Comparative Study of Antioxidant and Anti-Inflammatory Activities of Leaf Extract from Algerian *Phoenix Dactylifera* L Obtained by Different Methods

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ABSTRACT

The present study was designed to quantify the phytochemical composition, evaluation of antioxidant and anti-inflammatory activity of Phoenix dactylifera L leaf extract recovered by ultrasonic-assisted extraction (UAE), Soxhlet extraction (SE) and maceration extraction (CE), which has never been comprehensively investigated before. UAE showed the highest amount of total phenolics (625.17 ± 11.82 mg GAE /g) and revealed significant antioxidant activities (266.12±8.75 µg EDTA/g for the ferrous ion-chelating activity and 78.27±1.26 µg/ml for HOCl). From results, we conclude that there is a strong correlation between phenolic content, antioxidant indicating phenolics are the major compounds for these biological activities. Moreover, similar results observed for the anti-inflammatory activity that the potential of inhibition of nitrite oxide decreased in the following order: UAE> SE>CE. This study shows that Phoenix dactylifera L extracts contain anti-inflammatory and antioxidant substances and should be considered for use in pharmaceutical products for the treatment of several diseases. The advantage of the ultrasound, compared to the Soxhlet extraction and maceration extraction for polyphenols was obtained with a lower solvent consumption and a shorter extraction time

Key Words: Phoenix dactylifera L, phenolic content, metal chelating, Hypochlorous acid scavenging, technique extraction.

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INTRODUCTION

For the human health, the free radicals are an important factor with simple reason of their action in specific metabolic processes, the signal of intercellular and destroying of pathogenic microbes, and they are produced always intracellular as part of normal cellular function [1]. Although free radicals can explain the pathology of many toxicities and several diseases, they are the principal role in specific disorders continues to be difficult to determine. For example, the same free radical-mediated changes that may cause injury also occur secondary to that injury [2]. The higher levels of the dietary xenobiotic result in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [3,4]. ROS and RNS are responsible for the oxidative stress in different

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pathophysiological conditions. In addition, Oxidative stress on protein can be both irreversible and reversible protein oxidative modifications. Irreversible modifications mainly include protein carbonylation and tyrosine nitration [5,6,7].

The oxidative stress can be neutralized and potentially by enhancing cellular defenses in the form of antioxidants, some compounds act as in vivo antioxidants by raising the levels of endogenous antioxidant defenses [8.9.10]. Two types of antioxidant are existed: natural antioxidants such as polyphenols and synthetic antioxidant.

The plant is rich in phenolic compounds, the type and content of polyphenols differ substantially between different parts of the plant. Despite the fact that most foods containing phenolic compounds, they may be known best for the one with the highest proportion. Polyphenols are spliced into family groups based on their chemical structure [11,12,13]. There are many classes of polyphenols, but the major classes are the phenolic acids, flavonoids, stilbenes, and lignans [14]. Dietary phenolics are strong antioxidants in vitro, being able to neutralize free radicals by donating an electron or hydrogen atom to a wide range of reactive oxygen, nitrogen and chlorine species [15]. Polyphenols as metal chelators can directly scavenge Fe^{3+} reduction thereby reducing the production of reactive $OH^{\bullet}$ of Fenton reaction [16].

Theses compounds possess many characteristic therapeutic, such as antioxidant, antimutagenic, antiallergenic, antimicrobial effects [17], anticarcinogenic, antiatherogenic [18,19,20]. Moreover, are associated with a reduced risk of chronic inflammation, cancer and cardiovascular diseases [21,22,23]. On the other hand, the using of synthetic antioxidant, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), are extensively applied for the exhibit oxidative degradation of lipids due to their high oxidative potential. However, safety concerns regarding the use of synthetic antioxidants have increased globally and are inappropriate for chronically ill patients, and the prolonged usage of synthetic antioxidants is harmful to humans, potentially provoking the onset of degenerative diseases [24,25,26].

The date palm (*Phoenix dactylifera* L) is one of mankind's oldest cultivated plants, are an Arecales species widely distributed in North Africa and Southeast Asia [27]. *Phoenix dactylifera* L. is an evergreen tree and can grow in the high region of course in well-drained soils [28]. This tree involves many varieties, depending on the shape and the organoleptic properties of the fruits. It is estimated that there are more than 600 varieties of this species worldwide. The harvesting period of the fruits is spread out over dry months from July to October. Date palm or *Phoenix Dactylifera* L fruits are reported in several studies to have many medicinal properties, such as gastroprotective, hepato-protective, nephroprotective, immune-stimulant, antimutagenic, anticancer, anti-inflammatory, antioxidant, and anti-hyperglycemia activities [29]. Different extraction techniques, such as maceration, Soxhlet, and ultrasonic extraction, are widely used for obtaining extractive substances from different plant parts. The aim of present works is to study a phytochemical screening, in vitro antioxidant and anti-inflammatory activities of the acetone extracts of *Phoenix dactylifera* L obtained by different technique extraction.

MATERIALS AND METHODS

Origin of plant material

The leaves of *Phoenix dactylifera* L were collected in Mars 2016 from southeast of Algeria, El Oued (33° 07" 00" N 7° 11' 00" E). The leaves then separated from each other, washed and dried at room temperature. The plant material was ground to a powder and stored in the dark at room temperature before use.

Preparation of the extracts

Maceration or Classical extraction (CE)

Plant material weighing 50 g was extracted by maceration of 70% acetone (350 ml) for 48 h at room temperature. After filtration, the solvent was evaporated was rotary evaporated under vacuum at 45 ◦C, filtered and then stored at +4 °C. The extract obtained was used in antioxidant measurements.

Ultrasonic-assisted extraction (UAE)

Ultrasonic aid waves were used for accelerated extraction. Fifty grams (50 g) leaves were then extracted with acetone/water (350 ml: 70/30%) for 60 min. The extract was filtered (Whatman paper) the solids were washed with an additional 60 ml of 70% acetone. After, the filtrate evaporated to dryness under reduced pressure. The resulting solution was kept in a refrigerator at 4 °C

Soxhlet extraction (SE)

Fifty grams of powdered were subjected continuously Soxhlet extraction using 350 ml of 70% acetone for 6 h. The extracts concentrated under vacuum at 45 °C by using a rotary evaporator to obtain 70% acetone extract. Extracts were stored at +4 °C.

Determination of total phenolic content (TPC)

The total phenolic contents in three extracts were determined by the Folin-Ciocalteu method with some modification [30]. The reaction constituted of acetone extracts (400 µl) and 2 ml of (10%) Folin-Ciocalteu reagent. 1.6 ml of sodium carbonate solution (7.5%) was added to the mixture after 5 minutes. The mixture incubated for 30 min at ambient temperature. Absorbance was measured at 765 nm using spectrophotometer (Shimadzu UV-1800, Japan). Total phenolic content was quantification against gallic acid and expressed as milligrams of gallic acid equivalents (GAE) per gram of dry weight.

Determination of total flavonoid content (TFC)

The total flavonoid content in extracts was determined by spectrophotometric method [31]. The reaction mixture comprised 500 µl of extract, 500 µl of aluminium chloride ($AlCl_3$,10%) and 500 µl of potassium acetate solutions (1 M). After 30 min

incubation at room temperature. The absorbance values of the reaction mixtures were determined at 415 nm after 10 min duration against a blank. A standard curve was plotted using different concentrations of quercetin (0–150 µg/mL) and the concentration of total flavonoids was calculated as quercetin equivalents in mg per g of dry sample.

Determination of condensed tannin content (CTC)

Condensed tannin content was determined using the method of vanillin assay [32]. Firstly 1 ml acetone solution of samples or catechin was added to 5 ml vanillin acetone solution (4%), followed by 5ml concentrated HCl. The mixture was allowed to stand for 20 min and the absorbance was measured at 500 nm using a spectrophotometer (Shimadzu UV-1800, Japan). Results were expressed in mg of catechin equivalents/g of dry extract (mg CE/g). All samples were analyzed at least three times.

Antioxidant activity

Ferrous ion chelating ability assay

The chelating activity of leaves extracts from *Phoenix dactylifera* L for ferrous ions Fe^{2+} was measured by spectrophotometric methods [33]. 0.5 ml of extract at different concentrations, 1.6 ml of deionized water, $FeCl_2$ (2 mM) 0.05 ml and 0.1 ml ferrozine (5 mM) were added to the mixture. After 10 min at room temperature, the absorbance of the Fe^{2+}-ferrozine complex was measured at 562 nm. EDTA was used as positive control. The metal chelation activity was calculated using the following equation: Metal chelating activity (%) = $[(A_{control} - A_{sample}) / A_{control}] \times 100$. Where $A_{Control}$ is the absorbance of control devoid of the sample and A_{Sample} is the absorbance of the sample in the presence of the chelator. The extract concentration providing 50% metal chelating activity was calculated from the graph of Fe^{2+} chelating effects percentage against extract concentration.

Hypochlorous acid scavenging

The antioxidant properties of extracts against Hypochlorous acid (HOCl) were estimated according to the methods of Herza et al [34]. A solution of adjusting pH of a 10% (v/v) solution of NaOCl to 6.2 ml added to 0.6 M H_2SO_4 and the concentration of HOCl was determined by measuring the absorbance at 235 nm using the molar extinction coefficient of 100 M^{-1} cm^{-1}. The reaction mixture contained, 1.5 mM of HOCl and different concentration of the extract or standard ascorbic acid and incubated for 1 h at 37°C. After that taurine (30 mM) was added and incubate again 30 min at 37°C followed by the addition of thionitro benzoic acid (TNB). Absorbance was measured at 412 nm against blank and % scavenging was calculated according to the standard formula.

Determination of anti-inflammatory activity by Griess reagent

Sodium nitroprusside produced nitric oxide, it interacts with oxygen to produce nitrite ion and determined by the use of Griess reagent [35,36]. The mixture reaction constituted of 1 ml of sodium nitroprusside prepared in saline phosphate buffer (pH= 7.4, 20 mM), 1 ml of plant extracts and quercetin as standards. The temperature of the reaction is 25 °C for 150 min. 0.5 ml of Griess reagent (1% sulphanilamide, 2% H_3PO_4 and 0.1% ACS reagent) was added to 0.5 ml of above solutions. NO free radical scavenging activity was calculated and measured at 542 nm using the following equation: NO % scavenging activity (%) = $[(A_{control} - A_{sample}) / A_{control}] \times 100$.

Statistical analyses

Experimental values are given as means ± standard error (SEM) of three replicates. Results were processed by analysis of variance (ANOVA) using the linear regression models powered by Origin Lab version 9.2. The significance of the difference between means was considered at the level of $P < 0.05$.

RESULTS AND DISCUSSION

Conventional techniques of extraction, for example, Soxhlet, maceration demand long extraction time, high volume of solvents and very experience sometimes complicated [37]. Non-conventional extraction techniques such as ultrasonic-assisted extraction (UAE) have been developed, for their advantage (improved: efficiency, extract quality, extraction time or cost and volume of solvent) over conventional systems [38, 39]. These methods were employed for the extraction and isolation of phenolic compounds from plants [40]. Biologically active compounds naturally existed in very small quantity in plants extracts. The composition of herbal extracts dependent on the extraction technique, nature of phytochemicals, particle size, composition, nature of the solvent, and the presence of interfering substances [41,42]. Therefore, it is necessary to select the suitable extraction method as well as solvent based on sample matrix properties, chemical properties of the analytes, matrix-analyte interaction, efficiency and desired property.

Total phenolic, flavonoid and condensed tannin contents

The different extracts obtained by different techniques ME, SE and UAE used for quantification of total phenolic content, flavonoid, and condensed tannins of *Phoenix dactylifera* L. The results presented in fig. 1. The level of total phenolic content in different extraction technique ranged from 484.44 ± 8.38 mg, 528.81 ± 9.55 and 625.17 ± 11.82 mg GAE /g respectively for UAE, SE, and CE. For the content of flavonoids, the content similar results were found. The order for flavonoids content with respect to methods was decreased in the following manner: ultrasound-assisted extraction (UAE)>Soxhlet extraction (SE)>maceration (CE). The content of condensed tannins expressed in catechin equivalent varied from 269.94 ± 18.24, 246.19 ± 21.34 and 240.79 ± 20.37 successively for UAE, SE, and CE. The highest value of condensed tannins is shown in the ultrasonic-assisted extraction. Nile et al.[43] observed the maximum

amount of extractable phenolic compounds in the UAE from *R. cordifolia* and *R. serpentine* followed by SE and CE. Da Porto et al [44] reported similar findings by observing high phenolic content in an extract from *Vitis vinifera L*. seeds were decreased in the following order: UAE> SE>CE.

This high quantity of phytochemicals composition can be related with the larger the amplitude of ultrasonic wave traveling through the liquid medium, the more violently the bubbles collapse

enhancing cell tissues disruption and so improving the extraction capacity [45,46].

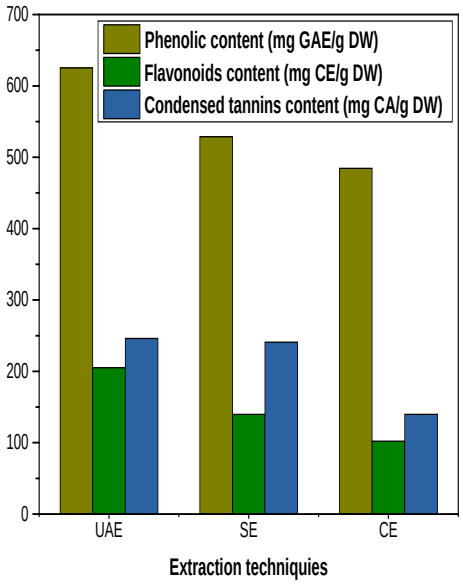

Fig. 1: Total phenolic, flavonoid and condensed tannin contents of different extract techniques from *Phoenix dactylifera* L

Total antioxidant activity

Ferrous ion chelating ability activity

To investigate the antioxidant activities of different extract techniques we used metal chelating activity. Results are resumed in Table 1, The Ferrous ion chelating activity scavenging of extracts ranged from 208.08±6.72 µg EDTA/g extract at 266.12±8.75 µg EDTA/g extract. UAE had significantly higher antioxidant properties (208.08±6.72 µg TE/g extract) than SE (238.93±1.38 µg EDTA/g extract) and the lowest value for CE (266.12±8.75µg TE/g extract). Metal chelating activity of a sample appears to be particularly important for diseases in which the high levels of metal ions leads to oxidation of proteins and lipids [47].Total phenolic content and metal chelating activity of different extraction techniques were highly correlated, providing strong evidence that the predominant source of antioxidant activity derives from phenolic compounds in wheat. A significant correlation was also found between total phenolics and antioxidant activity [48,49,50].

Table 1. Ferrous ion chelating and Hypochlorous acid scavenging activity of different extract of *Phoenix dactylifera* L recovered by UAE, SE, and CE.

	Ferrous ion chelating activity (µg EDTA/g extract)	HOCl IC_{50}= (µg/ml)
Classical extraction	208.08±6.72	86.12±1.31
Ultrasound extraction	266.12±8.75	78.27±1.26
Soxhlet extraction	238.93±1.38	103.87±1.68

Values are expressed as means ± SD of triplicate measurements.

Hypochlorous acid (HOCl)

Figure 2 shows the dose-dependent HOCl scavenging activity of different extract techniques leaf from *Phoenix dactylifera* L compared to that of ascorbic acid. The results indicate that the extracts scavenged hypochlorous acid more efficiently (IC_{50} ranges from 80.25 ± 1.26 to 102.23 ± 2.08 µg/ml). Similar results were observed for the ferrous ion-chelating activity, the strong inhibition registered for the UAE (80.25 ± 1.26 µg/ml), followed SE (IC_{50}=91.06 ± 1.31 µg/ml) and lowest inhibition in CE (IC_{50}=102.23± 1.68 µg/ml). Hypochlorous acid construct in stimulated neutrophils via the myeloperoxidase-catalyzed reaction of hydrogen peroxide with Cl^- considered important reactive oxidants [51]. It oxidizes unsaturated fatty acids and cholesterol to produce chlorohydrins [52] and reacts with amines to produce chloramines, which undergo decomposition to give carbon and nitrogen-centered radicals. It has been reported that the *in vitro* antioxidant activity of several polyphenols. Polyphenols have been reported to scavenge ROS and reactive nitrogen species, including hypochlorous acid (HOCl) [53,54].

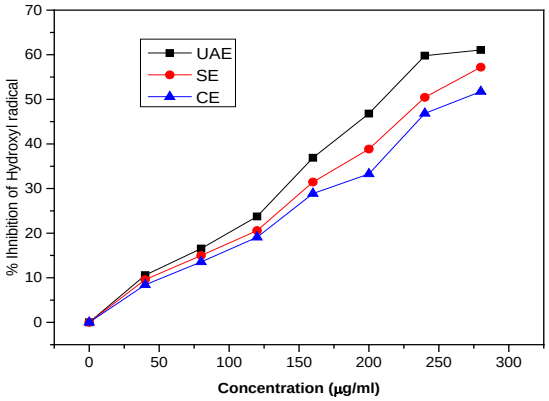

Fig. 2: Ferrous ion chelating scavenging radical activity of different extract techniques from *Phoenix dactylifera* L

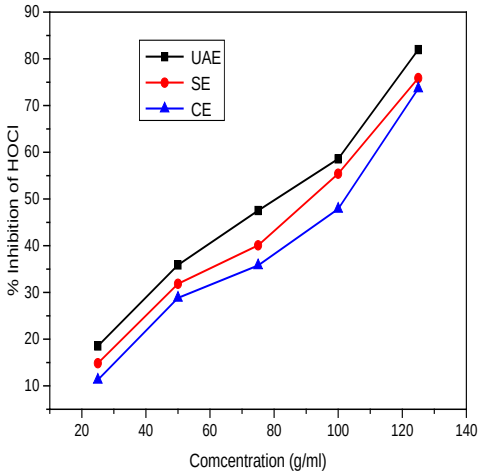

Fig. 3: HOCl scavenging activity of different extract techniques from *Phoenix dactylifera* L

Anti-inflammatory activity by nitrite assay

The scavenging activity of the extracts against nitric oxide was calculated. Figure 3 showed the dose-response curves of NO scavenging activities of different extracts recovered by UAE, SE and CE techniques, three extracts techniques down-regulated NO production with IC_{50} < 400 µg/ml. The NO percentage inhibition of all extracts started with low values of CE (384.80±8.74 µg/ml), followed by the SE (344.51±7.57 µg/ml) and highest inhibition founded for the UAE with value (309.94±7.39 µg/ml). Similar results were observed in antioxidant activity and anti-inflammatory. Inflammation is a complex process that results in up-regulation of a series of pro-inflammatory enzymes, cytokines, chemokines as well as signaling protein sat the site of infected tissues and cells [55]. Polyphenols and natural compounds from plants have already been described as a promising alternative for the treatment of inflammatory diseases [56]. These compounds suppress inflammation not only by acting as antioxidants but also by mediating cytokines and enzymes inhibition [57]. Many studies have demonstrated that polyphenols possess anti-inflammatory effects via scavenging ROS [58,59], and have been reported to be beneficial in the treatment of chronic inflammatory diseases associated with overproduction of nitric oxide (NO) [60]. In addition, for this reason, numerous plant rich in these potent antioxidant compounds have been investigated as potential inhibitors of NO production in inflammatory reactions [61].

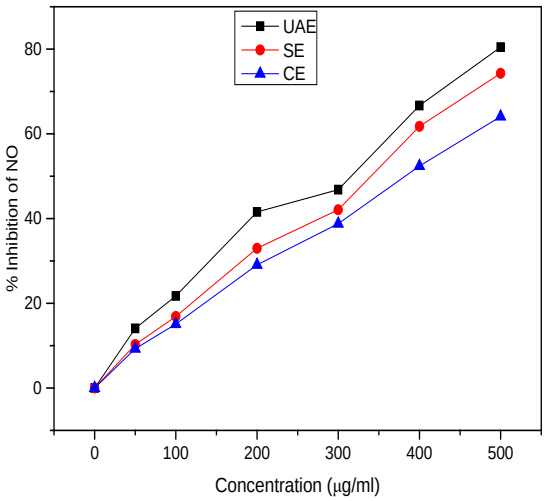

Fig. 4: Nitrite oxide inhibition of different extract techniques UAE, SE and CE of *Phoenix dactylifera* L

CONCLUSION

The present research provides new understanding of phytochemical screening, *in vitro* antioxidant activity and anti-inflammatory activity of leaf extract from *Phoenix dactylifera* L recovered by ultrasonic-assisted extraction, Soxhlet extraction, and maceration extraction.

The ultrasound-assisted extraction technique was shown to be very efficient in the extraction of phenolic compounds quantities from *Phoenix dactylifera* L against Soxhlet and maceration extraction. The contents of bioactive compounds phenolic content, flavonoids and condensed tannins of the extract were decreased with the following order: ultrasonic-assisted extraction> Soxhlet extraction>maceration extraction. The extraction of *Phoenix dactylifera* L with different techniques revealed UAE to be the best to recover the antioxidant and anti-inflammatory properties from the leaf of the plant studied, followed by SE, and CE. The main benefit of UAE can be observed in solid plant sample because ultrasound energy facilitates organic and inorganic compounds leaching from plant matrix. These results suggest that this plant has potent antioxidant and inflammatory activity, and natural preservative therapeutic resources for treating various diseases. Moreover,

these results could justify the use of *Phoenix dactylifera* L in traditional pharmacopeia for the treatment of certain diseases. However, it is interesting to characterize the compounds responsible for these biological activities.

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