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Full Length Article

The Nutritive Value and Biological Activity of Artichoke Wastes as Food Supplements or Adjunctive Agents for Chemotherapy and Radiotherapy

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Abstract

The agro-food industry produces high volumes of wastes with high functionality and/or bioactivity. This study aims to evaluate the nutritive value and biological activity of Artichoke Leave Wastes (ALW) and Artichoke Stem Wastes (ASW) and to study the potential role of γ-irradiation in improving utilization of these wastes. The nutritional value of ALW and ASW showed that they contain good levels of protein, carbohydrates, and fiber content, irradiation at doses of 4 and 8 kGy led to an improvement in their nutritional value. The results of biological activity revealed that ALW extract shows a higher concentration of the total phenolic, flavonoids, and antioxidant activity than that of ASW. The dose of 4 kGy led to an improvement in the content of total phenols, flavonoids and antioxidants in both ALW and ASW, this may be an evidence of the biological value of ALW and ASW. They had cytotoxicity effects against breast cancer cell line (MCF-7) and sufficient inhibitory effect against the pathogenic of *Candida albicans*. The nutritional value and multiple biological activities (antioxidant, anticancer and anticandidal) demonstrated by the ALW and ASW in this study recommends their possible use as food supplements, especially for tumor patients undergoing radiotherapy and chemotherapy or as an adjuvant agent for the improvement of traditional chemotherapy to reduce doses, toxicity, and side effects of these medications. Also, the plant phenolic compounds have a good antiviral effect, so in this study, phenolic and flavonoid of artichoke wastes may also be considered as promising candidates against COVED-19.

Keywords: Irradiated artichoke wastes; Antioxidant; Anticancer; Anticandidal activity; Food supplements; Adjunctive agents of chemotherapy and radiotherapy

Introduction

If food shows a beneficial effect on one or more of the target functions in the body, it is considered a functional food. In addition to its sufficient nutritional effects, functional food has a role in maintaining health and reducing the risk of diseases (Boggia *et al.* 2020).

The use of agricultural waste generated by plants or food processing in the production of high-added-value functional ingredients for use in the nutraceutical and pharmaceutical industries has recently become a goal of sustainable technological development (Maietta *et al.* 2018). The artichoke plant, in particular, is a good source of specific functional compounds including dietary fibers and active components (Li *et al.* 2015; Ma *et al.* 2017). The artichoke (*Cynara scolymus* L.) canning industry produces large quantities of waste material, comprising mainly leaves (Ruiz-Cano *et al.* 2014), stems and external parts of the flowers (bracts) which are not appropriate for human consumption (about 80–85% of the total biomass of the plant), and they can be recycled for the production of compounds of economic value, such as inulin. These can be used as a prebiotic for probiotic strains and polyphenols, which can be regarded as a raw material for the production of food additives and nutraceuticals (Abuajah *et al.* 2015; Carocho *et al.* 2015; Francavilla *et al.* 2021). Artichoke by-products could be good sources of biological activity (antioxidant, antibacterial, antiviral and anticancer) because they contain high levels of phenolic compounds, particularly chlorogenic acid and 1, 5-O-dicaffeoylquinic acid, 3,5-O-dicaffeoylquinic acid and 3,4-O-dicaffeoylquinic acid. The presence of luteolin-7-glucoside and hydrolyzable tannins in the phenolic fraction of artichoke extracts, in addition to caffeoylquin derivatives, could induce a good biological activity (Lattanzio *et al.* 2005; Peschel *et al.* 2006; Mabeau *et al.* 2007).

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Candidiasis is the most common oral fungal infection in humans, caused by yeasts from the genus Candida. *Candida albicans* is the most prevalent (McCarty and Pappas 2016). *Candida albicans* is not only responsible for the complications it causes to cancer patients or cancer-related therapy, but it is also responsible for the development of cancer. The relationship between candidiasis and cancer is of a great concern (Mesri *et al.* 2014). Oropharyngeal candidiasis is a widespread Candida infection in immunocompromised individuals. The cell-mediated immunity that predisposes the person to fungal infections is weakened by conditions such as malignancies, chemotherapy and radiotherapy (Alibek *et al.* 2013). Oral candidiasis is common among cancer patients (hematopoietic malignancy, solid tumors and head and neck malignancy) and it has been reported to range from 7% to 52% with chemotherapy and/or radiotherapy (Silva *et al.* 2017). Due to the increasing prevalence rate of the *C. albicans* in patients such as HIV/AIDS patients, diabetic individuals, a great number of antibiotics consumers and those who undergo chemotherapy, and due to the drug resistance, including the inherent or acquired resistance; plant bioactive compounds have been increasingly considered because of their high efficiency and low rate of side effects (Mashhadi *et al.* 2016). The antimicrobial activity of *Cynara cardunculus* extract can be attributed to the presence of high levels of chlorogenic acid, cynarin and epicatechin, which are likely to synergistically affect its antimicrobial activity (Fratianni *et al.* 2014).

The most prevalent malignancy in women worldwide is breast cancer (Ghoncheh *et al.* 2016). Many epidemiological studies indicate that phytochemicals, which are found in plants at high levels, have anticancer activity **(**Dandawate *et al.* 2016; Rothwell *et al.* 2017). The increasing interest in nutritional bioactive compounds has resulted in a renewed attention paid to the artichoke, due to its high content of polyphenols. Several in *vitro* and *in vivo* studies have shown that artichoke has diuretic, hepatoprotective, antioxidant and hypocholesterolemic (Rodriguez *et al.* 2002; Miccadei *et al.* 2008) and more recently, antitumor activities (Pulito *et al.* 2015). Artichoke extract protects hepatocytes from oxidative stress by activating apoptosis in human hepatoma cells and human breast cancer cell lines without any toxicity in the nontumorigenic MCF10A cells and demonstrates cancer chemopreventive properties (Mileo *et al.* 2020).

There are few studies on the utilization of Egyptian artichoke wastes in the food, pharmaceutical, and medical fields, and there are no studies on their use as an anticandidal or anticancer agents/compounds. Therefore, this study aims to:

1- The utilization of Egyptian artichoke wastes (leaves and stems) as a natural source of basic nutrients, phenolic compounds and as an economically viable solution to the problem of agricultural solid waste treatment.

2- Evaluate the potential role of artichoke wastes (leaves and stems) as a source of food supplements and health-promoting phenolics associated with their antioxidant, anticancer and anticandidal activities for cancer patients undergoing chemotherapy and radiotherapy.

3- Study the potential role of γ-irradiation in the enhancement of the nutritive value and biological activity of artichoke wastes.

Materials and Methods

Preparation of Artichoke wastes

Egyptian Artichoke samples (*Cynara scolymus*) were collected from the Egyptian Agricultural Research Center (Cairo, Egypt) and refrigerated at 4°C until being used. The outer leaves and stems (non-edible parts) were cut into 1–2 cm pieces using a knife and blanched in water at 85°C for 15 min to inhibit the enzymes that cause polyphenol degradation. Artichoke Leaves Waste (ALW) and Artichoke Stems Waste (ASW) were dried in the shade at room temperature and placed in sealed bags then irradiated at doses of 0, 4 and 8 kGy in the National Center for Radiation Research and Technology, NCRRT (Nasr City, Cairo, Egypt), using cobalt-60 irradiator source (Gamma Chamber 4000 Indian) at a dose rate of 3, 49269 kGy/h. The sample bags were kept at room temperature until use in the following estimates.

Nutritional value of artichoke wastes

AOAC (2010) methods were used to calculate crude protein, lipids, fiber, and carbohydrates of the irradiated and non-irradiated ALW and ASW. All of the above measurements were made in triplicate and expressed as g/100 g samples.

% carbohydrates = 100 - % (protein, fat, ash and fibers).

Determination of Biological Activity of Artichoke Wastes

Extraction of the bioactive compounds: A 500 g of the non-irradiated and irradiated (0, 4 and 8 kGy) ALW and ASW samples were extracted by soxhlet, using methanol as a solvent. The extracts were filtered and evaporated using a rotary evaporator under reduced pressure until dryness and then the collected amount was weighted. A known weight from the dried methanol artichoke extracts was dissolved in (DSMO 10%) to obtain the appropriate concentration as mg/mL to make the following estimations.

Total phenolic content determination: Spectrophotometrically, the total phenolic contents of the irradiated and non-irradiated ALW and ASW methanol extracts were calculated using the Folin-Ciocalteu method according to Singleton *et al.* (1999). 400 μL of extracts (ALW and ASW) were combined with 1000 μL of 1:10 Folin-Ciocalteau reagent and 1400 μL of sodium carbonate (7.5%) was added after 6 min in the dark. The absorbance at 740 nm was measured spectrophotometrically after 2 h of incubation in the dark at room temperature. The calibration curve was constructed using calibration standards of 1–200 mg/L gallic acid. The results were expressed in milligram gallic acid equivalents (GAE) per gram of dried weight (DW) of plant material (mg GAE/g DW).

Total flavonoids content determination: According to Matejic *et al.* (2012), the total flavonoid content of ALW and ASW methanol extracts were calculated using aluminium nitrate anhydrate. 400 μL of extracts were mixed with 2400 μL of the mixture (80% C_2H_5OH, 10% Al $(NO_3)_3 \times 9\ H_2O$ and 1 *M* $C_2\ H_3KO_2$), the absorbance at 415 nm was spectrophotometrically determined after 40 min of incubation at room temperature. The total flavonoids were calculated using a standard calibration curve of quercetin (1 – 400 mg/L) and expressed as quercetin equivalent (QE) per g of dry weight (DW) sample (mg QE/g DW).

Antioxidant activity of artichoke wastes

Determination of the scavenging effect on DPPH radicals: According to the method of Brand-Williams *et al*. (1995), the free radical scavenging activity of ALW and ASW methanol extracts was determined. The dried plant extract was diluted in methanol at different concentrations ranging from 10- to 320-μg/mL then 1 mL of alpha, alpha-diphenyl-β-picrylhydrazyl (DPPH) solution was added and incubated at room temperature (25°C) for 15 min. The absorbance was then measured by a spectrophotometer at 515 nm. The antioxidant activity of the test sample was calculated as the percentage of the reduction in initial DPPH absorption.

$$DPPH\ scavenging\ effect\ \% = [(A0 - At)/ A0] \times 100$$

A0 is the control absorption at zero time and A_t is the antioxidant absorption at 15 min. The IC_{50} is known as the antioxidant concentration required decreasing by 50% of the initial concentration of DPPH.

Determination of anticandidal activity of artichoke wastes

Collection of *Candida albicans*: Ten samples from *C. albicans* were collected from clinical microbiology laboratories in Cairo Hospitals, Cairo, Egypt. The samples were identified by the CHROM agar-Candida chromogenic media, followed by morphological and biochemical fermentation and carbohydrate absorption.

Disk diffusion method: The anticandidal activity of the methanolic extracts of ALW and ASW were assessed by the technique of paper disc diffusion according to (Kronvall *et al.* 2001). Stock culture of test *C. Albicans* was grown in medium Potato Dextrose Broth (PDB) for 24 h at 37°C. 100 μL of standardized broth inoculants of which isolate (10^8 CFU/mL with reference to the McFarland turbidmeter) was added on the surface of each plate containing Mueller-Hinton agar (MHA, Oxoid) by sterile cotton swab and allowed to remain in contact for 1 min. Both ALW and ASW extracts were dissolved in 5% aqueous DMSO to get a concentration of 10 mg/mL. Whatman No. 1 filter paper discs were prepared, sterilized and impregnated with 40 μL of the extract. The discs were placed on the PDA plates inoculated with *Candida* strains. The positive control was fluconazole (25 μg), and the negative control was DMSO fluconazole -soaked filter paper disk. At 35 ± 2°C, plates were incubated for 18 h. The inhibition zones were recorded after incubation as the diameter of the growth-free zones.

Determination of minimal inhibitory concentration (MIC) and minimal fungicidal concentration (MFC)

MIC of the methanolic extracts of ALW and ASW were determined by the micro-dilution method. Initially, 100 μL of PDB culture medium was distributed along all wells from a 96-well microtiter plate. After that, 100 μL of ALW and ASW (10,000 μg/mL) working solutions were added to the first line of the microtiter plate, followed by a two-fold serial dilution along all subsequent wells. Concentrations of ALW and ASW ranged from 1600 μg/mL to 12.5 μg/mL. Finally, 100 μL of *C. albicans* (1×10^3 CFU/mL) inoculum was added to each test well. Positive and negative controls consisted of wells without plant extracts and without microorganisms, respectively. Plates were then incubated at 37ºC, for 24 h. The MFC was determined by spreading 100 μL from the samples showing no visible growth on Potato Dextrose Agar (PDA) plate and it was further incubated for 18 h at 37°C (CLSI 2008).

Anticancer activity of artichoke wastes

This was performed via Cell viability assay (MTT assay). Human breast cancer cell line (MCF-7) was bought from CURP, The Faculty of Agriculture at Cairo University (Egypt). The cancer cells were grown in Eagle's minimum essential medium (EMEM) containing 10% fetal bovine serum (FBS) and maintained at 37 C, 5% CO2, 95% air and 100% relative humidity. 3-(4, 5-dimethylthiazoyl) -2, 5-diphenyltetrazolium bromide were used to assess cytotoxic activity of ALW and ASW extracts against breast cancer cell line MCF-7 (MTT dye). In short, an amount of 100 μL of cell suspension was added to the flat-bottomed micro-culture plate wells, triplicated separated plate for each cell line, and treated with 100 μL of partially purified methanolic extracts from ALW and ASW, incubated for 24 h, centrifuged to remove dead cells. An aliquot was added to each well containing 100 μL of 2 mg/mL MTT dye. The absorbance was read at 620 nm with an enzyme-linked immunosorbent assay reader. The average absorbance was calculated for each group of replicates. The percentage of cell viability exposed to different treatments was calculated as follows:

$$\%\ \text{Cell viability} = \text{Mean absorbance of treated sample} / \text{Mean absorbance of non-treated sample} \times 100$$

In all experiments that contained cells in the medium, only the control was non-treated cultures (Mosmann 1983).

Statistical analysis

According to Snedecor and Cochran (1989), all data were expressed as the mean ± SD (standard deviation) of three replicates. The significance of the data with different factors was evaluated using one-way and two-way analysis of variance ANOVA. All analyses were performed with SAS software package version 9.0.

Results

Nutritional value

The results of the nutritional value of both artichoke leaves, and stems (irradiated and non-irradiated) are reported in (Table 1). The obtained results showed that the nutritional values of ALW were different from those of ASW. The dietary fiber contents of ALW and ASW were 37.4 g/100 g and 31.9 g/100 g, respectively. The same trend was reported with the protein (5.7 and 9.1 g/100 g), lipids (0.52 and 0.61 g/100 g) and carbohydrate 40.1 and 39.3 g/100 g) contents, respectively. Irradiation at doses of 4 and 8 kGy led to an improvement in the nutritional value of both ALW and ASW (Table 1).

Biological activity of artichoke wastes (leaves and stems)

The total phenolic content (TPC) and total flavonoid content (TFC) of ALW and ASW are presented in (Table 2). Data indicated that the total phenol and flavonoid contents of ALW were higher than those of ASW, the total phenolic contents of ALW and ASW were 8.52 and 5.46 mg/g DW, respectively while the total flavonoids of ALW and ASW were 6.47 and 4.39 mg/g DW, respectively.

In addition, (Table 2) reveals the impact of γ-irradiation on total phenolic content (TPC) and total flavonoid contents (TFC) of both ALW and ASW. The dose of 4 kGy resulted in an increase in the contents of both total phenols and flavonoids, while the dose of 8 kGy did not have a significant effect on total phenols and flavonoids contents. Therefore, all upcoming biological tests in this study will be conducted on the irradiated artichoke wastes at 4 kGy.

Antioxidant activity

The antioxidant activity of methanolic extracts of ALW and ASW (irradiated at 4.0 kGy) which were estimated by DPPH and ascorbic acid was used as standard. ALW and ASW were found to have potent antioxidant and free radical scavenging activity and their effect was concentration-dependent, with the same pattern as ascorbic acid. The ascorbic acid revealed a higher antioxidant activity than both of ALW and ASW at the same concentrations. IC_{50} values of ALW and ASW were 81.76 and 149.98 μg/mL, respectively. Whereas IC_{50} value of ascorbic acid was 43.31 μg/mL. Generally, the data showed that both of ALW and ASW have significant antioxidant potential but the antioxidant activity of ALW was higher than that of ASW at the same concentrations ($P < 0.05$). A positive association between the antioxidant activity and the phenolic compounds was revealed in the obtained results (Table 3).

Anticandidal activity

In this study, the inhibition zone for ALW and ASW against ten strains of *C. albicans* was assayed by the disc diffusion method as shown in (Table 4). Generally, both ALW and ASW had sufficient inhibitory effects against all tested strains of *C. albicans*, but the anticandidal activity of ALW was higher than that of ASW, with an inhibition zone diameter size of 10–22 mm.

The results of MIC and MBC values of ALW and ASW were also illustrated in Table 4. The anticandidal activity was observed at varying degrees which was both strain and dose- dependent. The highest preventive concentration of ALW was 50 mg/mL and three strain of *C. albicans* (1, 6 and 10) were blocked in this concentration. On the other hand, the lowest preventive concentration of ALW was 12.5 mg/mL and four strains of *C. albicans* (2, 7 and 8) were blocked in this concentration. Moreover, the results of the present study showed that the highest preventive concentration for ASW was 100 mg/mL and six strains *C. albicans* were blocked in this concentration, while the lowest preventive concentration was 25 mg/mL and three strains *C. albicans* (2, 5 and 8) were blocked in this concentration.

Anticancer Activity

The results of a cell viability assay (MIT assay) using the breast cancer cell line Michigan Cancer Foundation-7 (MCF-7) treated with ALW and ASW revealed that the percentage of cytotoxicity increased with increasing concentration of artichoke wastes. Both ALW and ASW had cytotoxicity effects on cancer cells as shown in (Table 5). The highest viability reduction rates (39 and 58%) were observed for the breast cancer cell line at the highest concentration (800 g/mL) of ALW and ASW, respectively (Table 5). This study revealed a positive relationship between the cytotoxicity effect and phenolic compound contents.

Discussion

In this study, the results of nutritional values revealed that both artichoke wastes (leaves and stems) might be considered a good source for dietary fiber, protein and carbohydrate so they may be used as a food supplement, especially for cancer patients (Table 1). Another study showed that artichoke parts are rich in fibers, minerals, and

Table 1: Nutritional value of irradiated and non-irradiated Artichoke Leave Wastes (ALW) and Artichoke Stem Wastes (ASW)

Nutritional value (g/100 g)	Artichoke wastes					
	ALW			ASW		
	0	4.0 kGy	8.0 kGy	0	4.0 kGy	8.0 kGy
Dietary fiber	37.4^a ± 0.22	36.7^a ± 0.11	39.5^b ± 0.51	31.9 ^{a} ± 0.26	30.4 ^{a} ± 0.12	32.7 ^{b} ± 0.42
Proteins	5.7 ^{a} ± 0.19	6.1^b ± 0.22	6.8 ^{c} ± 0.34	9.1 ^{a} ± 0.17	9.3^a ± 0.26	10.6^b ± 0.24
Lipids	0.52^a ± 0.25	0.38^b ± 0.28	0.31^b ± 0.21	0.61^a ± 0.35	0.58^a ± 0.04	0.41 ^{a} ± 0.23
Carbohydrates	40.1 ^{a} ± 0.31	39.8^a ± 0.36	41.6^b ± 0.29	39.3^a ± 0.19	38.9 ^{b} ± 0.32	43.2 ^{c} ± 0.34

0 = Unirradiated, 2 and 4 kGy irradiated, All values are the mean of three replicates + SD. All values with the same letters are not significantly different at $P > 0.05$

Table 2: Total phenolic (TPC) and total flavonoids (TFC) content of irradiated and non-irradiated ALW and ASW

Doses (kGy)	Artichoke waste extracts			
	ALW		ASW	
	TPC (mg/g DW)	TFC (mg/g DW)	TPC (mg/g DW)	TFC (mg/g DW)
0	8.52a ^a_a ± 0.12	6.47 ^a_a ± 0.32	5.46 ^b_a ± 0.42	4.39 ^b_a ± 0.23
4 kGy	11.35 ^a_c ± 0.24	8.87 ^a_b ± 0.15	6.98 ^b_b ± 0.18	5.84 ^b_b ± 0.31
8 kGy	8.72 ^a_a ± 0.32	6.33 ^a_a ± 0.27	5.63^b_a ± 0.22	4.88 ^b_a ± 0.20

0 = non-irradiated, 2 and 4 kGy irradiated, TPC (total phenolic content), TFC (total flavonoid content), All values are the mean of three replicates + SD. Mean values followed by different superscript (within rows) and different superscript (within columns) are significantly different at *$P > 0.05$*

Table 3: Antioxidant capacity (% inhibition) of irradiated ALW and ASW at 4.0 kGy

Concentrations of extracts (μg/mL)	% inhibition		
	ALW	ASW	Ascorbic acid
10	12.74^a_a ± 0.21	5.81 ^b_a ± 0.15	18. 41^c_a ± 0.27
20	16.22 ^a_b ± 0.37	8.91 ^b_b ± 0.22	24. 15 ^c_b ± 0.18
40	26 .16 ^a_c ± 0.52	17. 52 ^b_c ± 0.41	46.17 ^c_c ± 0.46
80	48 .92 ^a_d ± 0.44	26 .19^b_d ± 0.26	59.32 ^c_d ± 0.71
160	74. 28 ^a_e ± 0.12	53.34 ^b_e ± 0.54	86.22 ^c_e ± 0.25
320	86. 63 ^a_f ± 0.28	69. 18^b_f ± 0.29	94.16 ^c_f ± 0.43

All values are the mean of three replicates + SD. Mean values followed by different superscript (within rows) and different superscripts (within columns) are significantly different at *$P > 0.05$*

Table 4: Anticandidal activity of irradiated ALW and ASW at 4.0 kGy

Strain of *Candida albicans*	ALW			ASW		
	Inhibition zone (mm)	MIC(mg/mL)	MFC(mg/mL)	Inhibition zone (mm)	MIC (mg/mL)	MFC (mg/mL)
1	12.21 $_g$ ± 1.6	50	100	8.16$_g$ ± 0.9	100	200
2	20.52 $_C$ ± 0.6	12.5	25	15.23 $_c$ ± 1.4	25	50
3	16.61$_e$ ± 0.3	25	50	11.41 $_e$ ± 0.7	100	200
4	14.34 $_f$ ± 1.2	25	50	10.18 $_f$ ± 0.9	100	200
5	22.21 $_a$ ± 0.6	12.5	25	17.35 $_a$ ± 1.2	25	50
6	11.70$_h$ ± 0.5	50	100	9.19 $_h$ ± 0.8	100	200
7	18.42 $_d$ ± 0.8	12.5	25	14.44 $_d$ ± 0.5	50	100
8	21.19 $_b$ ± 1.4	12.5	25	16.62 $_b$ ± 0.8	25	50
9	14.31 $_f$ ± 0.9	25	50	9.34 $_h$ ± 1.7	100	200
10	10.17 $_i$ ± 0.5	50	100	8.20 $_g$ ± 0.9	100	200

Minimal Inhibitory Concentration (MIC), Minimal Fungicidal Concentration (MFC), All values are the mean of three replicates + SD. All values with the same letters are not significantly different at *$P > 0.05$*

Table 5: Cytotoxic activity of irradiated ALW and ASW at 4.0 kGy

Concentrations of extracts μg/mL	ALW	ASW
	% Viability of MCF7	% Viability of MCF7
100	94^a_d ±1.30	98^b_d ± 1.12
200	82^a_c ±1.10	91^b_c ± 1.23
400	66^a_b ±1.31	76^b_b ± 1.20
800	39^a_a ±1.30	58^b_a ± 1.11

Michigan Cancer Foundation-7 (MCF-7), All values are the mean of three replicates + SD. Mean values followed by different superscript (within rows) and different superscript (within columns) are significantly different at *$P > 0.05$*

vitamins as and it is low in carbohydrates, calories and fat while having zero cholesterol content (Sayed *et al.* 2018). Fiber concentrate from artichoke stem byproducts can be used as ingredients in the bakery products, particularly for their nutritional and functional characteristics (Boubaker *et al.* 2016). Scientific data and human studies have shown that fiber can reduce the risk of colon cancer (Meyer *et al.* 2011). Dried Jerusalem artichoke powder presented a good health profile and high technological quality to be evaluated as inorganic phosphate replacers in the formulation of emulsified poultry products (Öztürk and Serdaroğlu 2018). The water-soluble polysaccharide inulin represents 75% of the total sugar content in artichoke parts. Inulin has dietary fibers and it can be considered as a functional food (Robenfroid 1999; Rubel *et al.* 2018).

In this study, irradiation at the dose of 4 and 8 kGy led to an improvement in the nutritional value of both ALW and ASW and this may be due to inhibition of anti-nutrient agents (Table 1). The bioavailability of nutrients decreases at high levels of plant antinutrients (phytic acid, protease inhibitors, non-starch polysaccharides, oligosaccharides and lectin). Ionizing radiation could be utilized as a potential additional method for blocking or lowering some antinutritional factors (Zarei 2013).

The results of phenolics and flavonoids content both artichoke wastes (leaves and stems) revealed that the total phenolic content differs according to the parts of the artichoke studied (Table 2). No distribution of the total phenolic in the Egyptian artichoke wastes is a in good agreement with previous studies of other artichoke taxa (Dabbou *et al.* 2017; Thabeta *et al.* 2019). Other studies indicated that the outer bracts and leaves of artichoke have higher polyphenolic concentrations, 10.23, 54.54 and 79.20 mg/g DW, (Claus *et al.* 2015; Dabbou *et al.* 2017; Salem *et al.* 2017). Francavilla *et al.* (2021) reported that phenols of globe artichoke plant wastes ranged between 6.94 mg g^{-1} dw (in leaves) and 3.28 mg g^{-1} dw (in roots). The variation in TPC within the artichoke plant parts reported here and, in the literature, was found to be in relation to biological, physiological stage of development, technical and environmental factors during plant growth (biotic and abiotic factors) such as taxa, genetic material, plant parts, season conditions, plant arrangements, tissue age and planting density (Lombardo *et al.* 2009; Rouphael *et al.* 2016).

Table 2 illustrates the effect of γ-irradiation on total phenolic content and total flavonoid content of ALW and ASW. The dose of 4 kGy resulted in a significant increase in the total phenols and flavonoids content, while the dose of 8 kGy had no effect on total phenols and flavonoids content. The results of the present study are in accordance with those of Beltagi *et al.* (2020), the total phenols and flavonoids contents in celery seed oil increased by increasing γ-irradiation dose level in addition there was a remarkable DPPH scavenging activity. Reports differed about the effect of irradiation on the biological activity of plant extracts. For example, the phenolic content of some plants is influenced by irradiation (Variyar *et al.* 1998), while the phenolic content remained unchanged in other plants (Pinela *et al.* 2015). Other studies have shown that the antioxidant properties of plant materials are negatively impacted by γ-irradiation (Ahn *et al.* 2004). Lee *et al.* (2013) showed that the biological activities of centipede grass were maintained or enhanced by gamma irradiation. The increasing attention in dietary phytochemicals has led to renewing attention being paid to artichoke wastes, due to their high content in polyphenols (chlorogenic acid, luteolin-7- glucoside, hydrolysable tannins, caffeoylquinic, hydroxycinnamic acid, 1,5-O-dicaffeoylquinic, and 3,4-O-dicaffeoylquinic acids) (Mabeau *et al.* 2007; Muthusamy *et al.* 2016).

Antiviral activity of phenolic and flavonoid compounds has been documented against, yellow fever17, HIV16, herpes simplex virus18, HCV15, rhinoviruses14 and COVED-19 (Li *et al.* 2020; El-Aziz *et al.* 2020). This study sheds light on the fact that the Egyptian artichoke wastes contain good proportions of the phenolic and flavonoid contents that may have a potential effect on the emerging coronavirus.

The synthesis of antioxidant-capable molecules such as polyphenols is very complicated, so one of the most useful methods is to extract them from plant sources. Therefore, the extraction of this kind of compound from artichoke wastes could be very useful (Jiménez-Moreno *et al.* 2019). The current study revealed that both ALW and ASW have the substantial antioxidant capacity, but at the same concentrations, ALW had a higher antioxidant activity than that of ASW ($P < 0.05$). The findings of the present study showed a positive relationship between antioxidant activity and phenolic contents. Phenolic compounds possess antioxidant activity due to emitting a hydrogen atom or electron. It bounds the free radicals and contributes to their stabilization and neutralization, thereby preventing their harmful oxidative action (Angelov *et al.* 2015). According to Jiménez-Moreno *et al*. (2019), the most important compounds responsible for the antioxidant activity of artichoke waste extracts are chlorogenic acid, luteolin-7-O-glucoside and luteolin-7-O-rutinoside. Artichoke extracts' antioxidant activity may also be attributed to their flavonoid content, which serves as hydrogen donors and metal chelators (Brown and Rice-Evans 1998).

In this study, the irradiation process caused an increase in the antioxidant activity due to the relationship between the total phenolics and antioxidant activity. Cho *et al*. (2017) reported that gamma irradiation elevates the phenolic content of persimmon leaf extract which can improve the anti-oxidative and anti-inflammatory activities.

Reactive oxygen species (ROS-)-induced oxidative stress plays a main role in cancer development and progression. Polyphenols have been shown to improve the anticancer properties of chemotherapy drugs (Mondal and Bennett 2016; Huang *et al.* 2017). A dual role of the edible part of artichoke (*Cynara scolymus* L.) extracts, as a prooxidant in breast cancer cells was reported (Mileo *et al.* 2012) and as an antioxidant in the normal hepatocyte (Miccadei *et al.* 2008). Mileo *et al*. (2015) reported that artichoke may selectively inhibit the growth of tumor cells with a little or no toxicity on normal cells based on their differential redox status.

There are very limited studies on the effect of the use of artichoke extracts and their wastes as an antifungal against the *Candida albicans* (*Anticandidal)*, so this study was conducted. Both ALW and ASW had adequate inhibitory effects against all *C. albicans* strains tested (Table 4). The results of the inhibition zone, MIC and MFC revealed that increased concentration of the extracts increased the anticandidal effects. ALW had a higher inhibitory effect compared to that of ASW. Also, the MFC concentrations of both two extracts were higher than the

MIC concentrations.

In this study, the effect of anticandidal activity of ALW and ASW may be due to their phenolic and flavonoids content. In another study, the antimicrobial effects of the Artichoke extract (*Cynara cardunculus*) against both Gram-positive and negative bacteria can suggest a wide range of antibiotic-activity compounds (Kukic *et al.* 2008). Natural products generally have an antimicrobial activity that provides a natural barrier against the invasion of microbes and blocks communication systems between pathogens. The antimicrobial activity of Artichoke extract can be attributed to the presence of high levels of chlorogenic acid, cynarin and epicatechin, which are likely to affect its antimicrobial activity synergistically (Fratianni *et al.* 2014). Zhu *et al*. (2004) found that artichoke leaf extract's n-butanol showed the most significant activities toward 7 species of bacteria, 4 yeasts and 4 molds. The antimicrobial activity of free and bound phenolic methanolic extracts in various parts of the artichoke can be attributed to the content of flavonoids and phenols found to be effective antimicrobials against a broad range of microorganisms *in vitro* (Varmanu *et al*. 2011).

Candida infection (CI) is a common side effect of cancer and cancer-related therapy and it may also play a role in the progression of cancer (Chung *et al.* 2017). Incidence of oral candidiasis has been reported to be ranging from 7 to 52% among cancer patients (head and neck malignancy, hematopoietic malignancy, and solid tumors) on chemotherapy and or radiotherapy (Lone *et al.* 2014; Silva *et al.* 2017). The recent increase in treatment failure in candidiasis patients has caused a pause in the series of successful chemotherapy (most widely used drug, azoles, faces drug resistance by the pathogen) and highlights the necessity of finding out new chemotherapeutic agents. This study proved that extracts of Egyptian artichoke wastes (leaves and steam) have an effect against the *Candida albicans*, so these extracts are considered possible solutions to eliminate this pathogen that causes serious health problems for tumor patients, and that through the use of these extracts as potential sources for anticandidal drugs or as adjuvant agents for the improvement of traditional chemotherapy and radiotherapy.

The most prevalent malignancy in women worldwide is breast cancer (Ghoncheh *et al.* 2016**)**. Chemoprevention is a promising approach to block, inhibit, reverse or delay the carcinogenesis process by using natural dietary substances (Mileo *et al.* 2015). This study discovered that both ALW and ASW have cytotoxic effects on breast cancer cells. ALW has the highest reduction of viability cytotoxicity of breast cancer cells compared to ASW.

This study shows that the polyphenols of artichoke wastes (leaves and stems) have an anticancer activity to reduce the growth of cancer cells. The biologically active components found in plants can prevent carcinogenesis by blocking metabolic activation, enhancing detoxification, or offering alternative targets for electrophonic metabolites. The compounds that suppress cancer initiation are traditionally called blocking agents (Keum *et al.* 2004; Sharma *et al.* 2017).

Breast cancers are hormone-dependent tumors because the expression of estrogen receptors may depend on their development and growth (ER). Most breast cancers consist of heterogeneous ER-positive and negative cells. Bioactive agents that can inhibit both ER-positive and negative tumor growth are therefore of a considerable interest (Guthrie *et al.* 1997). Dietary phenols and flavonoids seem to display such dual activity; inhibiting both receptor-positive and negative breast cancer cells (Wang *et al.* 2012).

The results of this study showed that the extract of Egyptian artichoke wastes (leaves and *steam*) has efficacy against breast cancer, this can be benefited from through the potential use of these extracts as natural adjuvant agents in the chemotherapy and radiotherapy for tumor patients to increase the efficiency of the treatment, reduce therapeutic doses and reduce the cost of treatment. However, the main goal is to reduce or remove the side effects of chemotherapy and radiotherapy. Karahan and Ilcim (2017) reported that some medicinal and aromatic plants are effective to remove the side effect of radiotherapy in cancer treatment.

The combined treatment of natural polyphenols and chemotherapeutic agents has recently been shown to be more efficient than the drug alone in hindering cancer cell growth (Piccolo *et al.* 2015; Zou *et al.* 2018). Mileo *et al.* (2020) demonstrate that artichoke polyphenols extracts (AEs) have been shown to synergize with PTX or ADR in preventing the growth of MDA-MB231 or MCF7 cells as compared to the drug alone. AEs increased the sensitivity of breast cancer to PTX. Plausible clinical evidence is available for adjuvant treatment with honey, zinc, selenium, topical vitamin E and glutamine to reduce the risk of developing oral mucositis during chemotherapy or radiotherapy (Thomsen and Vitetta 2018). Münstedta *et al*. (2019) reported that conventional honey seems to be a very interesting option for the prophylaxis and treatment of radiotherapy-induced oral mucositis. Chinese medicinal herbs are useful and safe for the prevention and/or recovery of oral mucositis caused by radiotherapy (OM) (Wang and Jia 2019).

Conclusion

This study demonstrated that the extracts of Egyptian artichoke wastes (leaves and stems) are characterized by multiple biological activities (antioxidant anticancer and anticandidal activities) that have health benefits, therefore this study highlights the possibility of a potential role in the use of these extracts as additives to food for cancer patients for inhibiting cancer cell growth. Furthermore, they can be used to, reduce the side effects caused by radiotherapy, or be combined with conventional chemotherapeutic agents in order to increase the sensitivity to conventional chemotherapeutic, reduce the doses, and minimize toxicity and side effects. Moreover, phenolic compounds and flavonoids in artichoke wastes may represent a potential treatment option for COVID-19. Thus, it is possible to take advantage of the Egyptian artichoke wastes as a renewable source of basic nutrients such as protein, carbohydrates and fibers that are nutritionally important and healthy for humans or as the source of newly added-value ingredients with active properties that will support the entire food industry.

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Author Contributions

HHA designed and supervised the study. HHA and BMY performed experiments and statistical analysis. All the authors contributed in writing and editing of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

No humans or animals were used in this work.

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