Hindawi
Journal of Food Quality
Volume 2023, Article ID 7584688, 13 pages
https://doi.org/10.1155/2023/7584688

Research Article

Antioxidant and Hepatoprotective Effects of Fig Fruit Extract with Olive Oil and Date-Palm Fruit Extract on Hepatic Toxicity of Oral Subchronic Exposure to Some Nanoparticles in Wistar Rats

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Received 14 September 2022; Revised 12 January 2023; Accepted 24 April 2023; Published 1 June 2023

Academic Editor: Wen yi Kang

The aim is to study the possible protection of fig fruit extract with olive oil and date-palm fruit extract (FOD) as natural antioxidants in decreasing the subchronic toxicity hazards of SiO_2NPs, Al_2O_3NPs, or ZnONPs in male rats treated for 75 days. We used 80 male Wistar rats distributed into eight groups according to the treatment. The FOD antioxidant treatments were used at their recommended antioxidant doses. All nanoparticles (100 mg/kg) were given orally and daily for 75 days. Compared with the control, the oral administration of different NPs alone led to dramatic oxidative stress, liver function parameters, histopathological, p53, and inflammatory markers (TNF-α and IL-6). The FOD-NPs-treated groups recorded significantly reduced hepatotoxicity effects compared to those treated with NPs alone. In conclusion, the FOD supplementations to the rats ameliorate the NP's hepatotoxicity.

1. Introduction

Nanotechnology provides solutions for diagnosing and treating complex diseases based on nanomaterial (particle size range from 1 to 100 nm) [1]. As nanotechnology develops, there is an increasing risk of human exposure to nanoparticles [2]. When ingested or inhaled, the different nanoparticles behave similarly to the tiny biological molecules due to their nanometer dimensions. Long-term and short-term toxicities due to exposure to other nanoparticles negatively impact humans and animals [3]. Nanoparticles may enter the human body via various routes and reach multiple organs and systems. The invasion of these systems by nanoparticles causes many pathological disorders, DNA mutations, and eventually cell apoptosis/death [4, 5].

Silicon technology is considered a favorable material widely used in electronic components with low manufacturing costs and a thermally stable nature, while its oxides are often employed in biomedical procedures [6]. The potential toxicity of SiO_2NPs is limited to certain aspects, including their cytotoxicity, cellular adhesion, their effect on cell proliferation, and distribution throughout the body [7, 8]. Aluminum oxide nanoparticles (Al_2O_3NPs) have a growing market in various industries and biomedical areas and are used in multiple aspects of life, such as drug delivery, treatment of diseases, and destruction of microbes [9]. Exposure to Al_2O_3NPs causes toxicity to various body organs [10, 11]. Zinc oxide NPs (ZnO NPs) are used in many applications, including UV detectors, varistors, cosmetic and other products, and antibacterial agents [12]. Some studies suggest that ZnONPs might be inducing damage and toxicity to the biomolecules due to ROS generation, their effect on the integrity of DNA, and apoptosis [13].

Functional foods (supplements) are now used to retard, block, or reverse the cytotoxicity processes [14]. When the endogenous antioxidant defenses are inadequate to prevent

the damage entirely, there is a need to use an appropriate antioxidant intervention to reduce and inhibit free radical toxicity. Diet-derived antioxidants are essential in maintaining health [15].

The olive oil was divided into central (glycerol more than 98%) and minor (more than 230 chemical compounds, about 2%) fractions. The minor components include carotenoids, phenolic compounds, and antioxidants [16]. The fig was indigenous in southwestern Asia to northwest India. In numerous scientific studies, fig fruit has been reported to possess antioxidant, hepatoprotective, hypoglycemic, hypolipidemic, hypocholesterolemic, antipyretic, immunomodulatory, and anti-inflammatory [17, 18]. Dates were found to contain high-quality essential amino acids [19]. The date-palm fruit extract has potent antioxidants, antimutagenic, hepatoprotective, and immunomodulatory benefits to health [20]. The current research objected to explore the possible chemoprevention of fig fruit extract with olive oil and date-palm fruit extract (FOD) as natural antioxidants against different nanoparticle-induced subchronic hepatotoxicity in Wistar rats, including hepatic oxidative stress, inflammatory, histopathological alterations, and P53 content in the liver tissue.

2. Materials and Methods

2.1. Chemicals. We used analytical chemicals from standard suppliers.

2.1.1. Reagents

(1) Absolute ethanol used to prepare graduated ethanol (50%, 70%, 95%, and 100%)

(2) Paraffin wax used for tissue blocking

(3) 10% formalin saline used for tissue fixation

(4) Xylene

(5) Hematoxylin stain

(6) Eosin stain

2.2. Nanoparticles. The SiO_2NPs, Al_2O_3NPs, or ZnONPs were prepared (average size of less than 50 nm) and characterized in a private laboratory (Nanogate Laboratory, Cairo, Egypt). The structure of the nanoparticle was confirmed using a transmission electron microscope (JEM-2100, Jeol, Akishima, Japan) at the voltage of 200 kV and X-ray diffraction (XRD) analysis using a powder diffractometer system (X'pertPro-Panalytical, Malvern, United Kingdom) as shown in Figure 1.

2.3. Preparation of Nanoparticle (NPs) Treatments. The nanoparticles (SiO_2NPs, Al_2O_3NPs, and ZnONPs) were suspended in water. This suspension was vibrated by vortex for 5 min before injection to aid in preparing a homogeneous suspension. All nanoparticles were given orally by oral gavages for 75 consecutive days. All nanoparticles (SiO_2NPs, Al_2O_3NPs, and ZnONPs) were administered to rats at 100 mg/kg. bwt for 75 consecutive days as confirmed by a pilot study (data not shown), and the selected doses and dose regimen were found following previously published studies. The doses of SiO_2NPs followed Gmoshinski et al. [21], while Al_2O_3NPs doses followed Park et al. [22], and the doses of ZnONPs were following Yousef et al. [23].

2.4. Plant Materials and Authorities. We purchased the extra-virgin olive oil from Spain (Grup Pons Company), the fig fruit from Turkey (Kafoods Ltd.), and the date-palm fruit from Saudi Arabia (Al-MADINA AL-MUBARAK market). The plants were authenticated by Dr. Al-Baraa El-Saied (Al-Azhar University). The voucher specimens were placed at the medicinal plant's station.

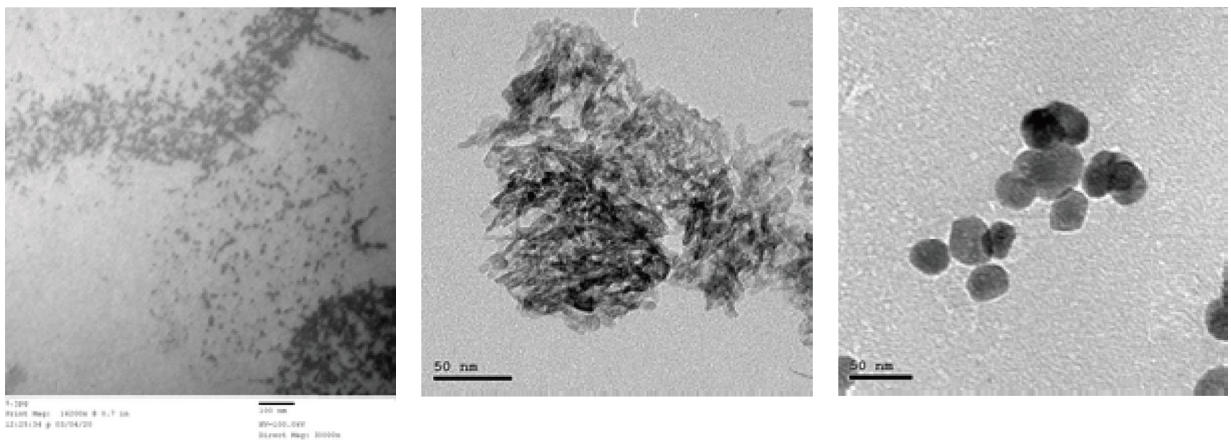
2.5. Preparation of Crude Extracts. Ficus carica fruit extract was prepared and lyophilized according to a previous method [17]. The fig fruit was cleaned of dirt, diced into little pieces, and dried in a 40°C oven. To preserve the active ingredients in the fig, the fig chunks were dried at this temperature before being electrically grounded coarsely. The powdered substance was combined five times with 80% ethanol for 72 hours while being sometimes shaken. On the plant debris, the previous extraction process was carried out twice. The filtrates were then mixed. The filtered material was evaporated on a rotary evaporator at a lower pressure, creating a thick paste-like substance that was dark brown in color.

The hydroalcoholic extract of the date fruit was made and lyophilized according to an earlier process [24]. The date-palm fruit was carefully removed from the pits and made clear of the surrounding dirt. Small chunks of the fruit's flesh were removed, dried in a 40°C oven, and coarsely grounded using an electrical tool. We created the extract by blending the crushed date fruit with 50% ethanol (1 : 3 mass to volume ratio) for 48 hours at 4°C while stirring continuously. A 20-minute, 1788 g centrifugation at 4°C was performed on the entire solution. The supernatant was gathered, dried, lyophilized, and kept at −20°C until it was needed.

2.6. Preparation of the Antioxidant Treatments. The olive oil oral supplementation doses (7 g/kg. bwt), fig, and date-palm fruit extracts (1 g/kg. bwt) were used according to Fathy et al. [25].

2.7. The Experimental Animals. The rats in the present study were purchased from VACSERA, Giza, Egypt, and were acclimated and housed under standard conditions at the animal facility, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

2.8. Animal Welfare. The animal study was conducted under the National Research Centre guidelines for the use and care of laboratory animals [26] and was approved by an independent ethics committee of the Faculty of Pharmacy, Ain Shams University.



(a) (b) (c)

Figure 1: Transmission electron microscope (TEM) images of silica nanoparticles (SiO2NPs): (a) alumina nanoparticles (Al_2O_3NPs) (b) and zinc oxide nanoparticles (ZnONPs) (c).

2.9. Experimental Design. We used 80 male Wistar rats average weight of 150–170 g divided into eight groups ($n = 10$) as the following:

(i) Group I (control): this group was supplied with standard pellets and water for 75 days

(ii) Group II (FOD): this antioxidant-treated group was orally supplied with extra-virgin olive oil (7 g/kg) and freshly prepared fig and date-palm fruit (1 g/kg) extracts daily for two weeks before and during the experimental period (75 days)

(iii) Group III (SiO_2NPs): this group was orally administered with SiO_2NPs (100 mg/kg) daily for 75 days

(iv) Group IV (FOD-SiO_2NPs): this group was supplied with FOD and SiO_2NPs as mentioned previously in groups II and III

(v) Group V (Al_2O_3NPs): this group was orally administered with Al_2O_3NPs (100 mg/kg) daily for 75 days

(vi Group VI (FOD-Al_2O_3NPs): this group was supplied with FOD and Al_2O_3NPs as mentioned previously in groups II and V

(vii) Group VII (ZnONPs): this group was orally administered with ZnONPs (100 mg/kg) daily for 75 days

(viii) Group VIII (FOD-ZnONPs): this group was supplied with FOD and ZnONPs as mentioned previously in groups II and VII

2.10. Preparation of Samples. At the end of each experiment, the rats were weighed, and the blood samples were collected from each animal under anesthesia (diethyl ether) from the retro-orbital venous plexus puncture using blood capillary tubes. The serum was prepared from the drained blood samples by centrifugation at 4000 rpm for 15 min. The prepared serum samples were frozen at −80°C until used. Then, the rats were dissected, and the liver tissues were removed, washed, and divided into two portions; one was used for the biochemical analysis, and the other was used for histopathology. The portion used for biochemical analysis was homogenized in a buffer solution using a rotor-stator homogenizer (USA). The homogenates were centrifuged, separated, and stored until used at −80°C.

2.11. Biochemical Study

2.11.1. Oxidative Stress Parameters. The oxidative stress markers (TAC, GSH, GR, GPx, GST, NO, SOD, CAT, and TBARS) were measured in the liver tissue homogenate by readymade kits purchased from Bio Diagnostic Co. for research kits, Egypt.

2.11.2. Inflammatory Markers. The tumor necrosis (TNF-α) was measured in the liver tissue homogenate using methods outlined in the ELISA kit (Catalog No: MBS2507393, MyBioSource, Inc. San Diego, USA). The interleukin-6 (IL-6) was measured in the liver tissue homogenate using methods outlined in the ELISA kit (Catalog No: E-EL-R0015, Elabscience Biotechnology, Inc., Texas, USA).

2.11.3. Apoptotic Biomarkers Estimation. The P53/tumor protein (p53/TP53) was measured in the liver tissue homogenate using methods outlined in the ELISA kit (Cusabio Technology LLC, Houston, USA).

2.11.4. Liver Function Tests. The liver parameters (AST, ALT, TBIL, GGT, TP, albumin, globulin, A/G ratio, and tissue ALP) were estimated by readymade kits purchased from Bio Diagnostic Co. for research kits, Egypt.

2.11.5. The Liver Tissue Histological Study. After the dissection of rats, the liver tissues were excised, washed in saline, fixed, processed (in alcohol series), sectioned (5 μm),

and stained (HX & E) following the micro techniques outlined in Bancroft and Gamble [27].

2.12. Statistical Analysis. The data analysis (SPSS/PC program) was conducted using ANOVA one-way followed by LSD post hoc. The results were shown as mean ± SE. The significance level was at $p < 0.05$.

3. Results

3.1. The Effects of the FOD on the Oxidative Stress Markers of the Liver Tissue of Male Rats Treated with SiO_2NPs, Al_2O_3NPs, or ZnONPs for 75 Days. The FOD and FOD-SiO_2NPs-treated groups showed insignificant changes in oxidative stress markers compared with control values (Table 1).

The SiO_2NPs-, Al_2O_3NPs-, and ZnONPs-treated groups showed a significant decrease in the TAC (11.76%, 29.58%, and 35.42%, respectively), GSH (16.49%, 37.36%, and 39.01%, respectively), GR (10.43%, 39.89%, and 43.26%, respectively), GPx (15.69%, 56.18%, and 59.54%, respectively), GST (16.05%, 42.58%, and 45.00%, respectively), CAT (11.88%, 23.30%, and 26.80%, respectively), and SOD (10.09%, 22.28%, and 24.07%, respectively), in the liver tissue in contrary to a significant increase in the NO (26.39%, 48.27%, and 57.97%, respectively), and TBARS (19.24%, 52.70%, and 58.26%, respectively) as compared with the control (Table 1).

Similarly, the groups treated with the FOD-Al_2O_3NPs, and FOD-ZnONPs recorded a significant decrease in the TAC (17.18%, and 24.12%, respectively), GSH (28.35%, and 31.64%, respectively), GR (20.12%, and 23.31%, respectively), GPx (12.86%, and 15.49%, respectively), GST (11.20%, and 11.51%, respectively), and CAT (15.02%, and 16.97%, respectively) SOD (8.05%, and 13.45%, respectively), in the liver tissue in contrary to a significant increase in the NO (16.51%, and 12.43%, respectively), and TBARS (26.53%, and 38.71%, respectively) as compared with the control group (Table 1).

The groups treated with the FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs recorded a significant increase in the TAC, GSH, GR, GPx, GST, CAT, and SOD in the liver tissue; on the contrary to a significant decrease in the NO, TBARS as compared with the groups treated with the SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively (Table 1).

3.2. The Effects of the FOD on the Hepatic Tumor Suppressor p53 and Inflammatory Markers of Male Rats Administered with SiO_2NPs, Al_2O_3NPs, or ZnONPs for 75 Days. Compared with the control, the FOD and FOD-SiO2NPs-treated groups show insignificant changes in the hepatic p53 and the measured inflammatory markers (Figures 2–4).

The groups treated with the SiO_2NPs, Al_2O_3NPs, and ZnONPs recorded a significant increase in the hepatic p53 (29.66%, 51.53%, and 52.14%, respectively), hepatic TNF-α (21.17%, 90.96%, and 140.50%, respectively), and hepatic IL-6 (11.11%, 25.50%, and 21.39%, respectively) as compared with the control group (Figures 2–4).

Similarly, the groups treated with the FOD-Al_2O_3NPs and FOD-ZnONPs recorded a significant increase in the hepatic p53 (42.85%, and 45.44%, respectively), hepatic TNF-α (74.83%, and 122.43%, respectively), and hepatic IL-6 (13.17%, and 10.53%, respectively) compared with the control group (Figures 2–4).

The groups treated with the FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs recorded a significant decrease in the hepatic p53, hepatic TNF-α, and hepatic IL-6 as compared with the groups treated with the SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively (Figures 2–4).

3.3. The Effects of FOD on the Liver Markers of Male Rats Treated with SiO_2NPs, Al_2O_3NPs, or ZnONPs for 75 Days. The FOD and the FOD-SiO_2NPs-treated groups showed insignificant changes in ALP, AST, ALT, TBIL, GGT, TP, albumin, and globulin in the serum compared with the control group (Table 2).

The groups treated with the SiO_2NPs, Al_2O_3NPs, and ZnONPs recorded a significant increase in the ALP (21.69%, 39.81%, and 45.86%, respectively), AST (14.24%, 25.99%, and 29.30%, respectively), ALT (14.58%, 31.12%, and 34.30%, respectively), TBIL (68.42%, 101.75%, and 128.07%, respectively), GGT (39.27%, 72.25%, and 76.28%, respectively), in the serum in contrary to a significant decrease in the TP (21.49%, 41.85%, and 48.50%, respectively), albumin (15.39%, 38.39%, and 39.28%, respectively), and globulin (28.25%, 45.69%, and 58.72%, respectively) in the serum compared with the control group (Table 2).

Similarly, the groups treated with the FOD-Al_2O_3NPs, and FOD-ZnONPs recorded a significant increase in the ALP (16.24%, and 24.67%, respectively), AST (13.58%, and 15.40%, respectively), ALT (21.21%, and 26.36%, respectively), TBIL (54.39%, and 63.16%, respectively), GGT (30.39%, and 45.22%, respectively), in the serum, in contrary to a significant decrease in the TP (27.61%, and 33.28%, respectively), albumin (18.88%, and 28.03%, respectively), and globulin (37.28%, and 39.09%, respectively) in the serum as compared with the control group (Table 2).

The groups treated with the FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs recorded a significant decrease in the serum ALP, AST, ALT, TBIL, and GGT in contrast to a significant increase in the TP and albumin in the serum as compared with the SiO_2NPs-, Al_2O_3NPs-, and ZnONPs-treated groups, respectively (Table 2).

The groups treated with the FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs recorded insignificant changes in the serum globulin compared with the groups treated with the SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively (Table 2).

3.4. The Effects of the FOD on the Liver Histopathological Characters of Male Rats Treated with SiO_2NPs, Al_2O_3NPs, or ZnONPs for 75 Days. The control liver showed a normal morphological appearance. However, the antioxidant-treated NPs administered groups (FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs) recorded significantly ameliorated liver histopathological characters as compared

Table 1: The effects of fig with olive oil and date-palm fruit extract on the oxidative stress markers in the liver tissue of male rats treated with silicon oxide nanoparticles, aluminum oxide nanoparticles, or zinc oxide nanoparticles for 75 days.

Parameters	Experimental groups							
	Control	FOD	SiO_2NPs	FOD-SiO_2NPs	Al_2O_3NPs	FOD-Al_2O_3NPs	ZnONPs	FOD-ZnONPs
Hepatic TAC (μmol/g tissue)	2.38 ± 0.03	2.33 ± 0.03 −1.85%	2.1 ± 0.03^{a} −11.76%	2.28 ± 0.03^{b} −4.20%	1.67 ± 0.08^{a} −29.58%	$1.97 \pm 0.09^{a,c}$ −17.18%	1.53 ± 0.08^{a} −35.42%	$1.80 \pm 0.10^{a,d}$ −24.12%
Hepatic GSH (mmol/g tissue)	5.26 ± 0.04	5.28 ± 0.01 0.40%	4.39 ± 0.06^{a} −16.49%	5.06 ± 0.12^{b} −3.84%	3.29 ± 0.12^{a} −37.36%	$3.77 \pm 0.16^{a,c}$ −28.35%	3.21 ± 0.09^{a} −39.01%	$3.59 \pm 0.14^{a,d}$ −31.64%
Hepatic GR activity (U/g tissue)	70.5 ± 0.66	71.5 ± 1.06 1.35%	63.2 ± 1.83^{a} −10.43%	67.9 ± 0.75^{b} −3.64%	42.4 ± 1.90^{a} −39.89%	$56.3 \pm 2.20^{a,c}$ −20.12%	40.0 ± 1.91^{a} −43.26%	$54.1 \pm 2.11^{a,d}$ −23.31%
Hepatic GPx activity (U/g tissue)	155 ± 2.09	155 ± 2.46 0.13%	131 ± 3.53^{a} −15.69%	150 ± 2.30^{b} −3.57%	68.1 ± 3.55^{a} −56.18%	$135 \pm 5.74^{a,c}$ −12.86%	62.9 ± 2.12a −59.54%	$131 \pm 4.34^{a,d}$ −15.49%
Hepatic GST activity (U/g tissue)	4.16 ± 0.07	4.20 ± 0.09 0.89%	3.5 ± 0.13^{a} −16.05%	4.02 ± 0.05^{b} −3.50%	2.39 ± 0.07^{a} −42.58%	$3.70 \pm 0.11^{a,c}$ −11.20%	2.29 ± 0.05^{a} −45.00%	$3.68 \pm 0.12^{a,d}$ −11.51%
Hepatic CAT activity (U/g tissue)	0.88 ± 0.00	0.90 ± 0.01 2.38%	0.77 ± 0.02^{a} −11.88%	0.85 ± 0.01^{b} −3.69%	0.67 ± 0.02^{a} −23.30%	$0.75 \pm 0.02^{a,c}$ −15.02%	0.64 ± 0.04^{a} −26.80%	$0.73 \pm 0.01^{a,d}$ −16.97%
Hepatic SOD activity (U/g tissue)	172 ± 2.62	173 ± 3.10 0.58%	155 ± 5.73^{a} −10.09%	167 ± 1.34^{b} −3.36%	134 ± 1.68^{a} −22.28%	$158 \pm 7.32^{a,c}$ −8.05%	131 ± 2.81^{a} −24.07%	$149 \pm 8.69^{a,d}$ −13.45%
Hepatic NO conc. (μmol/g tissue)	3.33 ± 0.18	3.14 ± 0.14 −5.61%	4.21 ± 0.21^{a} 26.39%	3.39 ± 0.14^{b} 1.98%	4.93 ± 0.14^{a} 48.27%	$3.88 \pm 0.19^{a,c}$ 16.51%	5.26 ± 0.11^{a} 57.97%	$3.74 \pm 0.20^{a,d}$ 12.43%
Hepatic TBARS conc. (nmol/g tissue)	32.5 ± 0.40	31.7 ± 1.13 −2.55%	38.8 ± 1.30^{a} 19.24%	33.9 ± 0.75^{b} 4.25%	49.6 ± 2.43^{a} 52.70%	$41.1 \pm 1.61^{a,c}$ 26.53%	51.4 ± 1.97^{a} 58.26%	$45.1 \pm 1.96^{a,d}$ 38.71%

Note. Results are the mean ± standard error; %, percent of change from the control value; FOD, fig with olive oil and date-palm fruit extracts; SiO_2NPs, silicon oxide nanoparticles; Al_2O_3NPs, aluminum oxide nanoparticles; ZnONPs, zinc oxide nanoparticles; TAC, total antioxidant capacity; GSH, reduced glutathione; GR, glutathione reductase; GPx, glutathione peroxidase; GST, glutathione S-transferase; NO; nitric oxide; SOD, superoxide dismutase; CAT, catalase; TBARS, thiobarbituric acid reactive substances. For each parameter: $^{a}p < 0.05$, versus the control group; $^{b}p < 0.05$, versus SiO_2NPs; $^{c}p < 0.05$, versus Al_2O_3NPs; $^{d}p < 0.05$, versus ZnONPs. The antioxidants (FOD) were used for two weeks before and during the administration of the nanoparticles (75 days).

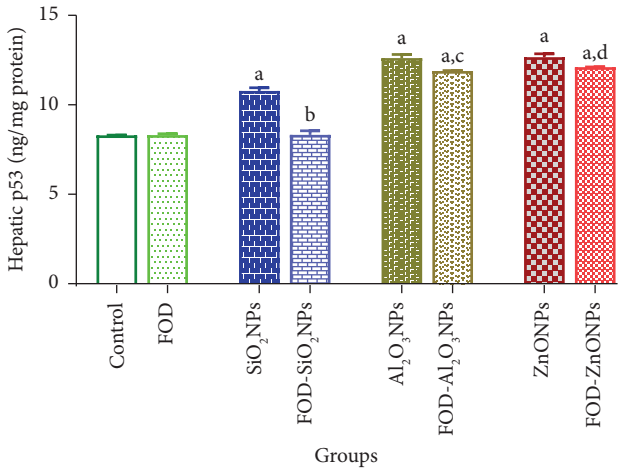


Figure 2: The effects of fig with olive oil and date-palm fruit extracts (FOD) on the hepatic tumor suppressor p53 (p53) in rats treated with different nanoparticles (NPs) for 75 days. $^{a}p < 0.05$, versus control group; $^{b}p < 0.05$, versus SiO_2NPs; $^{c}p < 0.05$, versus Al_2O_3NPs; $^{d}p < 0.05$, versus ZnONPs. Note: The antioxidants (FOD) treatments were used for two weeks before and during the administration of the nanoparticles.

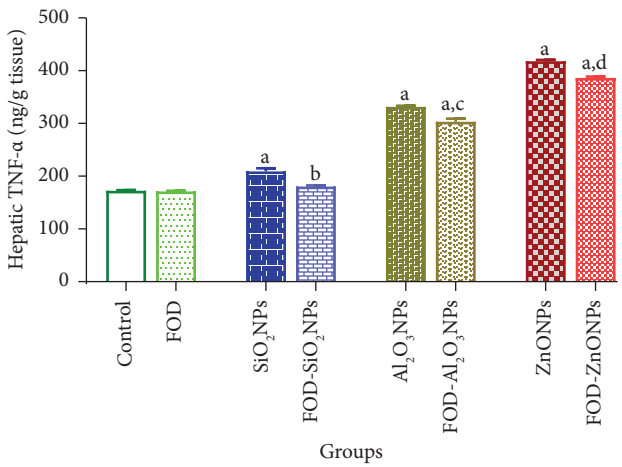


Figure 3: The effects of fig with olive oil and date-palm fruit extracts (FOD) on the hepatic tumor necrosis factor-α (TNF-α) in rats treated with different nanoparticles (NPs) for 75 days. $^{a}p < 0.05$, versus control group; $^{b}p < 0.05$, versus SiO_2NPs; $^{c}p < 0.05$, versus Al_2O_3NPs; $^{d}p < 0.05$, versus ZnONPs. Note: The antioxidants (FOD) treatments were used for two weeks before and during the administration of the nanoparticles.

with values in the nonantioxidant-treated NPs administered groups (SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively) as indicated in Table 3 and Figure 5.

4. Discussion

With the progress in the nanotechnology field, there may be an increase in the exposure of humans to various nanoparticles, so further urgent studies are required to study the possibility of any detrimental health impacts and their mechanisms [28, 29]. Nanoparticles can be translocated

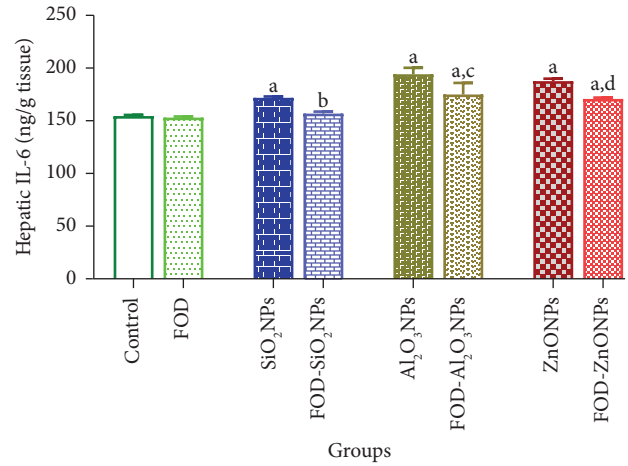


Figure 4: The effects of fig with olive oil and date-palm fruit extracts (FOD) on the hepatic interleukin-6 (IL-6) in rats treated with different nanoparticles (NPs) for 75 days. $^{a}p < 0.05$, versus control group; $^{b}p < 0.05$, versus SiO_2NPs; $^{c}p < 0.05$, versus Al_2O_3NPs; $^{d}p < 0.05$, versus ZnONPs. Note: The antioxidants (FOD) treatments were used for two weeks before and during the administration of the nanoparticles.

from the entry portals into the blood circulation and the lymphatic system and then to body organs and tissues. They can cause irreversible cell damage by oxidative stress and organelle injuries because of their sizes and structures, leading to severe cytotoxicities [30]. Body organ dysfunction may result from distributing these nanoparticles to other organs [23].

Our study confirmed the subchronic hepatic toxicity of rats treated with SiO_2NPs, Al_2O_3NPs, or ZnONPs for 75 days of oral administration as agreed with other studies [31, 32], which indicated that the liver toxicity due to NPs administration might be due to induction of lipid peroxidation, oxidative stress, systemic inflammation, and hepatic toxicity.

In the present study, regarding the liver oxidative stress markers, the subchronic oral administration of the SiO_2NPs, Al_2O_3NPs, and ZnONPs for consecutive 75 days recorded a significant reduction in the TAC, GSH, GR, GPx, GST, SOD, and CAT in contrast to a considerable elevation in the NO, and TBARS compared with their corresponding control values. That agrees with previous studies [3, 23, 32] that recorded a significant decrease in the antioxidants after SiO_2NPs, Al_2O_3NPs, or ZnONPs administration. In addition, Li et al. [33] and Yousef et al. [23] reported that nanoparticles such as SiO_2NPs, Al_2O_3NPs, or ZnONPs could generate many deleterious ROS that led to their toxic effects, cellular dysfunction, and cell death. The ROS interact with and cause damage to the cellular molecules [34].

The oxidative damage to cells caused an alteration in both lipid bilayer fluidity and permeability properties [35]. In agreement with the present results, there was a directly proportional relationship between TBARS and the oxidative stress that caused biochemical alterations in different parameters [36, 37]. The increased TBARS after SiO_2NPs, Al_2O_3NPs, or ZnONPs administration could be attributed to

Table 2: The effects of fig with olive oil and date-palm fruit extract on the liver function markers of male rats treated with silicon oxide nanoparticles, aluminum oxide nanoparticles, and zinc oxide nanoparticles for 75 days.

Parameters	Experimental groups							
	Control	FOD	SiO_2NPs	FOD-SiO_2NPs	Al_2O_3NPs	FOD-Al_2O_3NPs	ZnONPs	FOD-ZnONPs
Hepatic ALP (U/g tissue)	49.4 ± 0.77	48.9 ± 1.15 −1.12%	60.2 ± 3.49[a] 21.69%	52.2 ± 1.17[b] 5.61%	69.1 ± 1.95a 39.81%	57.5 ± 2.77[a,c] 16.24%	72.1 ± 1.42[a] 45.86%	61.6 ± 0.97[a,d] 24.67%
Serum AST (U/mL)	60.4 ± 2.15	60 ± 2.47 −0.66%	69 ± 1.73[a] 14.24%	63.5 ± 1.33[b] 5.13%	76.1 ± 1.62[a] 25.99%	68.6 ± 1.74[a,c] 13.58%	78.1 ± 1.61[a] 29.30%	69.7 ± 1.47[a,d] 15.40%
Serum ALT (U/mL)	107 ± 3.69	106 ± 3.15 −0.93%	122.±4.71[a] 14.58%	111.±3.14[b] 3.93%	140.±1.54[a] 31.12%	129.±3.97[a,c] 21.21%	143.±3.58[a] 34.30%	135.±3.01[a,d] 26.36%
Serum TBIL (mg/dL)	0.05 ± 0.00	0.05 ± 0.00 3.51%	0.09 ± 0.01[a] 68.42%	0.07 ± 0.00[b] 26.32%	0.11 ± 0.01[a] 101.75%	0.08 ± 0.00[a,c] 54.39%	0.13 ± 0.01[a] 128.07%	0.09 ± 0.01[a,d] 63.16%
Serum GGT (U/L)	2.08 ± 0.16	1.98 ± 0.15 −4.85%	2.90 ± 0.30[a] 39.27%	2.26 ± 0.26[b] 8.83%	3.58 ± 0.18[a] 72.25%	2.71 ± 0.14[a,c] 30.39%	3.67 ± 0.15[a] 76.28%	3.02 ± 0.26[a,d] 45.22%
Serum TP (g/dL)	7.89 ± 0.45	7.94 ± 0.53 0.60%	6.2 ± 0.37[a] −21.49%	7.77 ± 0.58[b] −1.49%	4.59 ± 0.18[a] −41.85%	5.71 ± 0.32[a,c] −27.61%	4.06 ± 0.31[a] −48.50%	5.26 ± 0.27[a,d] −33.28%
Serum albumin (g/dL)	4.15 ± 0.12	4.39 ± 0.18 5.76%	3.51 ± 0.15[a] −15.39%	4.03 ± 0.14[b] −2.84%	2.55 ± 0.18[a] −38.39%	3.36 ± 0.22[a,c] −18.88%	2.52 ± 0.20[a] −39.28%	2.98 ± 0.30[a,d] −28.03%
Serum globulin (g/dL)	3.74 ± 0.50	3.55 ± 0.61 −5.13%	2.68 ± 0.44[a] −28.25%	3.74 ± 0.61 10.00%	2.03 ± 0.29[a] −45.69%	2.34 ± 0.31[a] −37.28%	1.54 ± 0.34[a] −58.72%	2.28 ± 0.37[a] −39.09%
A/G ratio (g/dL)	1.36 ± 0.23	1.52 ± 0.32 11.19%	1.65 ± 0.42 21.02%	1.37 ± 0.41 0.38%	1.55 ± 0.43 13.89%	1.63 ± 0.30 19.37%	2.25 ± 0.61 64.58%	1.62 ± 0.38 18.68%

Note. Results are the mean ± standard error; %, percent of change from the control value; FOD, fig with olive oil and date-palm fruit extracts; SiO_2NPs, silicon oxide nanoparticles; Al_2O_3NPs, aluminum oxide nanoparticles; ZnONPs, zinc oxide nanoparticles; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; TBIL, total bilirubin; GGT, gamma-glutamyl transferase; TP, total protein; A/G, albumin-globulin ratio. For each parameter: [a]$p < 0.05$, versus the control group; [b]$p < 0.05$, versus SiO_2NPs; [c]$p < 0.05$, versus Al_2O_3NPs; [d]$p < 0.05$, versus ZnONPs. The antioxidants (FOD) were used for two weeks before and during the administration of the nanoparticles (75 days).

Table 3: The effects of fig with olive oil and date-palm fruit extract on the liver histopathological results of male rats treated with silicon oxide nanoparticles, aluminum oxide nanoparticles, or zinc oxide nanoparticles for 75 days.

	Portal tract				Peri-venular area			
	PV	Inflammatory infiltrate	Edema	Hepatocytes	CV	Blood sinusoids	Hepatocytes	Inflammatory infiltrate
Control	0	0	0	0	0	0	0	0
SiO_2NPs	++	0	+	++	++	+	++	0
FOD-SiO_2NPs	+	0	+	+	0	0	0	0
Al_2O_3NPs	+	+	0	+	0	0	0	0
FOD-Al_2O_3NPs	0	0	0	0	0	+	0	0
ZnONPs	0	+	0	+	+	0	+	0
FOD-ZnONPs	0	0	0	0	0	0	+	0

FOD, fig with olive oil and date-palm fruit extracts; SiO_2NPs, silicon oxide nanoparticles; Al_2O_3NPs, aluminum oxide nanoparticles; ZnONPs, zinc oxide nanoparticles. Portal tract: portal vein (PV): 0: average, +: mildly dilated/congested, ++: markedly dilated/congested. Inflammatory infiltrate: 0: no, +: mild, ++: moderate/marked. Edema: 0: no, +: mild, ++: moderate/marked. Hepatocytes: 0: average, +: few/scattered apoptoses, ++: marked apoptosis. Peri-venular area: central vein: 0: average, +: mildly dilated/congested, ++: markedly dilated/congested. Blood sinusoids: 0: average, +: mildly dilated/congested, ++: markedly dilated/congested. Hepatocytes: 0: average, +: few/scattered apoptoses, ++: marked apoptosis. Inflammatory infiltrate: 0: no, +: mild, ++: moderate/marked.

the produced ROS that interacts with the phospholipids portion of the cell membrane and initiates the lipid peroxidation chain reaction [23, 32].

The GSH maintains the normal reduced status of the cells and counteracts oxidative stress by conjugation with GPx and GST [29, 38]. In addition, GSH is a major endogenous antioxidant. Therefore, it is used as a marker for counteracting a variety of toxicants and can function as an antioxidant in many ways [39]. The present data confirmed the previous reports of Wu et al. [40] and Bashandy et al. [37], who revealed that the glutathione deficiency contributed to oxidative stress due to its diffusion or inhibition of GSH synthetase/reductase enzymes.

The antioxidant enzymes (SOD and CAT) play a vital role in antioxidant defense. The SOD utilizes free radicals as a substrate. The CAT is an index of increased H_2O_2 production and transforms it into water [41]. As in the present study, the depletion of these enzymes may be due to an enhanced radical production during SiO_2NPs, Al_2O_3NPs, or ZnONPs administration [4, 5, 23].

The oxidative stress due to NPs administration causes increased NO production, which reacts with superoxide to form peroxynitrite ($ONOO^-$) and peroxynitrous acid that initiates the cascade of lipid peroxidation and accelerate cell toxicity [3].

The present study demonstrated that the antioxidant-treated NPs administered groups (FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs) treated for two weeks before and during the administration of the nanoparticles (75 days) recorded significantly ameliorated hepatic oxidative stress markers when compared with the nonantioxidant-treated NPs administered groups (SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively). The FOD treatment counteracted the free radical toxicity in the present study due to many antioxidants [37, 42]. Our results showed that FOD effectively reduced oxidative stress induced by the NP administration. More attention has been paid to natural antioxidants due to their protective effects against metals-induced toxicity, especially when reactive oxygen species are involved. Olive oil is among these natural antioxidants [43]. Moreover, the antioxidant component cyanidin-3-rhamnoglucoside (C3R) present in the fig fruit may reduce oxidative stress and improve liver function [44]. In addition, it has been demonstrated by several phytochemical studies that date-palm fruits contain many antioxidants that act as free radical scavengers [45].

Regarding the inflammatory markers, the SiO_2NPs, Al_2O_3NPs, and ZnONPs-treated groups for consecutive 75 days as subchronic oral administration recorded significant elevation in the hepatic TNF-α and hepatic IL-6 compared with the control values. The liver can accumulate more than 90% of nanoparticles. Activation of Kupffer cells due to NPs administration elicits the release of different mediators such as TNF-α, IL-Iβ, and IL-6 [46]. When administrated to rats, NPs such as SiO_2NPs, Al_2O_3NPs, or ZnONPs entering the body cause changes in inflammatory cytokines. It causes the elevation of proinflammatory cytokines (IL-1β and IL-6) [23, 47]. In line with these data, amorphous silica (SiO_2NPs) nanoparticles significantly increased transient inflammatory response after intratracheal instillation [47] and induced proinflammatory responses such as IL-6, IL-Iβ, and TNF-α release. Moreover, Faddah et al. [48] found that ZnONPs administration can elevate the inflammatory markers in the blood. In addition, Hou et al. [49] described that exposure to Al_2O_3NPs stimulates the immune system and altered cytokine levels.

Understanding the effects of nanoparticles on the cellular genome is very important to evaluate the extent of toxicity [50]. In the present study, regarding the tumor suppressor p53, the SiO_2NPs, Al_2O_3NPs, and ZnONPs administered groups recorded a significant elevation in the p53 compared with the control group. That elevation may participate in inducing hepatocytes apoptosis in response to the NP's administration, as agreed by Yousef et al. [23]. Nanoparticles may also aggravate stress-induced apoptosis in the liver, suggesting that they may be dangerous to liver disease patients [51]. In addition, Vurusaner et al. [52] described the activation of p53 in response to oxidative stress, which performs antioxidant functions.

The present study demonstrated that the antioxidant-treated subchronic NPs administered groups (FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs) treated for

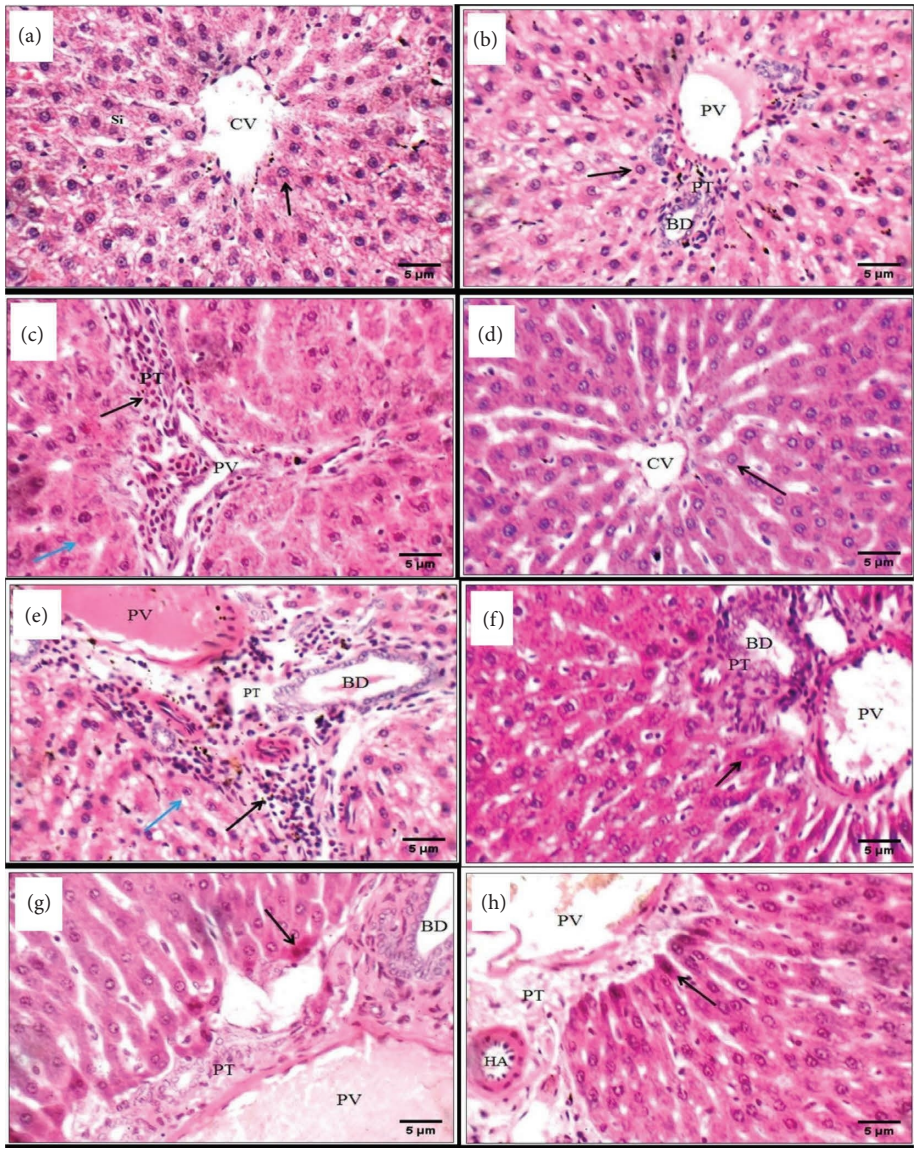


Figure 5: The effects of fig with olive oil and date-palm fruit extracts (FOD) on the microscopic histological appearance of livers treated with different nanoparticles (NPs) for 75 days. (a) Higher power view of the control liver showing average central veins (CV) and average hepatocytes in peri-venular area (black arrow) with average blood sinusoids (Si); (b) FOD-treated group showing average portal tracts (PT) with average portal veins (PV), average bile ducts (BD), and average hepatocytes in peri-portal area (black arrow); (c) SiO_2NPs-treated group showing portal tracts with mild portal inflammatory infiltrate (black arrow), average portal vein (PV), and scattered apoptotic hepatocytes in peri-portal area (blue arrow); (d) FOD-SiO_2NPs-treated group showing average central veins (CV) and average hepatocytes in peri-venular area (black arrow); (e) Al_2O_3NPs-treated group showing portal tracts with mild portal inflammatory infiltrate (black arrow) with mildly dilated congested portal veins (PV), average bile ducts (BD), and average hepatocytes in peri-portal area (blue arrow); (f) FOD-Al_2O_3NPs-treated group showing average portal tracts (PT) with average portal veins (PV), average bile ducts (BD), and average hepatocytes in peri-portal area (black arrow); (g) ZnO NPs-treated group showing mildly edematous portal tracts (PT) with markedly dilated congested portal veins (PV), average bile ducts (BD), and moderate apoptotic hepatocytes in peri-portal area (black arrow); (h) FOD-ZnO NPs-treated group showing mildly edematous portal tracts (PT) with mildly dilated portal veins (PV), average hepatic artery (HA), and few scattered apoptotic hepatocytes in peri-portal area (black arrow).

two weeks before and during the administration of the nanoparticles (75 days) significantly ameliorated hepatic p53 and inflammatory markers when compared with the nonantioxidant-treated NPs administered groups (SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively). In agreement, FOD has been studied as a potential antioxidant and anti-inflammatories because of their polyphenol contents which stimulate apoptosis and inhibit cell proliferation [53, 54]. Reporter assays indicated that many plants possessed antitoxic activity for different cell lines, including the colon, ovary, liver, kidney, central nervous system, and gastric cells treated with various toxic agents [55, 56]. These authors related this effect to the antiproliferative activity of these plants. In addition, the antitumor efficacy of FOD may

ascribe to the synergies between them [18, 37, 57]. In addition, oleuropein (major phenol for olive products) and hydroxytyrosol (one of the most potent antioxidants in olive oil) may also act through the modulation of oncogenic signaling pathways, leading to cell apoptosis [58]. In addition, few studies demonstrate that the different components of FOD could block and suppress tumor growth and inflammation [57, 59].

Any disruption of the function of hepatic cells can lead to alteration in the blood serum constituents and enzyme functions [55, 60]. The current study showed that SiO_2NPs, Al_2O_3NPs, or ZnONPs as subchronic oral administrations for 75 days have adverse influences on the liver and cause a significant effect on the liver function parameters, which was consistent with other studies [23, 61]. Changes in serum biochemical parameter levels directly indicate the pathological status of the liver. In clinical practice, high serum AST, ALT, and ALP levels produced from damaged hepatic cells in the circulation are related to severe liver dysfunctions [62, 63]. This finding suggests that the retention of nanoparticles injured hepatocytes. Many studies reported that SiO_2NPs, Al_2O_3NPs, or ZnONPs caused dose-dependent liver injury in rodents [23, 47].

The changes in AST, ALT, GGT, and ALP, besides the increase of TBIL, were markers of liver injury and indicated cellular leakage and impaired cell membranes [64]. The GGT is a hepatocyte plasma membrane enzyme found mainly in the canalicular domain and is considered the best indicator of liver damage. The increased serum GGT in response to the NPs administration in the present study indicates damage to the hepatic cells and liver injury, as agreed with other studies [63, 65]. The elevation in ALP activity and TBIL in NPs administration groups might be attributed to liver diseases or the bile duct obstruction that led to the release of this enzyme in the blood [23].

The serum proteins were synthesized and secreted by several cell types and function in the osmotic regulation of body fluids. In agreement, some studies [23, 66] suggested that decreased serum albumin in the SiO2NPs, Al_2O_3NPs, or ZnONPs administrated rats might be due to liver damage or changes in the permeability of liver cell membranes. The decreased albumin might also be due to the slower rate of its synthesis [4, 67].

The antioxidant-treated NPs administered groups (FOD-SiO_2NPs, FOD-Al_2O_3NPs, and FOD-ZnONPs) for two weeks before and during the administration of the nanoparticles (75 days) significantly ameliorated liver functions compared with the nonantioxidant-treated NPs administered groups (SiO_2NPs, Al_2O_3NPs, and ZnONPs, respectively). Our results showed that FOD effectively reduced the increased liver function parameters induced by the NP administration, which could be attributed to the many antioxidants and polyphenolic compounds found in FOD and responsible for hepatoprotective impacts of FOD against many toxins. In addition, the amelioration in the NP-administrated groups treated with FOD might be attributed to the existence of chemical components in the extract and the antihepatotoxic effects of FOD. [17, 68]. The reversal of plasma enzyme activity elevation in NPs-induced hepatotoxicity revealed that FOD could lower hepatocyte death. Thus, it probably effectively ameliorates NPs induced liver injury [69]. In addition, in the present work, the possible mechanism of hepatoprotection of FOD may be attributed to the antioxidant activity of its components [25, 70].

The current results are consistent with Domitrovic et al. [71], who stated that oleuropein decreased transaminases in a dose-dependent manner at carbon tetrachloride-induced liver damage in mice. In addition, the result of the current study was also in agreement with those of Amiri et al. [72], who stated that the administration of virgin olive oil to mice significantly decreases liver enzymes in the serum. Also, the results of the present study were similar to those of Al-Seeni et al. [73], who observed that rats injected with carbon tetrachloride (CCl_4) and cotreated with olive oil recorded significantly decreased liver enzymes, in contrast, to significantly increased total protein and albumin as compared with the control group. This improvement could be explained by Bulotta et al. [54], who stated that virgin olive oil contains natural antioxidants such as hydroxytyrosol and oleuropein that act as free radical scavengers. In agreement, Singhal et al. [74] and Bashandy et al. [37] reported that the fig fruit extract was responsible for improving various antioxidant and liver function parameters in irradiated rats. In agreement, the treatments with the fruit extract of the date palm ameliorate liver functions [75, 76].

As agreed with the present study, the liver damage caused by SiO_2NPs, Al_2O_3NPs, or ZnONPs is further confirmed by histopathological examination, which showed many pathological features, including necrosis, dilation of central veins, and their congestion with blood, edema, and degeneration of the hepatocytes [23, 61].

The antioxidant-treated NPs groups in the current work recorded significantly ameliorated histopathological characteristics when compared with the nonantioxidant-treated NPs groups. The protection of the liver in response to FOD administration may be due to decreased or prevented lipid peroxidation and protein oxidation [37, 77].

5. Conclusion

The FOD treatments in the NPs administered groups are protective against different NPs-induced subchronic hepatotoxicity in male Wistar albino rats. The present findings also revealed the ameliorative effects of FOD in the treatment of NPs toxicity by modulating oxidative stress, inflammation, apoptosis, and toxification hazards. In addition, the administration of FOD revealed a synergistic effect between their components.

Data Availability

The data supporting the current study are available from the corresponding author upon request.

Ethical Approval

The Research Ethical Committee approved the study protocol, Faculty of Pharmacy, Ain Shams University, and conducted it according to the regulations and recommendations of the ethical guidelines and complied with the guide for the care and use of laboratory animals.

Consent

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

This work was carried out in collaboration with all authors. All authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank all Animal House Facility Department staff, Faculty of Pharmacy, Ain shams University for their kind cooperation in completing the present study. The authors are profoundly grateful to Prof. Dr. Sayed Abdel Raheem, Professor of Histopathology, Al-Azhar Faculty of Medicine, Cairo, for his kind help during the histopathological investigation of liver tissues.

References

[1] W. R. Sanhai, J. H. Sakamoto, R. Canady, and M. Ferrari, "Seven challenges for nanomedicine," *Nature Nanotechnology*, vol. 3, no. 5, pp. 242–244, 2008.

[2] J. Wu, W. Liu, C. Xue et al., "Toxicity and penetration of TiO2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure," *Toxicology Letters*, vol. 191, no. 1, pp. 1–8, 2009.

[3] T. Wu and M. Tang, "Review of the effects of manufactured nanoparticles on mammalian target organs," *Journal of Applied Toxicology*, vol. 38, no. 1, pp. 25–40, 2018.

[4] Y. Zhang, Y. Bai, J. Jia et al., "Perturbation of physiological systems by nanoparticles," *Chemical Society Reviews*, vol. 43, no. 10, pp. 3762–3809, 2014.

[5] A. B. Sengul and E. Asmatulu, "Toxicity of metal and metal oxide nanoparticles: a review," *Environmental Chemistry Letters*, vol. 18, no. 5, pp. 1659–1683, 2020.

[6] V. Balakrishnan, H. A. Ab Wab, K. Abdul Razak, S. Shamsuddin, and S. Shamsuddin, "In vitro evaluation of cytotoxicity of colloidal amorphous silica nanoparticles designed for drug delivery on human cell lines," *Journal of Nanomaterials*, vol. 2013, Article ID 729306, 8 pages, 2013.

[7] K. S. Brammer, C. Choi, S. Oh et al., "Antibiofouling, sustained antibiotic release by Si nanowire templates," *Nano Letters*, vol. 9, no. 10, pp. 3570–3574, 2009.

[8] J. S. Kim, E. Kuk, K. N. Yu et al., "Antimicrobial effects of silver nanoparticles," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 3, no. 1, pp. 95–101, 2007.

[9] M. Sivakumar, N. Shanmuga Sundaram, R. Ramesh kumar, and M. H. Syed Thasthagir, "Effect of aluminium oxide nanoparticles blended pongamia methyl ester on performance, combustion and emission characteristics of diesel engine," *Renewable Energy*, vol. 116, pp. 518–526, 2018.

[10] M. Asztemborska, R. Steborowski, J. Kowalska, and G. Bystrzejewska-Piotrowska, "Accumulation ofAluminiumby plants exposed toNano-andMicrosized particles of Al2O3," *International Journal of Environmental Research*, vol. 9, no. 1, pp. 109–116, 2015.

[11] I. Gosteva, Y. Morgalev, T. Morgaleva, and S. Morgalev, "Effect of AL2O3 and TiO2 nanoparticles on aquatic organisms," in *IOP Conference Series: Materials Science and Engineering*IOP Publishing, Bristol, UK, 2015.

[12] S. Gulla, D. Lomada, V. V. Srikanth et al., "Recent advances in nanoparticles-based strategies for cancer therapeutics and antibacterial applications," *Methods in Microbiology*, vol. 46, pp. 255–293, 2019.

[13] E. Demir, A. Creus, and R. Marcos, "Genotoxicity and DNA repair processes of zinc oxide nanoparticles," *Journal of Toxicology and Environmental Health, Part A*, vol. 77, no. 21, pp. 1292–1303, 2014.

[14] B. I. Carr, *Hepatocellular Carcinoma Diagnosis and Treatment*, M. Markman, Ed., Springer, 3rd edition, 2016.

[15] B. Halliwell, "Antioxidants in human health and disease," *Annual Review of Nutrition*, vol. 16, no. 1, pp. 33–50, 1996.

[16] C. Luo, Y. Li, H. Wang et al., "Hydroxytyrosol promotes superoxide production and defects in autophagy leading to anti-proliferation and apoptosis on human prostate cancer cells," *Current Cancer Drug Targets*, vol. 13, no. 6, pp. 625–639, 2013.

[17] A. H. Gilani, M. H. Mehmood, K. H. Janbaz, A. U. Khan, and S. A. Saeed, "Ethnopharmacological studies on antispasmodic and antiplatelet activities of *Ficus carica*," *Journal of Ethnopharmacology*, vol. 119, no. 1, pp. 1–5, 2008.

[18] T. K. Lim, *Edible Medicinal and Non-Medicinal Plants*, Fruits Springer Dordrecht Heidelberg London, New York, NY, USA, 2012.

[19] I. Ahmed, A. W. Ahmed, and R. K. Robinson, "Chemical composition of date varieties as influenced by the stage of ripening," *Food Chemistry*, vol. 54, no. 3, pp. 305–309, 1995.

[20] O. S. Hassan and M. S. Shawky, "Effect of date palm (Phoenix Dactylifera L) seeds extracts on hematological, biochemical parameters and some fertility indices in male rats," *International Journal of Sciences: Basic and Applied Research*, vol. 17, no. 1, pp. 137–147, 2014.

[21] I. V. Gmoshinski, V. A. Shipelin, A. A. Shumakova et al., "Toxicity evaluation of nanostructured silica orally administered to rats: influence on immune system function," *Nanomaterials*, vol. 10, no. 11, Article ID 2126, 2020.

[22] E.-J. Park, H. Kim, Y. Kim, and K. Choi, "Repeated-dose toxicity attributed to aluminum nanoparticles following 28-day oral administration, particularly on gene expression in mouse brain," *Toxicological and Environmental Chemistry*, vol. 93, no. 1, pp. 120–133, 2011.

[23] M. I. Yousef, T. F. Mutar, and M. A. E. N. Kamel, "Hepatorenal toxicity of oral sub-chronic exposure to aluminum oxide and/or zinc oxide nanoparticles in rats," *Toxicology Reports*, vol. 6, pp. 336–346, 2019.

[24] A. A. Al-Qarawi, H. Abdel-Rahman, B. H. Ali, H. M. Mousa, and S. A. El-Mougy, "The ameliorative effect of dates (Phoenix dactylifera L.) on ethanol-induced gastric ulcer in rats," *Journal of Ethnopharmacology*, vol. 98, no. 3, pp. 313–317, 2005.

[25] A. H. Fathy, M. A. Bashandy, S. A. Bashandy, A. M. Mansour, and K. S. Azab, "The beneficial effect of natural antioxidants from olive oil with fig and date palm fruit extracts on biochemical and hematological parameters in rats treated with doxorubicin and γ-radiation," *Facets*, vol. 3, no. 1, pp. 722–735, 2018.

[26] Institute of Laboratory Animal Resources, "Guide for the care and use of laboratory animals," *Committee for the Update of the Guide and Use of Laboratory Animals*, National Academy Press, Washington, DC, USA, 8th edition, 1996.

[27] J. D. Bancroft and M. Gamble, *Theory and Practice of Histological Techniques*, Elsevier Health Sciences, Amsterdam, Netherland, 2008.

[28] Y. Yao, Y. Zang, J. Qu, M. Tang, and T. Zhang, "The toxicity of metallic nanoparticles on liver: the subcellular damages, mechanisms, and outcomes," *International Journal of Nanomedicine*, vol. 14, pp. 8787–8804, 2019.

[29] R. M. Naji, A. H. Fathy, and M. A. Bashandy, "The protective role of some natural antioxidants against some nanoparticles-induced subchronic nephrotoxicity in Wistar rats," *Archives of Pharmaceutical Sciences Ain Shams University*, vol. 6, no. 1, pp. 1–16, 2022.

[30] V. Chernyshev, A. Zakharenko, S. Ugay et al., "Morphologic and chemical composition of particulate matter in motorcycle engine exhaust," *Toxicology Reports*, vol. 5, pp. 224–230, 2018.

[31] L. Ding, Z. Liu, M. Aggrey, C. Li, J. Chen, and L. Tong, "Nanotoxicity: the toxicity research progress of metal and metal-containing nanoparticles," *Mini Reviews in Medicinal Chemistry*, vol. 15, no. 7, pp. 529–542, 2015.

[32] E. Demir, "A review on nanotoxicity and nanogenotoxicity of different shapes of nanomaterials," *Journal of Applied Toxicology*, vol. 41, no. 1, pp. 118–147, 2021.

[33] S.-Q. Li, R.-R. Zhu, H. Zhu et al., "Nanotoxicity of TiO2 nanoparticles to erythrocyte in vitro," *Food and Chemical Toxicology*, vol. 46, no. 12, pp. 3626–3631, 2008.

[34] H. Tominaga, S. Kodama, N. Matsuda, K. Suzuki1, and M. Watanabe, "Involvement of reactive oxygen species (ROS) in the induction of genetic instability by radiation," *Journal of Radiation Research*, vol. 45, no. 2, pp. 181–188, 2004.

[35] B. N. Pandey and K. P. Mishra, "In vitro studies on radiation induced membrane oxidative damage in apoptotic death of mouse thymocytes," *International Journal of Low Radiation*, vol. 1, pp. 113–119, 2003.

[36] A. Rashikh, K. K. Pillai, S. J. Ahmad, M. Akhtar, and A. K. Najmi, "Aliskiren alleviates doxorubicin-induced nephrotoxicity by inhibiting oxidative stress and podocyte injury," *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 14, no. 1, pp. 14–22, 2013.

[37] M. A. Bashandy, H. G. Abd El- Rasheid, H. F. Hasan, and A. Fathya, "Protective and therapeutic effects of olive oil and Ficus carica as natural antioxidants on some biochemical parameters in liver of γ-irradiated male albino rats," *Al Azhar Bulletin of science*, vol. 25, no. 1, pp. 1–16, 2014.

[38] G. Ramakrishnan, H. R. Raghavendran, R. Vinodhkumar, and T. Devaki, "Suppression of N-nitrosodiethylamine induced hepatocarcin-ogenesis by silymarin in rats," *Chemico-Biological Interactions*, vol. 161, no. 2, pp. 104–114, 2006.

[39] M. Dhanasekaran, A. A. Baskar, S. Ignacimuthu, P. Agastian, and V. Duraipandiyan, "Chemopreventive potential of Epoxy clerodane diterpene from Tinospora cordifolia against diethylnitrosamine-induced hepatocellular carcinoma," *Investigational New Drugs*, vol. 27, no. 4, pp. 347–355, 2009.

[40] G. Wu, J. R. Lupton, N. D. Turner, Y. Z. Fang, and S. Yang, "Glutathione metabolism and its implications for health," *The Journal of Nutrition*, vol. 134, no. 3, pp. 489–492, 2004.

[41] V. R. Vasquez-Garzon, J. Arellanes-Robledo, R. Garcia-Roman, D. I. Aparicio-Rautista, and S. Villa-Treviño, "Inhibition of reactive oxygen species and pre-neoplastic le-sions by quercetin through an antioxidant defense mechanism," *Free Radical Research*, vol. 43, no. 2, pp. 128–137, 2009.

[42] P. Viola and M. Viola, "Virgin olive oil as a fundamental nutritional component and skin protector," *Clinics in Dermatology*, vol. 27, no. 2, pp. 159–165, 2009.

[43] I. Ghorbel, A. Elwej, K. Jamoussi, T. Boudawara, N. G. Kamoun, and N. Zeghal, "Potential protective effects of extra virgin olive oil on the hepatotoxicity induced by co-exposure of adult rats to acrylamide and aluminum," *Food and Function*, vol. 6, no. 4, pp. 1126–1135, 2015.

[44] A. Solomon, S. Golubowicz, Z. Yablowicz et al., "Protection of fibroblasts (NIH-3T3) against oxidative damage by cyanidin-3-rhamnoglucoside isolated from fig fruits (*Ficus carica L.)*," *Journal of Agricultural and Food Chemistry*, vol. 58, no. 11, pp. 6660–6665, 2010.

[45] S. Mubarak, S. A. Hamid, A. R. Farrag, N. Samir, and J. S. Hussein, "Cardioprotective effect of date palm against doxorubicin-induced cardiotoxicity," *Asian Journal of Pharmaceutical and Clinical Research*, vol. 11, no. 7, pp. 141–146, 2018.

[46] M. E. Shakra, R. M. Salah El-Din, S. Y. M. Hamouda, A. A. R. Mohammed, R. A. A. Abd Al-Rahman, and R. Abd Allah, "Hepatotoxicity of bare and polyethylene glycol coated iron oxide nanoparticles and the protective role of virgin olive oil in male albino rats," *The Egyptian Journal of Hospital Medicine*, vol. 76, no. 2, pp. 3607–3617, 2019.

[47] Z. Du, D. Zhao, L. Jing et al., "Cardiovascular toxicity of different sizes amorphous silica nanoparticles in rats after intratracheal instillation," *Cardiovascular Toxicology*, vol. 13, no. 3, pp. 194–207, 2013.

[48] L. M. Faddah, N. A. A. Baky, N. M. Al-Rasheed, N. M. Al-Rasheed, A. J. Fatani, and M. Atteya, "Role of quercetin and arginine in ameliorating nano zinc oxide-induced nephrotoxicity in rats," *BMC Complementary and Alternative Medicine*, vol. 12, no. 1, pp. 1–14, 2012.

[49] L. Hou, K. Xie, M. Qin et al., "Effects of reactive oxygen species scavenger on the protective action of 100% oxygen treatment against sterile inflammation in mice," *Shock*, vol. 33, no. 6, pp. 646–654, 2010.

[50] S. A. Love, M. A. Maurer-Jones, J. W. Thompson, Y.-S. Lin, and C. L. Haynes, "Assessing nanoparticle toxicity," *Annual Review of Analytical Chemistry*, vol. 5, no. 1, pp. 181–205, 2012.

[51] J. H. Hwang, S. J. Kim, Y.-H. Kim et al., "Susceptibility to gold nanoparticle-induced hepatotoxicity is enhanced in a mouse model of nonalcoholic steatohepatitis," *Toxicology*, vol. 294, no. 1, pp. 27–35, 2012.

[52] B. Vurusaner, G. Poli, and H. Basaga, "Tumor suppressor genes and ROS: complex networks of interactions," *Free Radical Biology and Medicine*, vol. 52, no. 1, pp. 7–18, 2012.

[53] A. Solomon, S. Golubowicz, Z. Yablowicz et al., "Antioxidant activities and anthocyanin content of fresh fruits of common fig (*Ficus carica L.*)," *Journal of Agricultural and Food Chemistry*, vol. 54, no. 20, pp. 7717–7723, 2006.

[54] S. Bulotta, M. Celano, S. M. Lepore, T. Montalcini, A. Pujia, and D. Russo, "Beneficial effects of the olive oil phenolic components oleuropein and hydroxytyrosol: focus on protection against cardiovascular and metabolic diseases,"

Journal of Translational Medicine, vol. 12, no. 1, pp. 219–9, 2014.

[55] S. Govindan, A. Jayabal, J. Shanmugam, and P. Ramani, "Antioxidant and hepatoprotective effects of Hypsizygus ulmarius polysaccharide on alcoholic liver injury in rats," *Food Science and Human Wellness*, vol. 10, no. 4, pp. 523–535, 2021.

[56] S. M. Fathy and M. S. Mahmoud, "Moringa oleifera Lam. leaf extract mitigates carbon tetrachloride-mediated hepatic inflammation and apoptosis via targeting oxidative stress and toll-like receptor 4/nuclear factor kappa B pathway in mice," *Food Science and Human Wellness*, vol. 10, no. 3, pp. 383–391, 2021.

[57] S. Cicerale, L. J. Lucas, and R. S. Keast, "Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil," *Current Opinion in Biotechnology*, vol. 23, no. 2, pp. 129–135, 2012.

[58] I. Casaburi, F. Puoci, A. Chimento et al., "Potential of olive oil phenols as chemopreventive and therapeutic agents against cancer: a review of in vitro studies," *Molecular Nutrition and Food Research*, vol. 57, no. 1, pp. 71–83, 2013.

[59] E. A. Abd-Allah, N. S. Al-Abbas, M. M. Atia et al., "Can Fig and Olive Ameliorate the toxicity Induced by 2-nitropro-pane in some organs of mice? role of inflammatory versus anti-inflammatory genes," *Journal of Traditional Chinese Medicine*, vol. 41, no. 6, pp. 891–899, 2021.

[60] L. Wang, Q.-H. Huang, Y.-X. Li et al., "Protective effects of silymarin on triptolide-induced acute hepatotoxicity in rats," *Molecular Medicine Reports*, vol. 17, no. 1, pp. 789–800, 2018.

[61] M. I. Almansour, M. A. Alferah, Z. A. Shraideh, and B. M. Jarrar, "Zinc oxide nanoparticles hepatotoxicity: histological and histochemical study," *Environmental Toxicology and Pharmacology*, vol. 51, pp. 124–130, 2017.

[62] H. Singh, S. Sidhu, K. Chopra, and M. Khan, "Hepatoprotective effect of trans-chalcone on experimentally induced hepatic injury in rats: inhibition of hepatic inflammation and fibrosis," *Canadian Journal of Physiology and Pharmacology*, vol. 94, no. 8, pp. 879–887, 2016.

[63] A. H. Fathy, M. A. Bashandy, S. A. Bashandy, A. M. Mansour, and B. Elsadek, "Sequential analysis and staging of a diethylnitrosamine-induced hepatocellular carcinoma in male Wistar albino rat model," *Canadian Journal of Physiology and Pharmacology*, vol. 95, no. 12, pp. 1462–1472, 2017.

[64] J. Kolarovic, M. Popovic, J. Zlinska, S. Trivic, and M. Vojnovic, "Antioxidant activities of celery and parsley juices in rats treated with doxorubicin," *Molecules*, vol. 15, no. 9, pp. 6193–6204, 2010.

[65] F. Bulle, P. Mavier, E. S. Zafrani et al., "Mechanism of gamma-glutamyl transpeptidase release in serum during intrahepatic and extrahepatic cholestasis in the rat: a histochemical, biochemical and molecular approach," *Hepatology*, vol. 11, no. 4, pp. 545–550, 1990.

[66] R. Imamoto, J. I. Okano, S. Sawada, Y. Fujise, R. Abe, and Y. Murawaki, "Null anticarcinogenic effect of silymarin on diethylnitrosamine-induced hepatocarcinogenesis in rats," *Experimental and Therapeutic Medicine*, vol. 7, no. 1, pp. 31–38, 2014.

[67] B. Elsadek, A. Mansour, T. Saleem, A. Warnecke, and F. Kratz, "The antitumor activity of a lactosaminated albumin conjugate of doxorubicin in a chemically induced hepatocellular carcinoma rat model compared to sorafenib," *Digestive and Liver Disease*, vol. 49, no. 2, pp. 213–222, 2017.

[68] F. Bawazeer and S. Qahl, "Biochemical Study of the effect of mixture Fig [Ficus Carica L] and Olive oil on liver functions in nonalcoholic fatty liver disease in hyperlipidemic rat model," *Advances in Environmental Biology*, vol. 10, no. 1, pp. 201–207, 2016.

[69] J. Khalili Fard, S. Jafari, and M. A. Eghbal, "A review of molecular mechanisms involved in toxicity of nanoparticles," *Advanced Pharmaceutical Bulletin*, vol. 5, no. 4, pp. 447–454, 2015.

[70] H. A. Elgebaly, N. M. Mosa, M. Allach et al., "Olive oil and leaf extract prevent fluoxetine-induced hepatotoxicity by attenuating oxidative stress, inflammation and apoptosis," *Biomedicine & Pharmacotherapy*, vol. 98, pp. 446–453, 2018.

[71] R. Domitrovic, H. Jakovac, V. V. Marchesi, I. Sain, Z. Romic, and D. Rahelic, "Preventive and therapeutic effects of oleuropein against carbon tetrachloride-induced liver damage in mice," *Pharmacological Research*, vol. 65, no. 4, pp. 451–464, 2012.

[72] F. Amiri, M. Mohammadian, M. Mianabadi, M. Zargari, A. Karimpour, and M. Khalafi, "Effects of olive oil supplementation on sodium arsenate-induced hepatotoxicity in mice," *International Journal of Preventive Medicine*, vol. 9, no. 1, p. 59, 2018.

[73] M. N. Al-Seeni, H. A. El Rabey, M. A. Zamzami, and A. M. Alnefayee, "The hepatoprotective activity of olive oil and Nigella sativa oil against CCl 4 induced hepatotoxicity in male rats," *BMC Complementary and Alternative Medicine*, vol. 16, no. 1, pp. 1–14, 2016.

[74] A. Singhal, M. Jayaraman, D. N. Dhanasekaran, and V. Kohli, "Molecular and serum markers in hepatocellular carcinoma: predictive tools for prognosis and recurrence," *Critical Reviews in Oncology*, vol. 82, no. 2, pp. 116–140, 2012.

[75] M. M. Salman, "Effects of different doses of cerastes cerastes crude venom on biochemical parameters in serum of Guinea pigs at different times," *BFAI J*, vol. 6, no. 2, pp. 329–339, 2014.

[76] A. F. Ahmed, J. H. Al-Qahtani, H. M. Al-Yousef et al., "Proanthocyanidin-rich date seed extract protects against chemically induced hepatorenal toxicity," *Journal of Medicinal Food*, vol. 18, no. 3, pp. 280–289, 2015.

[77] C. Sánchez-Moreno, J. A. Larrauri, and F. Saura-Calixto, "A procedure to measure the antiradical efficiency of polyphenols," *Journal of the Science of Food and Agriculture*, vol. 76, no. 2, pp. 270–276, 1998.