research procedure and key findings**

Fig. 3: a. Summary of the research procedure and key findings and suggested mechanisms by which date palm fruit protects against mammary cancer

A study by El-sharkawy (2017)²⁸ reported that the inhibition of cell proliferation was 42% at 15 mg/ml concentration of extract. Inhibition values found in this research ranged from 9% to 92% and the results were close to those found by Odeh *et al.* (2014)³⁰ who found inhibition value of 50 mg/ml extracts of Barhi variety at both maturity stages.³² Figure 3 shows summarization of the experimental procedure as well as suggested mechanisms and functional compounds that are thought to protect against mammary cancer.

The various compounds in the date palm fruit render it capable of having an antioxidant capacity. This property has been proved at the *in vitro*^{8,33-35} and

the *in vivo* levels.³⁶⁻³⁸ A previous study by Vayalil (2002)¹⁴ showed the antioxidant and antimutagenic activity of the water extract of date palm fruit at the Tamr stage. The author found that the extract scavenged superoxide and hydroxyl radicals in a dose-dependent manner.¹⁴

The compounds that are thought to add the (functional) antioxidant property to the date palm fruit are metals such as Se, Cu,³⁹ Zn, and Mn, phenolic acids,³⁸ enzymes such as: phytase, invertase,⁴⁰ polyphenols specially flavonoids¹² such as catechins³⁸ and rutin,³⁴ antioxidant vitamins such as the vitamins C and E.⁴¹

Conclusion

This study revealed that the date palm fruit extract from *Barhi* and *Belle Huwaimil* varieties of Jordan provide a strong activity against MCF-7 cancer cell line proliferation. Given the folk claims of anticancer properties of *Barhi* and *Belle Huwaimil* date extract and our results on MCF-7 cells, the date fruits could be used as a supplemental food for chemoprotective effects against breast cancer and possibly other lesions. Results of this research supported the results of previous reports regarding *Medjool* variety. However, results of this study are limited by the type of extract, maturity stage, the indicators tested for anticarcinogenicity, and the lack of using control cell line like the MCF7-A10 to exclude general cytotoxicity effect on other cell line.

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Conflict of Interest

The author(s) declares no conflict of interest.

References

1. Aune D, Chan DSM, Vieira AR, *et al.* Fruits, vegetables and breast cancer risk: A systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat.* 2012;134(2):479-493. doi:10.1007/s10549-012-2118-1
2. Arsova-Sarafinovska Z, J. Dimovski A. Natural antioxidants in cancer prevention. *Maced Pharm Bull.* 2013;59:3-14. doi:10.33320/maced.pharm.bull.2013.59.001
3. Williams GM, Williams CL, Weisburger JH. Diet and cancer prevention: The fiber first diet. *Toxicol Sci.* 1999;52(2 SUPPL.):72-86. doi:10.1093/toxsci/52.2.72
4. Bhattacharya S, Muhammad N, Steele R, Peng G, Ray RB. Immunomodulatory role of bitter melon extract in inhibition of head and neck squamous cell carcinoma growth. *Oncotarget.* 2016;7(22):33202-33209. doi:10.18632/oncotarget.8898
5. Zehdi S, Gros-balthazard M. Biogeography of the date palm (*Phoenix dactylifera* L., Arecaceae): Insights on the origin and on the structure of modern diversity Biogeography of the Date Palm (*Phoenix dactylifera* L., Arecaceae): Insights on the Origin and on the Structure of Mode. 2013;(June):2016-2020. doi:10.17660/ActaHortic.2013.994.1
6. Altahat ES. Analysis of Agricultural Policies Affecting Medjool Date Palm Cultivation in Analysis of Agricultural Policies Affecting Medjool Date Palm Cultivation in Jordan. 2017;(March 2015). doi:10.5539/jas.v7n4p129
7. Hadrami A EI, Al-khayri JM. Socioeconomic and traditional importance of date palm. 2014;(October 2012).
8. Ali A, Waly M, Essa MM, Devarajan S. Nutritional and Medicinal Value of Date Fruit. *Dates Prod Process food Med values.* 2014:361-371.
9. Marwat SK, Khan M, Ahmad M, Zafar M. Fruit Plant Species Mentioned in the Holy Quran and Ahadith and Their Ethnomedicinal Importance. 2009;(January).
10. Sakka A EI, Salama M, Salama K. The Effect of Fenugreek Herbal Tea and Palm Dates on Breast Milk Production and Infant Weight The Effect of Fenugreek Herbal Tea and Palm Dates. *J Pediatr Sci.* 2014.
11. Rozila I, Abdul Manap N, Ghazali L, *et al.* The antioxidant properties and anticancer effect of Medjool dates (*Phoenix dactylifera* L.) on human breast adenocarcinoma (MCF-7) cells: in vitro study. *Front Pharmacol.* 2019;10(38). doi:10.3389/conf.fphar.2019.63.00038
12. Al-sayyed HF, Alkurd R. Antioxidant Content and Capacity of Jordanian Date Palm Fruit at two Australian Journal of Basic and Applied Sciences Antioxidant Content and Capacity of Jordanian Date Palm Fruit at two Maturity Stages. 2018;(October). doi:10.22587/

- ajbas.2018.12.9.10
13. Awad MA, Al-Qurashi AD, Mohamed SA. Antioxidant capacity, antioxidant compounds and antioxidant enzyme activities in five date cultivars during development and ripening. *Sci Horti* (Amsterdam). 2011;129(4):688-693. doi:10.1016/j.scienta.2011.05.019
 14. Vayalil PK. Antioxidant and antimutagenic properties of aqueous extract of date fruit (*Phoenix dactylifera* L. *Arecaceae*). *J Agric Food Chem*. 2002;50(3):610-617. doi:10.1021/jf010716t
 15. Khan F, Ahmed F, Pushparaj PN, Abuzenadah A. Ajwa Date (*Phoenix dactylifera* L.) Extract Inhibits Human Breast Adenocarcinoma (MCF7) Cells *In Vitro* by Inducing Apoptosis and Cell Cycle Arrest. 2016:1-17. doi:10.1371/journal.pone.0158963
 16. WHO. WHO Director-General's opening remarks at the mission briefing on COVID-19 -11 March 2020. 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mission-briefing-on-covid-19---26-february-2020>.
 17. WHO. Global Burden of Cancer.; 2020. https://www.who.int/cancer/country-profiles/Global_Cancer_Profile_2020.pdf.
 18. Chakroun M, Khemakhem B, Mabrouk H Ben, et al. Evaluation of anti-diabetic and anti-tumoral activities of bioactive compounds from *Phoenix dactylifera* L's leaf: *In vitro* and *in vivo* approach. *Biomed Pharmacother*. 2016;84:415-422. doi:10.1016/j.biopha.2016.09.062
 19. Al-sayyed HF, Takruri HR, Shomaf Ms. Research Opinions In Animal & Veterinary Sciences The Effect of date palm fruit (*Phoenix dactylifera* L.) on 7, 12-dimethylbenz (α). 2008:11-18.
 20. Al-Sayyed HF, Takruri HR, Shomaf MS, Al-Saleh A. The effect of date palm fruit (*Phoenix dactylifera* L.) on the hormone 17- β -estradiol in 7,12-dimethylbenz(α)anthracene-induced mammary cancer in rats. *Med J Nutrition Metab*. 2014;7(1). doi:10.3233/MNM-140001
 21. Al-Sayyed HF, Takruri HH, Shomaf MS. The effect of date palm fruit (*Phoenix dactylifera* L.) on the enzyme glutathione-S-transferase activity in Sprague-Dawley rats. *Pakistan J Nutr*. 2013;12(5). doi:10.3923/pjn.2013.410.415
 22. Attaha AHM, Malik Al-Saadi SAA, Barhee C V, et al. Anatomical and Hormonal Studies of Floral and Fruiting Behavior of *Phoenix Dactylifera*, Cv. Barhee. *Int J Curr Adv Res*. 2015;4(12):531-536.
 23. Mosmann T. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J Immunol Methods*. 1983;65(1-2):55-63. doi:10.1016/0022-1759(83)90303-4
 24. Lund A. Laerd statistics. 2018. Laerdstatistics.com.
 25. Baig M, Elkady AI, Al-attar AM, Quadri F. Induction of apoptosis and cell cycle arrest by ethyl acetate fraction of *Phoenix dactylifera* L. (Ajwa dates) in prostate cancer cells Induction of apoptosis and cell cycle arrest by ethyl acetate fraction of *Phoenix dactylifera* L. (Ajwa dates) in p. *J Ethnopharmacol*. 2018;218(February):35-44. doi:10.1016/j.jep.2018.02.030
 26. Abed H El, Chakroun M, Abdelkafi-koubaa Z, et al. Effects of Aqueous Ethanolic Extract from *Phoenix dactylifera* L. *Parthenocarpic Dates*. 2018;2018.
 27. Zhang CR, Aldosari SA, Vidyasagar PSPV, Shukla P, Nair MG. Health-benefits of date fruits produced in Saudi Arabia based on *in vitro* antioxidant, anti-inflammatory and human tumor cell proliferation inhibitory assays. *J Saudi Soc Agric Sci*. 2017;16(3):287-293. doi:10.1016/j.jssas.2015.09.004
 28. El-sharkawy A. Principles and Practice of Cancer Prevention and Control Redhwan Ahmed Al-Naggar Edited by. 2017;(December).
 29. Salomón-Torres R, Ortiz-Uribe N, Valdez-Salas B, et al. Nutritional assessment, phytochemical composition and antioxidant analysis of the pulp and seed of medjool date grown in Mexico. *PeerJ*. 2019;7:1-19. doi:10.7717/peerj.6821
 30. Odeh I, Al-Rimawi F, Abbadi J, Obeyat L, Qabbajeh M, Hroub A. Effect of Harvesting Date and Variety of Date Palm on Antioxidant Capacity, Phenolic and Flavonoid Content of Date Palm (*Phoenix Dactylifera*). *J Food Nutr Res*. 2014;2(8):499-505. doi:10.12691/jfnr-2-8-11
 31. Rozila I, Abdul Manap N, Ghazali L, et al. The antioxidant properties

- and anticancer effect of Medjool dates (*Phoenix dactylifera* L.) on human breast adenocarcinoma (MCF-7) cells: *in vitro* study. *Front Pharmacol.* 2019;10(January):63-65. doi:10.3389/conf.fphar.2019.63.00038
32. Parle and Khanna. Phytopharmacology of Khajur (*Phoenix dactylifera* L.). *Ann Pharm Pharm Sci.* 2010;1(2):109-115.
33. Khanavi M, Saghari Z, Mohammadirad A, Khademi R, Hadjiakhoondi A, Abdollahi M. Comparison of antioxidant activity and total phenols of some date varieties. *Daru.* 2009;17(2):104-108.
34. Saleh EA, Tawfik MS, Abu-Tarboush HM. Phenolic Contents and Antioxidant Activity of Various Date Palm (<i>Phoenix dactylifera </i> L.) Fruits from Saudi Arabia. *Food Nutr Sci.* 2011;02(10):1134-1141. doi:10.4236/fns.2011.210152
35. Lines HC, Ramazani A, Mashhadi M, Kamalinejad M, Tavakolizadeh M, Balaghi F. *Phoenix dactylifera* L. Fruit Induces Cell Proliferation of A2780, A172 and. 2016;12(1):35-44.
36. Fathy AH, Bashandy MA, Bashandy SA, Mansour AM. The beneficial effect of natural antioxidants from olive oil with fig and date palm fruit extracts on biochemical and hematological parameters in rats during diethylnitrosamine-induced carcinogenesis. 2018;(Iarc 1987):584-597. doi:10.1139/facets-2017-0075
37. Indrayani, Suharti, Rahmadi A, Diana O, Zeranika N. How do Muslims consume dates? *Pakistan J Med Heal Sci.* 2018;12(4):1732-1743. doi:10.5281/zenodo.2586225
38. Al-orf SM, Ahmed MHM, Atwai NA-, *et al.* Review: Nutritional Properties and Benefits of the Date Fruits (*Phoenix dactylifera* L.). *Jo.* 2012;39:97-129.
39. Nasir MU, Hussain S, Jabbar S, Rashid F, Khalid N, Mehmood A. A review on the nutritional content, functional properties and medicinal potential of dates Date varieties of the world Nutritional value and functional properties of dates Proximate composition of dates. 2015;3(1):17-22.
40. Deshpande, N.M. and Deshpande MM. World Journal of Pharmaceutical Research Nutritional Values, *Phytochemicals And. World J Pharm Res.* 2018;6(8):419-426. doi:10.20959/wjpr20178-8943
41. Al-habsi N, Al-khusaibi M. The Potential Antioxidant Properties of Date Products: A Concise Update. 2018;(June). doi:10.14206/canad.j.clin.nutr.2018.02.08