IJPSR (2019), Volume 10, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 October 2018; received in revised form, 16 October 2019; accepted, 20 October 2019; published 01 November 2019

THE POTENTIAL PROTECTIVE EFFECT OF ROASTED DATE PALM CAKE EXTRACTS (*PHOENIX DACTYLIFERA* L.) AGAINST NICKEL CHLORIDE-INDUCED INFERTILITY IN MALE MICE

Salah Elnaeem M. Eltom [*1], Mugahid A. Mobark [2], Mohsen Saleh Al-Omer [1], Hamdoon A. Mohammed [1, 3], Eiman M. E. Agabein [4], Mustafa H. Alqambar [5] and Mansour Alhawsawi [5]

Department of Medicinal Chemistry and Pharmacognosy [1], Department of Pharmacy Practice [2], Department of Histology, College of Medicine [4], College of Pharmacy [5], Qassim University, KSA.
Department of Pharmacognosy [3], Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

Keywords:

Antioxidant activity, Date palm cake, Infertility, *Phoenix dactylifera* L., Total phenols

Correspondence to Author:
Salah Elnaeem M. Eltom

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, KSA.

E-mail: salaheltom9999@gmail.com

ABSTRACT: The powder date palm cake is sold in coffee and confectionary shops in the central region of the Kingdom of Saudi Arabia, where it is used as a hot drink in the form of decoction. It is alleged by users in the local community in Saudi Arabia to improve fertility. The date palm cake is the roasted grounded seeds of the date palm (*Phoenix dactylifera* L.). The objective of this study is to evaluate the potential protective effect of the date palm extracts against nickel chloride-induced infertility in male mice. The effects of nickel compounds on reproduction in rodent models are well documented. The method adopted is the injection of nickel chloride (10 mg/kg) intra-peritoneal to induce infertility in male mice. The chloroform and ethyl acetate extracts were used to assess their protective effects. Sperm abnormalities and testicular histopathology were evaluated. The results showed that the administration of chloroform extract enhanced the sperm count and reduced sperm abnormalities. Moreover, the abnormalities induced by nickel chloride were restored to a great extent compared to that of ethyl acetate extract. The chloroform extract also showed the highest total phenol and antioxidant activity, besides that it showed a reduction of empty spaces and decreased the germ epithelium distortion effects produced by the nickel chloride, however, the large dose of ethyl acetate induce mortality. This study partly aligned with the folk use of the date cake as a drink.

INTRODUCTION: Infertility is a worldwide problem and can be defined as the inability to achieve conception after one year of regular unprotected intercourse [1]. About 70 million couples around the world are suffering from infertility, and most of them are living in developing countries [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(11).4988-94

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(11).4988-94

Nickel is a metallic compound that is commonly used in various daily used substances such as kitchen utensils. Nickel is also an important component found in the cigarette. Exposure to nickel can occur through various routes such as food, water, and inhalation.

Some studies suggest an over-exposure of nickel can produce several health complications such as gastrointestinal and respiratory diseases and can even result in cancers of various origins [3]. The deleterious effects of nickel exposure on the reproductive system are also reported in the literature and are found to affect the fertility in both

males and females [4]. One of the main causes that contribute to male infertility is the reactive oxygen species (ROS) that were reported for their damaging effect for the spermatozoa. The polyunsaturated fatty acid membrane of the spermatozoa is highly susceptible to damage by ROS.

Accordingly, the antioxidant enzymes such as superoxide dismutase and glutathione peroxidases [5], in addition to non-enzymatic antioxidant molecules such as ascorbic acid and vitamin E are present in seminal fluid and play an important role and protecting sperms against oxidative damage and improve their quality and motility [6, 7]. The oxidative stress produced by nickel chloride induces the testicular male germ cells impairment leading to testicular dysfunction and infertility [8]. Furthermore, exogenous antioxidants could protect sperms during their maturation and migration processes [6]. The qualitative and quantitative analyses of the sperms are an established technique to detect the damages that are induced on the male reproductive organs [9].

Date palm (*Phoenix dactylifera*) is a tree that grows in hot climatic places of Middle East, Asia and Africa [10]. Date palm is a source of energy; it contains vital vitamins such as riboflavin, biotin, thiamine and folic acid and also antioxidants like ascorbic acid and carotenoids [11]. The worldwide waste of date palm production about two million tons per year [10]. The information accumulated in the past four decades suggested that dates have various medicinal properties like anti-cancer, anti-hyperlipidemic, gastroprotective, nephroprotective and hepatoprotective effects thus indicating its importance in the healthy human diet [11, 12]. The date seed oils were also reported to protect the spermatozoa against oxidative stress induced by hydrogen peroxide and enhances the sperms mobility *in-vitro* [13].

The date palm cake is a seed of the date palm that was roasted and grounded. It is commercially available as a powder that is meant to be used as a hot drink [14, 15], and has been alleged by users to improve fertility. However, in the literature, there is limited data about the beneficial effects of date palm cake in the treatment of reproductive health issues induced by metallic ions such as nickel. Hence, the present study was planned to extract the active ingredients of the date palm cake, measure the best extract accounted for the total phenols and antioxidant activity and evaluated their role on the nickel chloride induced reproductive damages in male mice. We embarked first for the determination of the total phenols and the anti-oxidant activity of the powder seed cake, although this activity is well established for the date flesh or the seed [11], at present, there is no published work done on the roasted date palm cake.

MATERIALS AND METHODS:

Plant Materials and Extraction Method: The roasted date palm seeds cake was purchased from the local market in Medina, Saudi Arabia. Amount of 1 kg of the cake powder was subjected to extract three times with *n*-hexane (1 liter) by cold maceration for 24 h, and the combined *n*-hexane extracts were filtrated and evaporated to dryness under vacuum at 40 °C. The residue left after *n*-hexane extraction was then extracted with the same manner as *n*-hexane by chloroform, ethyl acetate, and ethanol in succession. The dried extracts were then stored in the -20 °C fridge for further experimental work.

Determination of Total Phenolic Content: Total phenolic content of different extracts was determined using Folin Ciocalteu method described by Kaur and Kapoor [16]. In brief, 1 ml of different crude extracts (100 µg/mL) were mixed with 2.5 ml of Folin Ciocalteu reagent (diluted with distilled water 10% v/v) for 5 min; 2.5 ml of 20% (w/v) sodium carbonate was added, and the mixture was allowed to stand for 60 min in the dark. The absorbance was measured at the UV-Vis absorbance at 760 nm using JASCO UV-Visible spectrophotometer (Model V-630, JASCO Co., Japan). The analysis was done in triplicates. The total phenolic content was calculated from the calibration curve of gallic acid, and the result is expressed in mg of gallic acid equivalent (GAE) per 100 g of dry extract **Table 1**.

Determination of Free Radical Scavenging Activity by DPPH Method: The scavenging activity of the extracts was estimated by using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) as a free radical model according to the method described by Mohammed Hosny [17] with some modifications.

A stock standard solution of DPPH (1 mg/mL) was prepared by dissolving 25 mg of DPPH in 25 ml methanol. A 2.5 ml of an aliquot of each extract in different concentrations (5-50 mg/mL) were mixed with 400 µl of (DPPH) in absolute methanol. Antioxidant compounds, quercetin, and trolox ((±)-6- Hydroxy-2, 5, 7, 8-tetramethyl chromane-2-carboxylic acid) were used as standards for comparison. The mixture was vortexed thoroughly for 5 min and left in the dark at room temperature for 20 min. The mixture was measured spectrophotometrically at 517 nm to measure the reduction in DPPH color intensity. The scavenging activity of the extracts as well as standard controls was calculated in **Table 1**, by the following equation:

Scavenging activity = Absorbance of sample / Control × 100

Animals Experimentation:

Animals: Swiss albino mice (male) weighing 12-30 g was used in the experiment. The rats were kindly provided from the animal house, Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Saudi Arabia. The animals were housed in polyacrylic cages and maintained at room temperature (21-25 °C) and relative humidity of 45-65% with a controlled light-dark cycle. The mice were housed in groups of about six per cage and acclimatized for at least five days before the experiment.

The Institutional Animal Ethics Committee approved the experimental procedure, College of Pharmacy, Qassim University, Saudi Arabia Ethical research committee approval number – 2019-CP-3 and the care of laboratory animals was carried out as per the Guide for the Care and Use of Laboratory Animals (National Research Council) [18]. The number of mice randomly divided into six groups (n=6) [19, 20]. The first group served as a normal control that received vehicle (0.5% w/v of carboxymethyl cellulose). The second group served as a positive control that received nickel chloride ($NiCl_2$ - 10 mg/kg, i.p). Third and fourth groups were served as a treated group that received $NiCl_2$ with low and high doses of chloroform extract at 250 and 500 mg/kg, 10 days daily per oral. While the fifth and sixth groups were received $NiCl_2$ with ethyl acetate extract at 250 and 500 mg/kg, 10 days daily per oral for low and high doses respectively.

Induction of Reproductive Damages in Male Mice: The amount of 10 mg/kg of the nickel chloride was dissolved in distilled water and injected intra-peritoneal to the animals. The reproductive damages were measured by estimating the total sperm count and sperm shape abnormalities as per the procedures mentioned by Mohanty P. K. in 1987. [19]

Preparation of the Oral Dosage Form from the Extracts: Corn oil was used as a vehicle for preparing the dosage forms of the chloroform and ethyl acetate extracts of date palm cake to be administered by oral route in mice [21]. One daily oral dose of 250 and 500 mg/kg of the prepared extracts was fed to the mice by oral route after 72h of nickel chloride treatment of the animals. The mice were treated by the extracts for 10 days, and on the 11th day, the assessing parameters were studied after sacrificing the animals under light-diethyl ether anesthesia.

Testis and Sperm Assessment:

Sperm Count Test: The total sperm count was done as per the procedure described by D'Souza [22]. Using Neubauer's chamber for counting the sperms and expressed as million per ml **Table 2**.

Sperm Shape Abnormality Test: The staining solution of sperms was smeared on a clean glass slide. The air-dried smear was observed under 10X magnification using a binocular microscope to screen different types of sperm abnormalities such as headless, tailless, broken and curve shaped as described by Wyrobek [23]. We count the abnormalities in 200 sperm, and the results were expressed as percentage relatively representative for the whole sperm **Table 2**.

Histological Evaluation of Testis: The testis from each animal were sliced and fixed in 10% formalin and left for 24 h for proper penetration and fixation of tissue. The formalin-fixed testis was further processed using an automated tissue processor machine (Leica TP1020), and paraffin embedded sections were prepared. Serial 5-µm sections were prepared using microtome (Leica RM2245) and stained by hematoxylin and eosin stain. All tissue sections were examined by a light microscope (Olympus BX41) using 4X, 10X and 40X magnifications and digital images were taken.

Statistical Analysis of Results: The sperm counts were expressed as mean ± Standard Error of Mean. One Way ANOVA test was used to compare the mean of sperms count between different groups. The f-ratio value was found to be 133.08582. The P- value is <0.00001, and the result was considered significant at P<0.05.

RESULTS AND DISCUSSION:

Total Phenols and Antioxidant Activity: Phenolic constituents, as well as antioxidant potency, is an essential factor for the anti-infertility activity of the date palm [12, 24]. The phenolic contents and antioxidant activity of the date palm fruits and seeds are well established in the literature [12, 25, 26]. Therefore, it was necessary to ensure that the roasting procedure of the date palm cake does not affect the phenolic constituents or at least still containing a measurable amount of the total phenol with antioxidant potency. The results of total phenols and antioxidant activity showed in table1 confirmed that the roasted date palm cake seeds retained their phenolic constituents and antioxidant capacity.

TABLE 1: TOTAL PHENOLS AND ANTIOXIDANT ACTIVITY OF THE ROASTED DATE PALM EXTRACTS

Extracts and standard antioxidant controls	Total phenols content (mg/100 g GAE)	DPPH scavenging activity* (10 mg/mL)
Hexane extract	180.32 ± 2.05	51.63 ± 0.02
Chloroform extract	645.39 ± 1.66	85.02 ± 1.03
Ethyl acetate	417.12 ± 3.08	67.52 ± 1.81
Ethanol extract	243.53 ± 0.99	42.57 ± 3.44
Trolox	NA	25.49 ± 1.70
Quercetin	NA	93.04 ± 1.62

* Calculated as a percentage of reduction in the DPPH color at 10 mg/mL sample concentration.

The results demonstrated in **Table 1** indicate that chloroform and ethyl acetate extracts having the highest quantity of the phenols among other extracts with 645 and 417 mg GAE per 100 g of the dried extracts, respectively. The antioxidant activity of the extract expressed as DPPH scavenging power at 10 mg/mL was coupled with the result of the total phenol contents as chloroform and ethyl acetate extracts also showed the highest antioxidant activity among all other extracts. Furthermore, chloroform extract showed scavenging power slightly less than quercetin (93%) and much more than Trolox (25%) **Table 1**.

Nickel Chloride Testicular Toxicity and Protective Effect of the Date Palm Cake Extracts: Nickel (Ni^{2+}) in the body is required in micro quantities for the regulation of homeostasis of blood and functioning of enzymes [19]; however this study showed both qualitative and quantitative effect on male reproductive cells of mice. The administration of nickel chloride at 10 mg/kg induced reduction in the total sperm count and enhanced the sperm shape abnormalities **Table 2**. The abnormal exposure of nickel metal can complicate the host physiology by forming a bonding with DNA of the nucleus. The interaction between the nuclear component and nickel results in cardiovascular, respiratory, reproductive and carcinogenic complications [3]. The complications associated with the reproductive cells are more serious because it is not only affecting the fertility in the present generation but may be transferred to future progeny in the form of teratogenicity and mutagenicities [4].

Total Sperm Counts and Sperms Shape Abnormalities: The result of total sperms counts indicates that chloroform extract of the date palm seeds cake protect sperms against the effect of the nickel chloride. The mice that treated with nickel chloride for three days showed a reduction in sperms counts by 4×10^6/mL in comparison with the control group. Administration of the date palm cake chloroform extract at 250 mg/kg increased the sperm count to 7.5×10^6/mL. The sperms count was protected against the toxicity of nickel chloride at the concentration of 500 mg/kg of the chloroform extract.

Furthermore, the sperms number in mice treated with a high dose of chloroform increased even above the control group by 1.3×10^6/mL. In the ethyl acetate extract, the administration of 250 mg/kg had no effect on nickel chloride induced toxicity regarding sperms number, while high dose of ethyl acetate (500 mg/kg) induced mortality in mice **Table 2**. Statistical analysis using one way ANOVA test to compare between means of different groups showed that the comparison was statistically significant as the f-ratio value is 133.08582 and the P- value is <0.00001, and we considered the result was significant at P<0.05. The sperms morphology test was conducted to evaluate the influence of the chloroform and ethyl acetate

extracts on the extent of damage induced by nickel chloride. The data showed in **Table 2**, indicated that nickel chloride at 10 mg/kg produced total abnormalities in the sperm shape and the maximum anomalies found was in the tailless sperms (70%). The abnormalities were found to be increased when compared with control animals.

TABLE 2: EFFECT OF DATE PALM CAKE EXTRACTS ON THE SPERMS NUMBER AND SPERM SHAPE ABNORMALITIES INDUCED BY NICKEL CHLORIDE

S. no.	Groups	Total sperm count (10^6/mL)	% Normal sperms	Sperm abnormalities %					Total % abnormalities
				Headless	Tailless	Broken	Double head	Double tail	
1	Control	10.12 ± 0.368	97.5	1.15	1.33	0.52	-	-	2.5
2	$NiCl_2$	6.05 ± 0.099	zero	18	70	3	7.5	1.5	100
3	$CHCl_3$ extract Dose-1	7.45 ± 0.178	zero	35	48.75	1.25	13.75	1.25	100
4	$CHCl_3$ extract Dose-2	10.92 ± 0.149	20	16.25	47.5	2.5	5	8.75	80
5	EtOAc extract Dose-1	5.78 ± 0.083	2.5	35	40	13.75	5	3.75	97.5
6	EtOAc extract Dose-2	*	*	*	*	*	*	*	*

***** Animals died during experimentation. The data expresses as mean ± SEM, The P- value is <0.00001. The result is significant at P<0.05.

Besides its protective effect on sperm number, the chloroform extract at a dose of 250 mg/kg did not affect sperm shape abnormality that induced by nickel chloride. Better protection for the sperms shape abnormalities was seen in the group of mice that were treated by the high dose of chloroform extract (500 mg/kg). The high dose of the chloroform protects 20% of the sperms from nickel chloride induced abnormality. Furthermore, the percentage of the headless and double head sperms were reduced by 1.75% and 2.5% respectively, moreover, the tailless abnormality was reduced by 22.5%. The 250 mg/kg ethyl acetate extract induced protection to the sperm shape with 2.5%. Unfortunately, the same dose of ethyl acetate increases the percentage of the broken sperms by 10.75% compared to the nickel chloride group. Furthermore, the higher dose of extract (500 mg/kg) produced mortality in the animals.

Histopathological Evaluation of the Testis: The histopathological assessment of the testicular tissue was done for the control group, mice exposed to nickel chloride, mice exposed to nickel chloride and chloroform extracts at doses of 250 and 500 mg/kg and ethyl acetate extracts at a dose of 250 mg/kg. The histopathological findings showed that nickel chloride induced distortion of germ cell orientation with prominent apoptotic changes in the germ epithelium(short arrow), beside that multiple empty spaces appeared within the germ epithelium (long arrow) with evidence of increased tubular irregularity and luminization **Fig. 1-3**. This partly agreed with finding noted by Toman *et al*., 2012 and Chandel and Jain, 2014, they mentioned that the appearance of empty spaces and disorganization of the germ epithelium as effects induced by nickel chloride on testicular tissue of mice [27, 28].

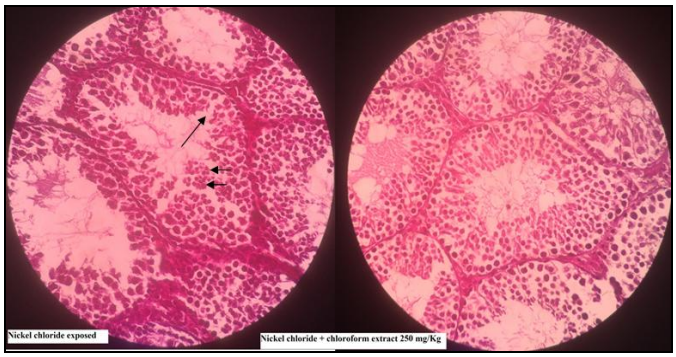

FIG. 1: THE EFFECT OF DATE PALM CAKE (CHLOROFORM EXTRACTS 250 mg/kg) ON TESTICULAR TISSUE EXPOSED TO NICKEL CHLORIDE (H & E STAIN; 40X)

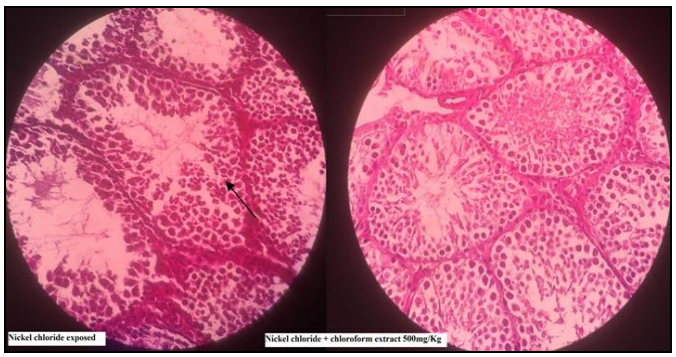

FIG. 2: THE EFFECT OF DATE PALM CAKE (CHLOROFORM EXTRACTS 500 mg/kg) ON TESTICULAR TISSUE EXPOSED TO NICKEL CHLORIDE (H & E STAIN; 40X)

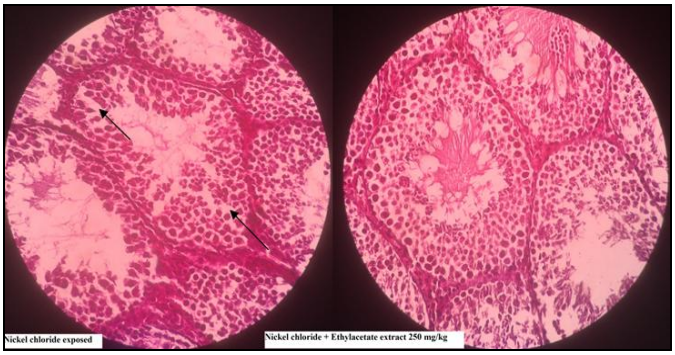

FIG. 3: THE EFFECT OF DATE PALM CAKE (ETHYL ACETATE EXTRACT 250 mg/kg) ON TESTICULAR TISSUE EXPOSED TO NICKEL CHLORIDE (H & E STAIN; 40X)

The histopathological findings from mice exposed to chloroform extracts (tested doses 250 & 500 mg/kg) reveled prominent reduction in the empty spaces within the germ epithelium with even regularity of the tubules which was more pronounced in the animal exposed to a higher dose of chloroform extract.

Besides that, the number of apoptotic and exfoliated cells was markedly reduced, and better organization and orientation of germ cells maturation was also observed. In ethyl acetate extract (250 mg/kg), the degree of germ epithelial orientation is pronounced while the effect in tubular regularity and empty spaces is less than that observed in chloroform extract.

CONCLUSION: The present study indicated that chloroform extract of date palm cake at 250 and 500 mg/kg reduced the qualitative and quantitative defects of sperms induced by the nickel chloride in tested male mice. Moreover, it showed the highest total phenol and antioxidant activity. Beside that minimization of empty spaces within tubules and reduction of apoptotic activity with the better orientation of germ, epithelium was seen in histopathological assessment of testis. The ethyl acetate extracts at low dose produced a similar but less effect, however, at a high dose produced mortality to draw a precise inference of the role of the extract on the reproductive damages.

ACKNOWLEDGEMENT: The authors would like to acknowledge the College of Pharmacy and the College of Medicine, Qassim University, KSA for their help and the facilities available without their support this work would not have been accomplished.

CONFLICT OF INTEREST: The authors confirm that this article content has no conflict of interest.

REFERENCES:

1. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R and Nygren K: International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Steril 2009; 92(5): 1520-4.
2. Ombelet W, Cooke I, Dyer S, Serour G and Devroey P: Infertility and the provision of infertility medical services in developing countries. Hum Reprod Update 2008; 14(6): 605-21.
3. Kampa M and Castanas E: Human health effects of air pollution. Environ Pollut 2008; 151(2): 362-7.
4. Duda-Chodak A and Baszczyk U: The impact of nickel on human health. Journal of Elementology 2008; 13(4): 685-93.
5. Garrido N, Meseguer M, Simon C, Pellicer A and Remohi J: Pro-oxidative and anti-oxidative imbalance in human semen and its relation with male fertility. Asian J Androl 2004; 6(1): 59-66.
6. Piomboni P, Gambera L, Serafini F, Campanella G, Morgante G and De Leo V: Sperm quality improvement after natural anti-oxidant treatment of asthenoterato-spermic men with leukocytospermia. Asian J Androl 2008; 10(2): 201-6.
7. Sikka S: Relative impact of oxidative stress on male reproductive function. Curr Med Chem 2001; 8(7): 851-62.
8. Hassan AM and Barakat IAH: Assessment of oxidative stress induced by nickel chloride and antioxidant effects of basil (*Ocimum basilicum* L.) and thyme (*Thymus vulgaris* L.). J Genet Eng Biotechnol 2008; 6(2): 29-38.
9. Creasy DM: Evaluation of testicular toxicity in safety evaluation studies: The appropriate use of spermatogenic staging. Toxicol Pathol 1997; 25(2): 119-31.
10. Besbes S, Drira L, Blecker C, Deroanne C and Attia H: Adding value to hard date (*Phoenix dactylifera* L.): Compositional, functional and sensory characteristics of date jam. Food Chem 2009; 112(2): 406-11.
11. Anjum F, Bukhat SI, El-Ghorab A, Khan M, Nadeem M and Hussain S: Phytochemical characteristics of date palm (*Phoenix dactylifera*) fruit extracts. Pak J Food Sci 2012; 22: 117-27.
12. Baliga MS, Baliga BRV, Kandathil SM, Bhat HP and Vayalil PK: A review of the chemistry and pharmacology of the date fruits (*Phoenix dactylifera* L.). Food Res Int 2011; 44(7): 1812-22.
13. Fatma BA, Nozha CF, Ines D, Hamadi A, Basma H and Leila AK: Sperm quality improvement after date seed oil *in-vitro* supplementation in spontaneous and induced oxidative stress. Asian J Androl 2009; 11(3): 393-8.
14. Rahman MS, Kasapis S, Al-Kharusi NSZ, Al-Marhubi IM and Khan AJ: Composition characterisation and thermal transition of date pits powders. J Food Eng 2007; 80(1): 1-10.
15. Selim S, Alfy SE, Al-Ruwaili M, Abdo A and Jaouni SA: Susceptibility of imipenem-resistant *Pseudomonas aeruginosa* to flavonoid glycosides of date palm (*Phoenix dactylifera* L.) tamar growing in Al Madinah, Saudi Arabia. African Journal of biotechnology 2012; 11(2): 416-22.

16. Kaur C and Kapoor HC: Anti-oxidant activity and total phenolic content of some Asian vegetables. Int J Food Sci Technol 2002; 37(2): 153-61.
17. Hosny M, Johnson HA, Ueltschy AK and Rosazza JPN: Oxidation, reduction, and methylation of carnosic acid by Nocardia. J Nat Prod 2002; 65(9): 1266-9.
18. National Research Council. Guide for the care and use of laboratory animals. National Academies Press 2010.
19. Mohanty PK: Cytotoxic effect of nickel chloride on the somatic chromosomes of Swiss albino mice *Mus muscu*lus. Curr Sci 1987; 56(22): 1154-7.
20. Jahromi A, Rasooli R, Kamali Y, Ahmadi N and Sattari E: Short-term effects of date palm extract (*Phoenix dactylifera*) on ischemia/reperfusion injury induced by testicular torsion/detorsion in rats. Pharmacognosy Res 2017; 9(1): 69.
21. Gad SC, Cassidy CD, Aubert N, Spainhour B and Robbe H: Nonclinical vehicle use in studies by multiple routes in multiple species. Int J Toxicol 2006; 25(6): 499-521.
22. Leong CT, D'Souza UJA, Iqbal M and Mustapha ZA: Lipid peroxidation and decline in antioxidant status as one of the toxicity measures of diazinon in the testis. Redox Rep 2013; 18(4): 155-64.
23. Wyrobek AJ: The induction of sperm-shape abnormalities in mice and humans. Chem Mutagen 1978; 5: 257-85.
24. Rahmani AH, Aly SM, Ali H, Babiker AY and Srikar S: Therapeutic effects of date fruits (*Phoenix dactylifera*) in the prevention of diseases *via* modulation of anti-inflammatory, anti-oxidant and anti-tumor activity. Int J Clin Exp Med 2014; 7(3): 483.
25. Ardekani MRS, Khanavi M, Hajimahmoodi M, Jahangiri M and Hadjiakhoondi A: Comparison of antioxidant activity and total phenol contents of some date seed varieties from Iran. Iran J Pharm Res 2010; 9(2): 141.
26. Mohamed DA and Al-Okbi SY: *In-vivo* evaluation of antioxidant and anti-inflammatory activity of different extracts of date fruits in adjuvant arthritis. Pol J Food Nutr Sci 2004; 13(54): 397-4-02.
27. Chandel M and Jain G: Toxic effects of transition metals on male reproductive system: A review. J Environ Occup Sci 2014; 3(4): 204.
28. Toman R, Massányi P, Adamkovicova M, Lukac N, Cabaj M and Martiniakova M: Quantitative histological analysis of the mouse testis after the long-term administration of nickel in the feed. J Environ Sci Heal Part A 2012; 47(9): 1272-9.

How to cite this article:
Eltom SEM, Mobark MA, Al-Omer MS, Mohammed HA, Agabein EME, Alqambar MH and Alhawsawi M: The potential protective effect of roasted date palm cake extracts (*Phoenix dactylifera* L.) against nickel chloride-induced infertility in male mice. Int J Pharm Sci & Res 2019; 10(11): 4988-94. doi: 10.13040/IJPSR.0975-8232.10(11).4988-94.