Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2022.139449.2569 Volume 30, Issue 1.1, - January 2024, Supplement Issue
Manuscript ID ZUMJ-2205-2569 (R1)
DOI 10.21608/ZUMJ.2022.139449.2569

ORIGINAL ARTICLE

# Metabolite Profiling of Date Palm Fruit (*Phoenix dactylifera* L.) And Its Cytoprotective Effects Versus Vitamin C Against Mobile Phone Radiation-Induced Adrenal Gland Damage In Rats

**Rasha M.S.M. Mohamed[1]*, Maha M. Ahmed Abdul Rahman[2], May Ahmed El-Sayed[3], Mahitab Mostafa Elsayed[4], Heba S Ahmed[1] and Sahar Kamal Younes Ali[1]**

[1] Department of Clinical Pharmacology, Faculty of Medicine, Zagazig University, Egypt
[2] Department of Human Anatomy and Embryology, Faculty of Medicine, Zagazig University, Egypt
[3] Department of Pharmacognosy, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
[4] Department of Clinical Pharmacy, Faculty of Pharmacy, Modern University for Technology & Information, Egypt

***Corresponding author:**
Rasha Mohamed Sabry Mohamed Mohamed
Clinical Pharmacology Department, Faculty of Medicine, Zagazig, University.

**E-mail:**
rmsabry@medicine.zu.edu.eg

**Submit Date** 19-05-2022
**Revise Date** 02-06-2022
**Accept Date** 07-06-2022

## ABSTRACT

**Background**: Date palm fruit (*Phoenix dactylifera* L.) can be used as a pharmaceutical product because of its rich phytochemical composition. Mobile phone radiation is a type of electromagnetic radiation (EMR) that has been confirmed to exert several adverse effects on living tissues.
**Methods**: In this study, we investigated the phytochemicals of the Egyptian date palm fruit using ultra-performance liquid chromatography with electrospray ionization quadrupole- linear ion trap tandem mass spectrometry analysis (UPLC-ESI-MS/MS) in negative and positive ionization modes. Adult male Wister albino rats were exposed to mobile phone induced electromagnetic radiations (EMR) for 1 hour per day for 4 weeks. We evaluated the possible cytoprotective effects of date palm fruits compared with vitamin C on mobile phone induced EMR. Rats were divided into the control, EMR, and two EMR groups treated with either vitamin C or date palm fruit.
**Results**: The analysis of date resulted in the tentative identification of 29 compounds, including 13 free organic acids and their derivatives, 9 flavonoids and their glycosides, 3 fatty acids, and 4 miscellaneous compounds. Both biochemical and histopathological examinations of adrenal tissues confirmed that mobile phone radiation caused significant increases in oxidative stress, DNA damage, inflammatory marker levels, fibrosis, and apoptosis in adrenal tissues compared with the control group. Both vitamin C and date palm fruit significantly reduced these damaging effects with superior cytoprotective effect for date palm fruit over vitamin C.
**Conclusion**: Date palm fruits could protect the adrenal glands due to its antiapoptotic, antioxidant, antifibrotic and anti-inflammatory properties.
**Keywords:** Date palm fruit (*Phoenix dactylifera* L); UPLC-ESI-MS/MS; Adrenal gland; Mobile (cell) phone radiation; Tumor necrosis factor α.

## INTRODUCTION

Phoenix dactylifera L., a monocotyledonous dioecious woody perennial plant belonging to the Palmaceae (Arecaceae) family, has been one of the most important fruit crops in the Middle East and North Africa's dry regions. It is commonly known as date and is the only species of the genus Phoenix that is cultivated for its edible sweet fruit. There are approximately 3000 distinct groups of date palms, which differ in size, color, and sugar content of their fruits. There is extensive information regarding the chemical composition of the date palm fruit. The bioactive non-nutrient phytochemical

ingredients of date palms are responsible for their interesting pharmacological actions [1].

Previous studies have shown that date palms are rich in carotenoids, fatty materials, sterols, tannins, low-fat content, and saponins, in addition to polyphenols such as flavonoids, isoflavones, lignans, and phenolic acids (*p*-coumaric, ferulic, caffeic, sinapic, syringic, protocatechuic, and gallic acids), a substrate for enzymatic browning in dates, the isomers of caffeoyl shikimic acids (3-, 4-, and 5-CSAs) were separated from *P. dactylifera* dates. Date pulps are rich in easily digestible simple sugars (70%) such as glucose, fructose, and sucrose; unsaturated fats, lipids, proteins, and dietary fibers; and essential minerals and vitamins that are important for the body such as vitamins A, B, C, folic acid, biotin, thiamine, riboflavin, and ascorbic acid [1].

The extensive use of mobile phones has attracted considerable attention because of their health hazards. In 1973, the term mobile phone was introduced to describe any portable phone, whereas the term cellular (cell) phone describes newer generations of mobile phones. The Global System for Mobile Communications (GSM) is the second-generation (2G) cellular network used by mobile phones. In 2008, the number of GSM users exceeded three billion. Mobile phones emit radiations when they are in the switched-on mode, and the emission of these radiations increases during calls. The intensity of these radiation waves can be decreased by increasing the distance from the device. Most GSM mobile phones emit radiofrequency RF-EMR in the range of 900 or 1800 MHz [2].

EMR consists of a spectrum of radiations arranged, from the lowest to highest frequency, as radio waves, microwaves, infrared light, visible light, ultraviolet light, X-rays, and gamma rays [3]. Bioelectromagnetic studies examining the health hazards of mobile phone EMR on living organisms have shown that these hazards depend on the distance from the device. These health hazards are either thermal or nonthermal [2]. The thermal effect is due to the heating of the nearest parts of the head or body to the mobile phone, which can cause temporary facial nerve dysfunction [4].

Another more mysterious and conflicting hazardous effect of mobile phone EMR is the nonthermal effect. The World Health Organization has classified RF-EMR as group 2B, a possible human carcinogen. [5].

There are also reports on the effects of EMR on the apoptotic pathway of mitochondria, cell differentiation, free radical metabolism, heat shock proteins, DNA damage, and the plasma membrane [6].

Oxidative stress is the imbalance between the synthesis and degradation of reactive oxygen species (ROS) in the cell and the ability of the body tissues to get rid of these reactive products. These hazardous products are generated during normal metabolism and in response to stressors (i.e., radiations). Furthermore, ROS causes oxidative degeneration in reproductive cells [7], heart, lungs, liver [8], and kidneys [9]. The exposure to mobile phone EMR for 16 weeks induces oxidative stress, inflammatory response, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation in rats [10]. Mobile phone radiation was also confirmed to induce oxidative stress and DNA damage in the brain tissue of rats. Additionally, chronic inflammation is related to the continuous production of ROS, which in turn causes tissue damage, including lipid peroxidation, protein degradation, and DNA damage, with the formation of 8-hydroxy-2′deoxyguanosine (8-OHdG) [11].

Vitamin C (ascorbic acid) is water-soluble and cannot be synthesized by the human body. It is essential for several body functions, including collagen synthesis, enzyme function, and most importantly acting as an oxidative scavenger, it reduces the comorbidities of diabetes mellitus because of its antioxidant and anti-inflammatory properties [12].

The date fruit can act as an antioxidant as it contains phenolic components such as flavonoids, procyanidins, and *p*-coumaric, ferulic, and sinapic acids. It reduces the risk of developing cancer [13], and cardiovascular disease [14]. Traditional medicines use almost all the parts of this plant to treat inflammation [15], diabetes [16] and renal disorders [17].

This study aimed to investigate the chemical composition and protective effects of the Egyptian date palm fruit compared with vitamin C against mobile phone-induced adrenal gland damage in adult male Wistar albino rats to develop a novel and natural cytoprotective medication with fewer side effects.

## MATERIALS AND METHODS

### Plant material and UPLC-ESI-MS/MS analysis

**Preparation of date sample for UPLC-ESI-MS/MS analysis**

*P. dactylifera* L. was purchased from a local market in Egypt in the form of paste of the fleshy part. The methodology used in this preparation was based on the protocol developed previously [18]. The date paste was lyophilized then stored at −20°C for use in analysis. For the UPLC-ESI-MS/MS analysis, it was diluted with 10 mL MeOH at room temperature for 2 h on an orbital shaker set at 200 rpm. To obtain the extract, the homogenate was centrifuged at 4°C for 15 min at 1000 *g* to remove plant debris, and the supernatant was decanted. The extract was stored in the dark and preserved at 18°C until further use.

**UPLC-ESI-MS/MS instrument and separation technique**

The methanolic solution of the date paste was prepared as a 0.3 mg/mL solution using HPLC-grade methanol, filtered using a membrane disk filter (0.2 μm), and then analyzed using UPLC-ESI-MS/MS as described previously [19].

**Experimental procedure**

**Experimental animals and ethical statement**

A total of 16 healthy, adult male Wistar rats, weighing approximately 150 g, were purchased from the Faculty of Veterinary Medicine, Zagazig University, Egypt. Rats were distributed into cages and acclimated for 1 week, with free access to food and water. Temperature, humidity, and light/dark cycles were maintained constant at 23°C ± 2°C, 60% ± 10%, and 12/12 h, respectively. All animal experiments comply with the ARRIVE guidelines and carried out in accordance with the U.K. Animals Act. All animal handling procedures were approved by the Ethical Committee for Animal Handling at the Faculty of Medicine, Zagazig University, Egypt, with approval no. ZU-IACUC/3/F/91/2021.

**Exposure to mobile phone radiation**

A mobile phone (Darago D5, 2G, GSM: 900 MHz) was used for generating EMR. It was kept in the silent switched-on mode and installed close to the rat cages for the entire experimental duration. The radiation groups were exposed to continuous missed calls for 1 h/day for 4 weeks.

**Treatment groups**

1. Control group (n = 4)
2. EMR group (EMR) (n = 4)

Rats were exposed to mobile phone radiation (1 h/day for 4 weeks) [20].

3. EMR + vitamin C group (n = 4)

The EMR-exposed rats received vitamin C at 100 mg/kg body weight daily dissolved in drinking water (Vitacid-C effervescent 1 g, Chemical Industries Development, Giza, ARE), coinciding with the initiation of EMR exposure (ANTUNES, DARIN, and BIANCHI 2000).

4. EMR + Date group (n = 4)

The EMR-exposed rats received the Egyptian date palm fruit paste, coinciding with the initiation of EMR exposure. One-third of rat food consisted of the date palm fruit paste mixed with the standard chow diet (**Fig. 1**).

**Collection of adrenal gland samples**

At the end of the experiment, rats were anesthetized with urethane (1.3 g/kg, ip, Sigma-Aldrich, USA). The adrenal glands were dissected, and half of them were washed with ice-cold saline, placed on ice, and then stored at −20°C until performing an enzyme-linked immunosorbent assay (ELISA). The other half of the glands was processed for histopathological analysis.

**Enzyme-linked immunosorbent assays (ELISA)**

The adrenal levels of malondialdehyde (MDA; Biodiagnostic, Giza, Egypt), superoxide dismutase (SOD; Biodiagnostic, Giza, Egypt), caspase 3 (Cloud-Clone Corporation, Fernhurst Dr., Katy, USA), and 8-OHdG (MyBioSource, San Diego, USA) were measured using rat ELISA kits. All procedures were performed according to the manufacturers' instructions.

**Histopathological analysis**

**Preparation of samples**

After careful dissection of adrenal glands, they were fixed in 10% neutral buffered formalin solution and then prepared as described previously [21].

The adrenal gland sections were stained as follows:

1. Hematoxylin and eosin (H&E) staining for examination of the general histological structure of the adrenal gland at magnifications of ×100 and ×400 [21].
2. Mallory's trichrome (MT) staining for the examination of collagen fibre deposition to evaluate fibrosis at a magnification of ×400.

3. Immunohistochemical staining for tumor necrosis factor-alpha (TNF-α) was conducted to detect inflammation (Abcam, ab6671, Cambridge, UK) based on blocking the unspecific binding, specific anti-TNF-α was used to detect cellular content, and finally, the sections were counterstained with Mayer's hematoxylin, dehydrated, and examined under a light microscope at a magnification of ×1000. Positive reaction was indicated by brown color [22].

**Evaluation of fibrotic and TNF-α-positive areas**

Light microscopic examination and photography were conducted for all the stained sections of the adrenal gland using a Leica ICC50W photomicroscope. To detect the extent of fibrosis, sections were evaluated and quantified via digital image analysis using the computer software Scion Image Beta 4.03 (Scion Corporation, Frederick, MD, USA). Area percentage of collagen fibres in the MT-stained sections and the percentage area of TNF-α-positive cytoplasm in the immunostained sections were measured. All tissue processing procedures, microscopic analyses, and measurements were conducted in six nonoverlapping fields in six random sections in three different rats in each group, in a blinded manner, at the Image Analysis Unit of the Human Anatomy & Embryology Department, Faculty of Medicine, Zagazig University.

**Statistical analysis**

Data are presented as mean ± SE. Statistical analysis was conducted using GraphPad Prism version 5 (GraphPad Software, Inc., CA, USA). Groups were compared using one-way analysis of variance and post hoc Tukey test. P values of <0.05 were considered significant.

## RESULTS

**Phytochemical profiling**

The chemical composition of the aqueous fraction of *P. dactylifera* was determined using UPLC-ESI-MS/MS in negative and positive ion modes. A total of 29 secondary metabolites arranged according to the retention time ($R_t$) were tentatively identified depending on their $MS^2$ information given by the precursor ion's mass, their fragments, known fragmentation patterns for the given classes of compounds, and neutral mass loss, as well as by comparing with the available previously published literature, as shown in **Table 1**. Among the identified compounds, there were thirteen free organic acids and their derivatives, nine flavonoids and their glycosides, three fatty acids, and four miscellaneous compounds. **Fig. 2** shows the base peak chromatograms of the tested sample.

**Date palm fruit and vitamin C were effective in modulating the adrenal oxidative stress markers**

Oxidative stress was determined by measuring the adrenal levels of MDA, the lipid peroxidation marker; SOD, the first-line defence antioxidant in the cell, and 8-OHdG, a product of DNA oxidative damage (**Fig. 3**). Rats exposed to EMR demonstrated a significant increase in the levels of MDA (2.86 ± 0.24 vs 0.51 ± 0.05 and 1.32 ± 0.29 and 0.93 ± 0.03 nmol/mg, respectively) compared with those of rats i in the control, vitamin C, and date palm fruit groups, respectively. Also, 8-OHdG was significantly increased (3.41 ± 0.29 vs 0.9 ± 0.05 and 2.01 ± 0.01 and 1.36 ± 0.27 mmol/mg, respectively) compared with those of rats in the control, vitamin C, and date palm fruit groups, respectively ($P < 0.001$) (**Fig. 3A and 3B**) and a significant decrease in SOD levels (19.75 ± 0.92 vs 40.55 ± 0.99 and 29.71 ± 0.35 and 35.59 ± 1.58 mmol/mg, respectively) (**Fig. 3C**) in the adrenal tissues compared with those of rats in the control, vitamin C, and date palm fruit groups, respectively ($P < 0.001$). These results indicated increased lipid peroxidation and DNA damage and reduced tissue antioxidant activity under the effect of mobile phone EMR.

Interestingly, rats that received the date palm fruit showed significantly increased SOD levels (30%, $P < 0.05$) **(Fig. 3C)** and reduced, but not significantly, MDA and 8-OHdG levels (32% and 20%, respectively) compared with rats in the vitamin C group **(Fig. 3A and 3B)**, indicating higher tissue antioxidant activity and subsequent tissue protection under the effect of the date palm fruit.

**Date palm fruit exhibited higher cytoprotective properties than vitamin C by attenuating adrenal cell apoptosis**

Cell apoptosis was evaluated by measuring the adrenal levels of caspase 3, the hallmark of both intrinsic and extrinsic apoptotic pathways, and examining the histopathological changes in

the adrenal tissue (**Fig. 4A**). Rats exposed to EMR showed significantly increased caspase 3 levels in the adrenal tissues compared with rats in the control group ($P < 0.001$), vitamin C group, and date palm fruit group (10.35 ± 0.67 vs 4.37 ± 0.34, 8.19 ± 0.19, and 6.86 ± 0.14 pg/mg, respectively), indicating increased cell death under the effect of mobile phone EMR.

Interestingly, rats that received the date palm fruit showed significantly reduced caspase 3 levels in the adrenal tissues compared with rats in the vitamin C group ($P < 0.01$) (**Fig. 4A)**, indicating a higher cytoprotective effect of the date palm fruit.

**Effect of vitamin C and date palm fruit on adrenal gland structure analysed by H&E staining**

Histopathological changes were examined by H&E staining of the adrenal gland tissue sections of all groups, as shown in **Fig. 4B and 4C**.

**Fig. 4B** shows the morphometric analysis of zona fasciculata (ZF) thickness as an indicator of adrenal gland hypertrophy. Rats exposed to EMR displayed significant adrenal gland hypertrophy compared with rats in the control ($P < 0.001$), vitamin C ($P < 0.05$), and date palm fruit ($P < 0.001$) groups, indicating tissue disruption under the effect of mobile phone EMR.

Interestingly, the morphometric analysis of rats that received the date palm fruit exhibited significantly reduced adrenal gland hypertrophy compared with rats in the vitamin C group ($P < 0.05$) (**Fig. 4B)**, indicating a higher cytoprotective effect of the date palm fruit.

**Fig. 4C** shows histopathological analysis of tissue sections of the control group. this revealed the characteristic histological structure of the normal adult adrenal gland. The adrenal cortex showed the zona glomerulosa (ZG) beneath the adrenal gland connective tissue capsule that surrounds the gland. The ZG formed a thin, discontinuous layer of cells. The ZG cells were arranged in arched clusters with densely packed nuclei. Underneath the ZG was the ZF consisting of long, straight almost parallel cords of polyhedral cells with regular-shaped rounded vesicular nuclei and lipid-rich cytoplasm. These cords were separated by longitudinally arranged blood sinusoids. The ZF occupied most of the cortex. The zona reticularis had interconnecting and anastomosing short cords of cells with compact, eosinophilic cytoplasm. The adrenal medulla was formed of anastomosing cords of large chromaffin cells with large vesicular nuclei **(Fig. 4C: a & b)**.

However, the tissue sections of EMR-exposed rats demonstrated disruption of the regular architectural pattern of the adrenal cortex with lamellar separation in the capsule with indentation. Moreover, the EMR group demonstrated disturbed arrangement of ZG cells, and thin capsular vessels overlaid the capsule. The three zones of the gland exhibited disorganized cells. Cells of both ZG and ZF appeared with deeply stained nuclei and multiple vacuoles and absent cordonnal aspect of ZF cells **(Fig. 4C: c & d)**.

By contrast, rats exposed to EMR and treated with either vitamin C or date palm fruit showed an apparent normal capsule surrounding the adrenal gland. The cells of the three zones regained their normal arrangement; however, some vacuoles still appeared within the cells along with some dilated congested blood sinusoids. The adrenal medulla was formed of anastomosing cords of large chromaffin cells **(Fig. 4C: e, f, g, & h)**.

**Date palm fruit was more effective than vitamin C in reducing adrenal fibrous tissue deposition and inflammation**

The degree of collagen fibre deposition in the adrenal gland tissues was evaluated by MT staining of the sections of the adrenal gland tissues of all groups. **Fig. 5A and B** demonstrate the morphometric analysis and photomicrographs of the adrenal gland. **(Fig. 5B: a)** shows the average amount of collagen fibre deposition in the control group, which formed the capsule surrounding the gland, with a minimal amount of collagen fibres appearing between the ZG arches **(Fig. 5B: a)**.

However, in the EMR group **(Fig. 5B: b & c)**, there was an apparent increase in the capsule thickness surrounding the gland with extensive fibrous tissue deposition in the capsule with fibrosed blood vessels and in between the cells of both ZG and ZF, compared with the control, vitamin C, and date palm fruit groups (**Fig. 5B: a, d, & e,** respectively) (50.59% ± 1.622%, 19.49% ± 0.3657%, 28.63% ± 0.6284%, and 25.54% ± 0.3110%, $P < 0.01$). Interestingly, the mean area percentage of adrenal collagen fibre

deposition was significantly lower in the date palm fruit group than in the vitamin C group (10%, P < 0.01) (**Fig. 5A**).

**Figures 6A and 6B** show the morphometric analysis of TNF-α-immunopositive cells (brown color staining). The EMR-exposed group showed significantly increased number of TNF-α-immunopositive cells compared with the control (**Fig. 6B: a**), vitamin C (**Fig. 6B: c**), and date palm fruit (**Fig. 6B: d**) groups (29.08% ± 0.3844%, 6.660% ± 0.3453%, 25.42% ± 0.4403%, and 22.86% ± 0.3940%, respectively, P < 0.01). Interestingly, the mean area percentage of adrenal tissue localization of TNF-α was significantly reduced in the date palm fruit group compared with that in the vitamin C group (10%, P < 0.01).

**Table 1:** Identified metabolites in date palm fruits (*Phoenix dactylifera* L.) using UPLC-ESI-MS/MS analysis in negative and positive ionization modes.

| No. | Compound name | $R_t$ (min) | $[M-H]^-$ (*m/z*) | $[M+H]^+$ (*m/z*) | $MS^2$ fragments (*m/z*) |
|---|---|---|---|---|---|
| **1** | Sucrose | 0.71 | 341 | | 179 (M- H-162)$^-$, 161. 131, 119, 117, 113, 103 |
| **2** | L-ascorbic acid | 0.81 | | 177 | 133, 129, 127, 113, 103, 101, 57 |
| **3** | L-ascorbic acid isomer | 0.82 | 175 | | 143, 113, 101 |
| **4** | (Iso)citric acid | 0.94 | 191 | | 173, 147, 111 |
| **5** | Caffeoyl shikimic acid hexoside | 1.06 | 497 | | 341, 335,179, 161 |
| **6** | Protocatechuic acid | 1.34 | 153 | | 109 |
| **7** | *p*-Hydroxy benzoic acid | 1.49 | 137 | | 93 |
| **8** | Di-caffeoyl shikimic acid | 1.58 | 497 | | 335, 179, 161 |
| **9** | Caffeoyl shikimic acid | 1.82 | 335 | | 179, 135 |
| **10** | *p*-Coumaric acid | 1.89 | 163 | | 119 |
| **11** | Syringic acid | 1.96 | 197 | | 197, 182 (M-H-$CH_3$)$^-$, 167 (M-H-2$CH_3$)$^-$, 153 (M-H-$CO_2$)$^-$ |
| **12** | Caffeic acid | 2.07 | 179 | | 135 (100%) [M-H-COOH]$^-$ |
| **13** | Sinapic acid | 2.19 | 223 | | 208 ([M- H]$^-$-$CH_3$), 179 ([M- H]$^-$–$CO_2$), 164 |
| **14** | Ferulic acid | 8.82 | | 195 | 177 (M+H –$H_2O$) $^+$ |
| **15** | 3,7-dimethylquercetin | 8.94 | 329 | | 314, 299 |
| **16** | (-)-Pinellic acid | 9.36 | 329 | | 329, 311, 229, 211, 171, 139, 99 |
| **17** | Hexitol | 14.29 | 181 | | 163, 101 |
| **18** | Rutin | 15.28 | 609 | | 463, 301 |
| **19** | Phytol | 15.38 | 295 | | 277, 171, 195, 233, 251 |
| **20** | Isoferulic acid | 18.43 | | 195 | 177 (M+H –$H_2O$) $^+$ |
| **21** | Cyanidin 3-*O*-hexoside | 19.75 | | 449 | 287 (M + H-162) $^+$, 137 |
| **22** | (+)- Catechin | 20.30 | | 291 | 273, 249, 165, 151, 139, 123, 119 |
| **23** | Trihydroxy-octadecadienoic acid | 20.81 | 327 | | 171, 137 |
| **24** | (-)-Epicatechin | 22.63 | | 291 | 331 [M + $H_2O$ + Na]$^+$, 291 |
| **25** | Oleic acid | 22.79 | 281 | | 281, 111 |
| **26** | Quercetin | 30.08 | 301 | | 227, 151 |
| **27** | Luteolin | 31.06 | 285 | | 285, 243, 241, 217, 199, 175, 151 |
| **28** | Chrysoeriol | 31.26 | 299 | | 299, 284 |
| **29** | Apigenin | 31.26 | | 271 | 271, 153 |

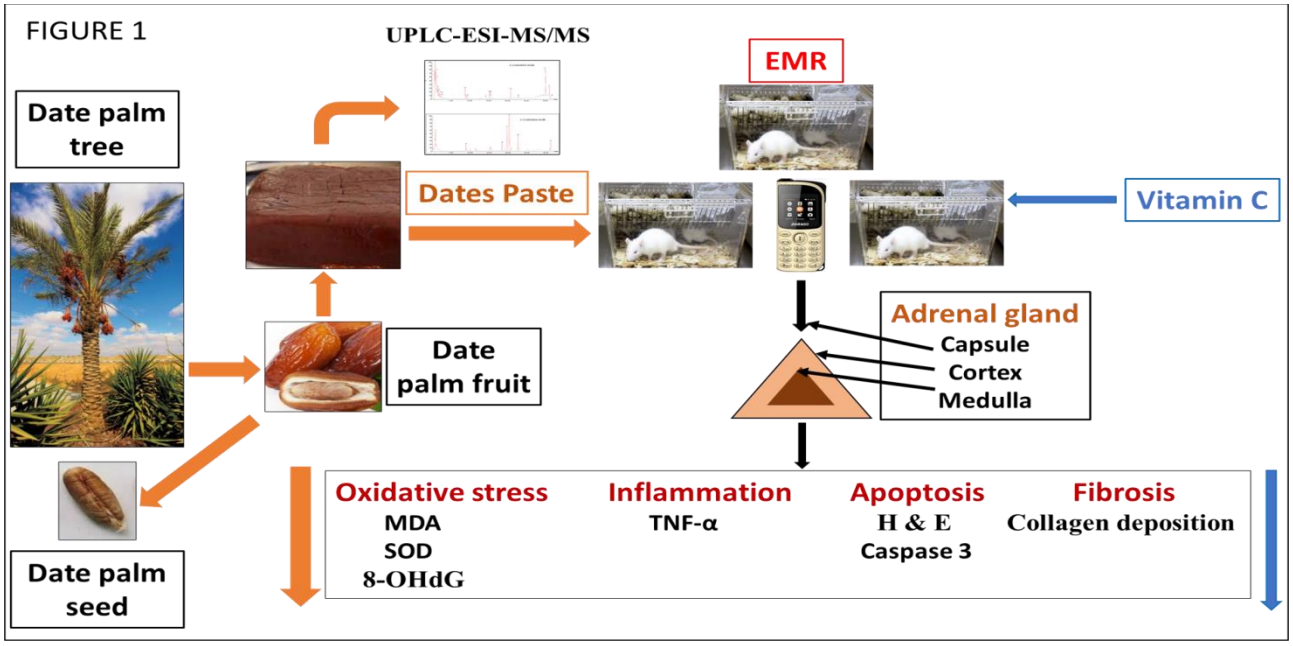


**Fig. 1 Experimental design**

FIGURE 2

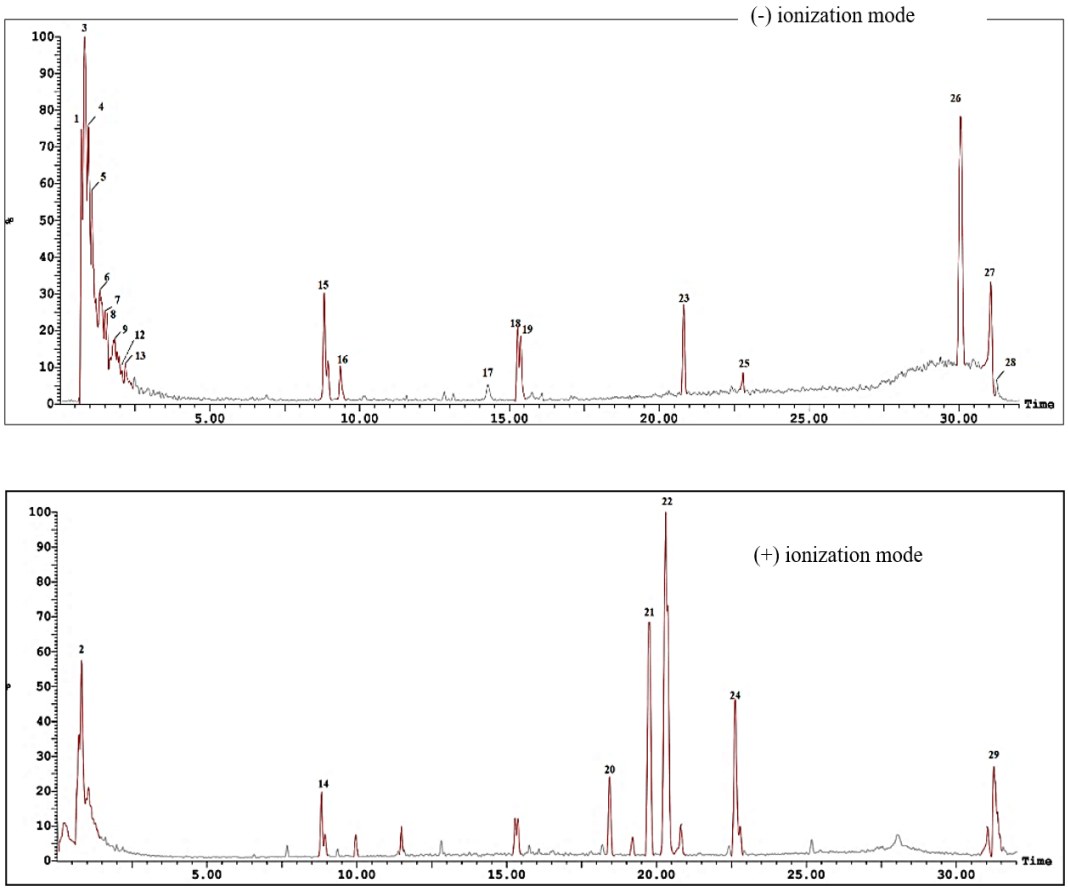


**Fig. 2: UPLS-ESI-MS chromatograms of *Phoenix dactylifera* L. in negative (−) and positive (+) ionization modes.**

FIGURE 3

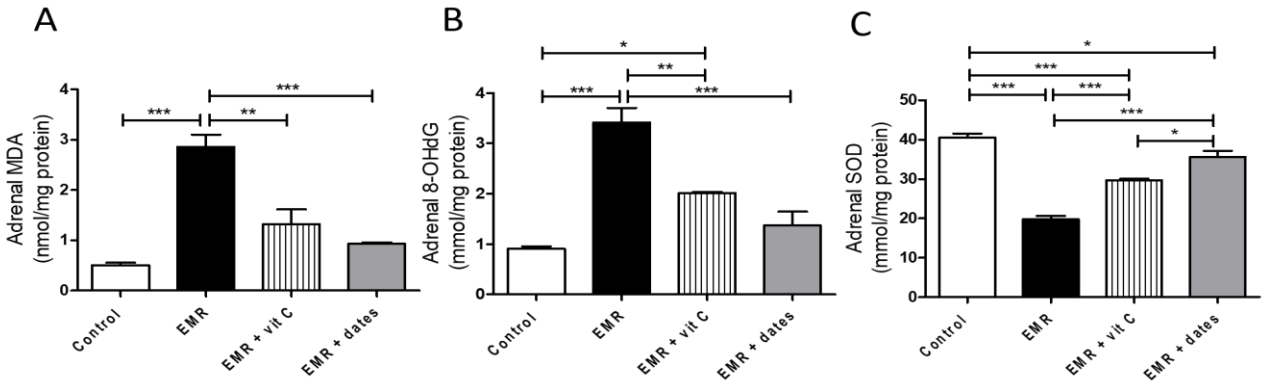


**Fig. 3. Protective effect of vitamin C and date palm fruits on mobile phone EMR-induced oxidative stress in the adrenal gland.** Graphical presentation of malondialdehyde (MDA) (A), 8-hydroxy-2′deoxyguanosine (8-OHdG) (B), and superoxide dismutase (SOD) (C). Rats were exposed to mobile phone electromagnetic radiations (EMR) for 1 h/day for 4 weeks. Rats were divided into the following four groups: control normal, EMR, EMR + vitamin C (100 mg/kg orally), and EMR + date palm fruit. Groups were analyzed using one-way ANOVA and post hoc Tukey test. All values were shown as mean ± SE (n = 3). * P < 0.05, ** P < 0.01, and *** P < 0.001.

FIGURE 4

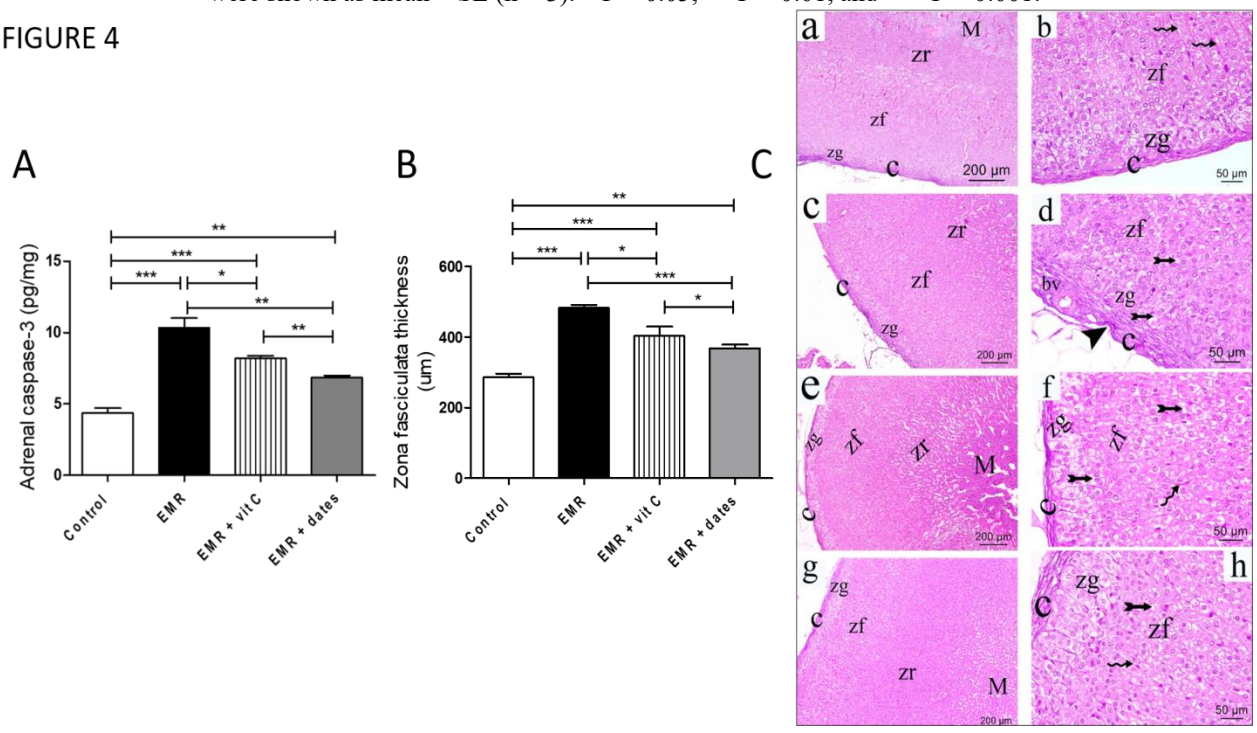


**Fig. 4. Effect of vitamin C and date palm fruits on mobile phone EMR-induced DNA damage and apoptosis in the adrenal gland.** (A) Graphical presentation of caspase 3, (B) morphometric analysis of rat adrenal tissues (thickness of zona fasciculata). (C) a photomicrograph of adrenal cortex (a) ×100 & (b) ×400. Rats were exposed to mobile phone electromagnetic radiation (EMR) for 1 h/day for 4 weeks. Rats were divided into 4 groups: control normal (a, b), EMR (c, d), EMR+ vitamin C (e, f) (100 mg/kg orally) and EMR+ date palm fruit groups (g, h). Groups were analyzed using one-way ANOVA and post hoc Tukey test. All values were shown as mean ± SE (n = 3). * P < 0.05, ** P < 0.01, and *** P < 0.001.

FIGURE 5

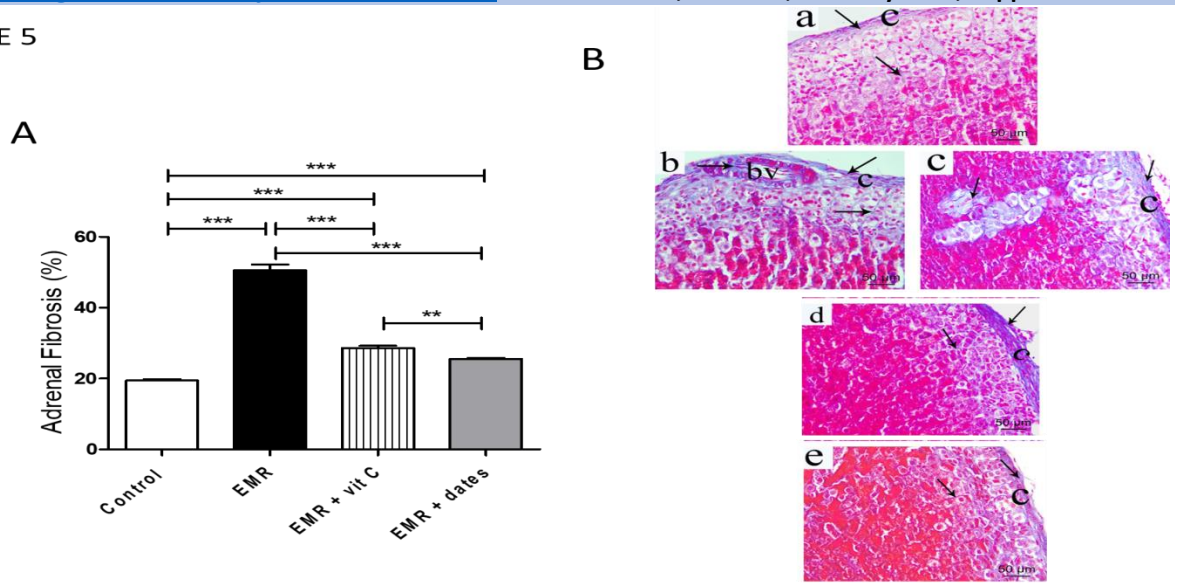


**Fig. 5: Effect of vitamin C and date palm fruits on mobile phone EMR-induced adrenal gland fibrosis.** (A) Graphical presentation of percentage of adrenal fibrosis. (B) a photomicrograph of adrenal gland stained with Mallory's trichrome stain at a magnification of X400. Rats were exposed to mobile phone electromagnetic radiations (EMR) for 1 hour per day for 4 weeks. Rats were divided into 4 groups: control normal (a), EMR (b, c), EMR+ vitamin C (d) (100 mg/kg orally) and EMR+ date palm fruit groups (e). Groups were analyzed using one-way ANOVA and post-hoc Tukey test. All values were shown as mean ± SE. (n= 3). * P < 0.05, ** P < 0.01, and *** P < 0.001.

FIGURE 6

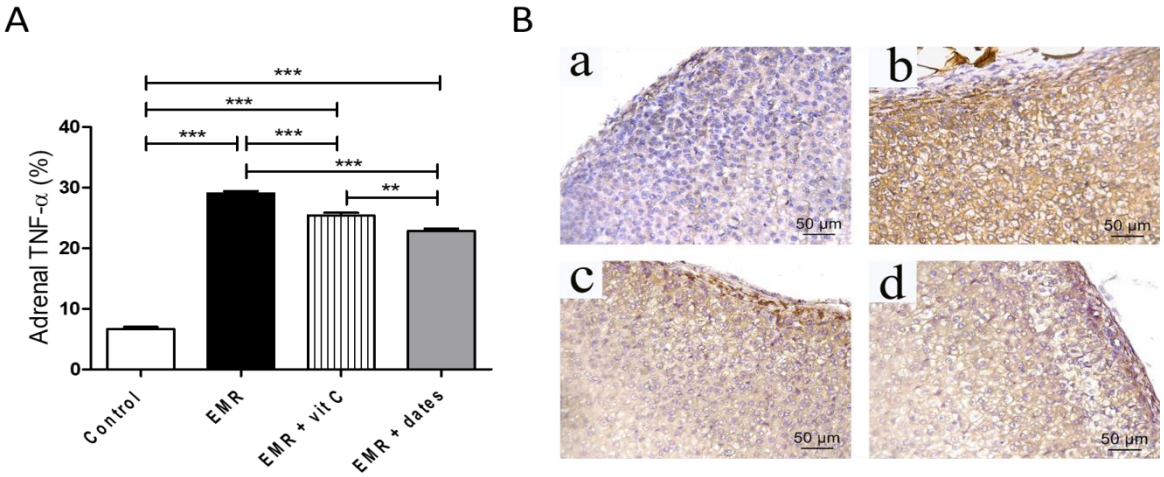


**Fig. 6. Effect of vitamin C and date palm fruits on mobile phone EMR-induced adrenal gland inflammation.** (A) Graphical presentation of percentage of TNF-α immunopositively stained cells (brown color staining). (B) a photomicrograph of Immunohistochemical staining of the adrenal gland stained for Tumor Necrosis Factor alpha at magnification of X 1000. Rats were exposed to mobile phone electromagnetic radiations (EMR) for 1 hour per day for 4 weeks. Rats were divided into 4 groups: control normal (a), EMR (b), EMR+ vitamin C (c) (100 mg/kg orally) and EMR+ date palm fruit groups (d). Groups were analyzed using one-way ANOVA and post-hoc Tukey test. All values were shown as mean ± SE. (n= 3). * P < 0.05, ** P < 0.01, and *** P < 0.001.

## DISCUSSION

L-ascorbic acid (**2**)[19] and its isomer (**3**), sinapic acid (**13**) and isoferulic acid (**20**) [23], iso(citric) acid (**4**) [24], protocatechuic acid (**6**) [25], *p*-hydroxy benzoic acid (**7**) [26], *p*-coumaric acid (**10**) [27], syringic acid (**11**), ferulic acid (**14**) [28], and caffeic acid (**12**) [29] were identified in the date palm fruit as reported previously.

Two compounds (**5** & **8**) that exhibited the diagnostic product ion at $[M-H]^-$ at *m/z* 497

revealed common daughter ions at *m/z* 335, 179, and 161. Compound **5** ($R_t$ 1.06 min) was tentatively identified as caffeoyl shikimic acid hexoside from the $ESI^-$ mass data and the presence of daughter ions at *m/z* 341 $[M-H-156]^-$, corresponding to the loss of shikimic acid moiety, and at *m/z* 335 $[M-H-162]^-$, corresponding to the loss of a hexose moiety in addition to the early retention time ($R_t$ = 1.06 min) (i.e., highly polar due to the presence of sugar moiety) [30]. Similarly, compound **8** ($R_t$ 1.58 min) was identified as di-caffeoyl shikimic acid as its $MS^2$ ions at *m/z* 335 $[M-H-162]^-$, corresponding to the loss of caffeoyl moiety, and a low intense peak for caffeic acid at *m/z* 179 $[M-H-162-156]^-$, corresponding to the loss of additional shikimic acid moiety. This phenolic molecule has two caffeoyl moieties. Di-caffeoyl shikimic acid was reported for the first time in date palm fruits [27]. According to a previous study, this phenolic acid derivative has already been found in two Tunisian cultivars [30].

In the present study, caffeoyl shikimic acid (**9**) ($[M-H]^-$ at *m/z* 335) was detected and identified. It is fragmented to caffeic acid, which was indicated by a low intense peak at *m/z* 179 because of the loss of shikimic acid moiety (156 Da), followed by caffeic acid decarboxylation that was indicated by the daughter ion at *m/z* 135 [27].

Several date varieties from various geographical origins produce caffeoyl shikimic acid and its isomers. Caffeoyl shikimic acid produced by *P. dactylifera* was successfully isolated and identified for the first time in 1963 as dactyliferic acid [30].

Seven flavonoid aglycones were detected in the *P. dactylifera* aqueous fraction based on comparison with previous literatures as 3,7-dimethylquercetin (**15**) [31], (+)-catechin (**22**) and its isomer (−)-epicatechin (**24**), quercetin (**26**), apigenin **(29)** [26], luteolin (**27**), and chrysoeriol (**28**) [23].

One compound with a pseudomolecular ion $[M-H]^-$ at *m/z* 609 was detected and annotated as rutin (quercetin-3-*O*-rutinoside) (**18**) with the $MS^2$ daughter ion peak at *m/z* 301 for quercetin aglycone after the loss of rutinosyl moiety $[M-H-308]^-$ [25].

Three fatty acids, including (−)-pinellic acid (**16**) [26], trihydroxy-octadecadienoic acid (**23**) [31], and oleic acid (**25**) [29] were identified as previously published.

Other compounds were also detected in the aqueous fraction of *P. dactylifera*, such as sucrose (**1**), the sugar alcohol hexitol (**17**), the acyclic diterpene alcohol phytol (**19**), and cyanidin-3-*O*-hexoside (**21**).

Sucrose (**1**) has pseudomolecular ion at *m/z* 341 $[M-H]^-$, $MS^2$ at *m/z* 179 $[M-H-hex.]^-$, indicating the neutral loss of the hexose moiety of the sucrose molecule) [28].

Additionally, compound (**21**) was proposed to be cyanidin 3-*O*-hexoside ($[M+H]^+$ at *m/z* 449) and the presence of fragment ion at *m/z* 287 $[M+H-162]^+$, indicating cyanidin and the neutral loss of the hexose moiety [19]. **Fig. 2** shows that (+)-catechin, cyanidin 3-*O*-hexoside, ascorbic acid, (−)-epicatechin, and apigenin were represented as the major compounds in the spectrum (in the positive mode), whereas ascorbic acid, (iso)citric acid, sucrose, caffeoyl shikimic acid hexoside, ferulic acid, rutin, quercetin, and luteolin were represented as the major compounds in the spectrum (in the negative mode).

It has been documented that EMR induces histopathological changes in the adrenal gland [32], which has increased the research focus on developing new methods to alleviate EMR-induced tissue damage. In the present study, we explored the date palm fruit as a cytoprotective agent for adrenal gland in rats.

In our experiment, Wistar albino rats exposed to mobile phone radiation (1 h/day for 4 weeks) showed significant increases in the levels of MDA, a marker of oxidative stress; 8-OHdG, a marker of oxidative DNA damage [33]; and caspase 3, a marker of cell apoptosis, and significant decreases in the levels of SOD, a marker of antioxidant activity, compared with rats in the control group. Moreover, the EMR-exposed rats showed hypertrophy of the adrenal gland manifested by significant thickening of the ZF layer with significantly increased adrenal collagen fibre deposition. Additionally, adrenal localization of TNF-α, an inflammatory cytokine, was significantly elevated, indicating inflammatory reaction in response to radiation. These results suggest that 1 h/day exposure to mobile phone EMR is sufficient to induce adrenal tissue damage and cell apoptosis.

Our findings are consistent with those previously reported who demonstrated increased MDA and reduced SOD levels in rat brain, liver, kidneys, and myocardial tissues

after exposure to cell phone radiation, confirming that the detrimental role of EMR is largely due to oxidative stress. Moreover, mobile phone EMR significantly increased endometrial oxidative damage and apoptosis [9] [34]. However, no significant changes in MDA and SOD activity were found in brain samples after 4 weeks of exposure to EMR in Wistar albino rats [35]. These contradictory results can be explained by the different duration of exposure to EMR. In the study of Shehu et al., the rats were exposed to EMR for only 10 min/day, suggesting that EMR-induced tissue damage is time-dependent. Similarly, Shahabi et al. found significant increases in adrenal gland thickness after exposure to mobile radiation [32]. Previous studies also demonstrated a combined significant increase in the levels of oxidative stress markers, apoptosis, DNA damage, and TNF-α in the rat brain [36] and adrenal glands [32] after exposure to mobile phone radiation.

TNF-α is an important proinflammatory cytokine, and its receptor is associated with the induction of other cytokines, cell survival, proliferation, and differentiation or cell death. It plays an important role in the regulation of the HPA axis. TNF-α may also play a vital role in normal human adrenal physiology [37]. Mikhaylova et al. confirmed that TNF-α exhibits potent regulatory effects on corticosteroid production and apoptosis in adrenocortical cells [38]. Death induced by TNF-α is most tightly organized by the nuclear factor kappa light chain enhancer of activated B cells (NF-κB). The principal mechanism underlying apoptosis is either the stimulation of DNA single-strand breaks or the triggering of TNF-α. Under the effect of DNA damage, TNF-α has been confirmed to activate the apoptotic pathway leading to cell death [39] [40].

The present study demonstrated that rats exposed to cell phone radiation and concomitantly treated with vitamin C showed significant reductions in oxidative stress, DNA damage, apoptosis, inflammation, and fibrous tissue deposition in the adrenal glands compared with rats in the EMR group.

Vitamin C is a potent natural oxidative scavenger. Previous research has confirmed that vitamin C can ameliorate mobile phone radiation-induced histopathological changes and reduce TNF-α levels in the rat spleen [41].

Interestingly, concomitant exposure to EMR with the addition of the date palm fruit to rat food reduced all the manifestations of adrenal damage. The prophylactic effects of date palm fruit were more significant than those of vitamin C. These findings are consistent with previous studies that reported that date palm fruit extract could significantly reduce the levels of oxidative stress markers and increase antioxidant activity in liver and kidney injuries [17]. Our results are also in accordance with those reported by Attia et al. who confirmed that date palm fruit extract can prevent both oxidative stress and DNA damage in case of hepatotoxicity [42]. A more interesting study confirmed that date palm fruit extract can be a potent anticancer agent in the case of pancreatic cancer because of its antifibrotic effect [13].

The synergistic effects of phenolic compounds (caffeic acid, ferulic acid, luteolin, rutin, and quercetin) identified in the date fruit may be responsible for the potent anti-inflammatory activity due to inhibition of key enzymes associated with the inflammatory process or inhibition of the production of proinflammatory cytokines such as TNF-α [43,44] or because of the increase in the levels of plasma antioxidants such as vitamins C, E, A, and $\beta$-carotene and decrease in the levels of lipid peroxides or by targeting ROS and prostaglandins, which are involved in the late phase of acute inflammation and pain or by the inhibition of immune cell infiltration to the inflammation site [18,45].

Anti-inflammatory drugs have the capacity to cause alterations in cancer cells, enhance apoptosis, and reduce migration. Natural phenolics may possess anti-inflammatory characteristics and play a role in cancer prevention through a variety of fundamental cellular pathways [46].

## CONCLUSION

Considering previous findings, this study confirms that the date palm fruit can provide a safe, affordable, and effective approach to alleviate the hazardous effects of chronic exposure to stressors such as cell phone radiation.

Additional research on the fractionation, separation, identification, and quantitative determination of bioactive compounds (particularly minor compounds), their modes of action, and bioavailability and clinical

studies, in combination with advanced technological procedures, should represent a significant step forward in introducing new opportunities for the development and innovative knowledge on the functional and medicinal use of palms, with significant beneficial health effects.

**Funding**

This research did not receive any grant from any funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Author contributions:**

All authors made considerable contributions to the manuscript. RMSM, MMAA and MAE designed the study. All authors helped in the methodology. RMSM, MMAA, MAE, MME and HSA interpreted the results. RMSM, MMAA, MAE and SKYA wrote the manuscript. All authors revised the manuscript to the present form and approved it for publication.

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## TO CITE

Mohamed, R., Abdul Rahman, M., Ahmed El-Sayed, M., Mostafa Elsayed, M., Sabry Ahmed, H., Ali, S. Metabolite Profiling of Date Palm Fruit (Phoenix dactylifera L.) And Its Cytoprotective Effects Versus Vitamin C Against Mobile Phone Radiation-Induced Adrenal Gland Damage In Rats. *Zagazig University Medical Journal*, 2024; (328-341): -. doi: 10.21608/zumj.2022.139449.2569