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REVIEW

The antioxidant activity of artichoke (*Cynara scolymus*): A systematic review and meta-analysis of animal studies

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Current evidence has shown antioxidant activity of artichoke as a potent source of antioxidant compounds. However, it seems that the antioxidant activity of artichoke has not yet been reviewed. Therefore, the present study was designed to perform a systematic review of human studies, animal models, and in vitro systems and to conduct a meta-analysis of animal studies on the antioxidant effects of artichoke. We searched four electronic databases till April 2018 using relevant keywords. All English language articles were assessed. For animal studies, standardized mean difference was pooled using a random effects model. The included studies were evaluated for eligibility and risk of bias. Thirty-nine articles (two human, 23 animal, and 14 in vitro studies) were reviewed. The results of in vitro systems supported the antioxidant effect of artichoke, whereas limited clinical trials indicated no change or a slight improvement of antioxidant status. Finding of animal studies indicated that artichoke extract supplementation increased superoxide dismutase, catalase, glutathione, and glutathione peroxidase level in liver, as well as, decreased malondialdehyde level in liver and plasma of animals with induced disease significantly compared with comparison group. This meta-analysis provided convincing evidence for antioxidant activity of artichoke in animals.

KEYWORDS

antioxidant, artichoke, *Cynara scolymus*, oxidative stress, reactive oxygen species

1 | INTRODUCTION

Oxidative stress is characterized by a disturbance in the prooxidant–antioxidant balance where generation of reactive oxygen species (ROS) exceeds the capacity of enzymatic and nonenzymatic antioxidant defense system on a cellular or systemic level (Droge, 2002). The pathophysiological implications of oxidative stress has been demonstrated in ageing and many human diseases including diabetes mellitus, rheumatoid arthritis, hypertension, cardiovascular disease, cancer, and neurodegenerative disease of the nervous system such as Parkinson and Alzheimer (Valko et al., 2007).

It has been suggested that some herbs that possess potent antioxidant activity could diminish the risk of oxidative stress-related disease through improvement of antioxidant defense system, inhibition of *production of ROS, and redox properties (Rubió, Motilva, & Romero*, 2013*)*.

Globe artichoke, *Cynara cardunculus L. subsp*. Scolymus (L.) Hayek is an antioxidant rich herb (Carlsen et al., 2010), belongs to the family Asteraceae (Compositae). Artichoke contains polyphenolic compounds, fibers, inulin, minerals (potassium, sodium, and phosphorus), and vitamin C. The major bioactive components of head and leaves of artichoke are polyphenolic compounds including mono- and

Abbreviations: 8-OHdG, 8-hydroxydeoxyguanosine; ALE, artichoke leaf extract; AOPP, Advanced oxidation protein product; CAT, Catalase; DC, Diene conjugate; FMLP, N-formyl-methionyl-leucyl-phenylalanine; FRAP, Ferric reducing/antioxidant power; GPx, Glutathione peroxidase; GR, Glutathione reductase; GSH, Glutathione; GST, Glutathione-S-transferase; HCD, High-cholesterol diet; LP, Lipopolysaccharide; MDA, Malondialdehyde; ox-LDL, Oxidized low density lipoprotein; PMA, PhorboM2-myristate-13-acerate; ROS, Reactive oxygen species; SMD, Standardized mean differences; SOD, Superoxide dismutase; TAC, Total antioxidant capacity; TBARS, Thiobarbituric-acid-reactive substances

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dicaffeoylquinic acids (e.g., chlorogenic acid and cynarin) and flavonoids (e.g., luteolin, apigenin and their glucosides and rutinosides; Ben Salem et al., 2015).

Artichoke is native to the Mediterranean Basin and is cultivated all over the world for edible and medicinal purposes. The head or capitula, a large immature flower, and fleshy leaves, are edible portions of artichoke (De Falco, Incerti, Amato, & Lanzotti, 2015). Traditionally, artichoke has been used as a remedy to treat hepato-biliary disease and dyspepsia (LaGow, 2004). In previous in vitro and in vivo studies, extracts of artichoke heads and leaves have shown antimicrobial, hepatoprotective, cholerectic, hypocholesterlomic, hypoglycemic, and anticancer effects (Al-Ahdab, 2014; Ebrahimi-Mameghani, Asghari-Jafarabadi, & Rezazadeh, 2018; El Sohaimy, 2014; Emanue, Adrian, Sultana, & Svetlana, 2011; Gebhardt & Fausel, 1997; Rezazadeh, Rahmati-Yamchi, Mohammadnejad, Ebrahimi-Mameghani, & Delazar, 2018; Rezazadeh, Rezazadeh, & Ebrahimi-Mamaghani, 2018; Rondanelli et al., 2014; Rondanelli, Giacosa, Orsini, Opizzi, & Villani, 2011).

The antioxidant activity of artichoke has also been demonstrated in experimental studies (Gebhardt, 1997; Gebhardt & Fausel, 1997; Brown & Rice-Evans, 1998; Perez-Garcia, Adzet, & Canigueral, 2000; Zapolska-Downar et al., 2002; Rahimuddin, Khoja, Zuhair, Howell, & Brown, 2007; Juzyszyn, Czerny, Pawlik, & Drozdzik, 2008; Miccadei et al., 2008; Löhr, Deters, & Hensel, 2009; Mileo, Di Venere, Abbruzzese, & Miccadei, 2015; Takei et al., 2015; Miláčková, Kapustová, Mučaji, & Hošek, 2017; Jiménez-Escrig, Dragsted, Daneshvar, Pulido, & Saura-Calixto, 2003; Goñi, Jiménez-Escrig, Gudiel, & Saura-Calixto, 2005; Mehmetcik, Ozdemirler, Kocak-Toker, Cevikbas, & Uysal, 2008; Kucukgergin et al., 2010; Kusku-Kiraz, Mehmetcik, Dogru-Abbasoglu, & Uysal, 2010; Heidarian, Jafari-Dehkordi, & Seidkhani-Nahal, 2011a; Heidarian & Soofiniya, 2011; Song et al., 2012; Heidarian & Rafieian-Kopaei, 2013; Abdel-Kader et al., 2014; Al-Ahdab, 2014; Magielse et al., 2014; El Morsy & Kamel, 2015; Najim, Numan, & Hamad, 2015; Colak et al., 2016; Jaleel, Saleh, & El-Awdan, 2016; Khattab, Wazzan, & Al-Ahdab, 2016; Mocelin et al., 2016; Ben Salem et al., 2017; El-Boshy et al., 2017; Kaymaz, Kandemir, Pamukçu, Eröksüz, & Özdemir, 2017; Tang, Wei, Deng, & Lei, 2017).

However, there are very limited clinical trials considering antioxidant properties of artichoke (Rezazadeh, Aliashrafi, Asghari-Jafarabadi, & Ebrahimi-Mameghani, 2018; Skarpanska-Stejnborn, Pilaczynska-Szczesniak, Basta, Deskur-Smielcka, & Horoszkiewicz-Hassan, 2008). It is hypothesized that the head and leaves of artichoke and their extract could protect the body against oxidative stress induced by various active oxidant or toxins. Although there are some narrative review studies on medicinal effects of artichoke, it seems that the antioxidant effects of artichoke and its extract has not yet been systematically reviewed. Accordingly, the present study was designed to review the antioxidant effects of *Cynara scolymus* in human studies, animal models and in vitro systems. Furthermore, this study was set out to perform a meta-analysis on the effects of artichoke supplementation on superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), and malondialdehyde (MDA) level in liver, as well as, MDA level in plasma using data from animal studies.

2 | MATERIALS AND METHODS

2.1 | Article selection

We searched PubMed/Medline, Scopus, the Cochrane Library, and Google scholar electronic databases. The search terms were "*C. scolymus*" or "artichoke," "*Cynara cardunculus*"or "cynara," "oxidative stress" or "free radicals," "free radical scavengers" or "glutathione peroxidase," "reactive oxygen species" or "oxidized low density lipoprotein," "antioxidants" or "total antioxidant status," and "total antioxidant capacity" or "superoxide dismutase." Two authors (K.R., S.S.) independently conducted the searching and data extraction, and then duplicated studies were deleted. Overall, there was an agreement between authors on the selection of studies, and some differences were resolved by third the author (M.E.).

We included only English-language articles published from 1995 until April 2018. We excluded review articles, abstracts in congress, case reports, and articles that examined the effects of artichoke mixed with other plants, or examined other properties of artichoke. We also excluded mechanistic studies on artichoke compounds, irrelevant articles, and studies on Jerusalem artichoke (*Helianthus tuberosus* L.). We hand searched the references of included studies. After critical appraisal of articles, 39 articles were selected and reviewed (two human, 23 animal, and 14 in vitro studies). The flowchart of screening and selecting of articles was shown in Figure 1.

2.2 | Data extraction

We extracted the following information from the full-text papers of eligible studies: the first author, publication year, subject characteristics, sex, age, weight, type of intervention, dosage, duration of study, sample size per comparison group, and results of studies on oxidant/antioxidant parameters. A summary of the included studies is presented in Tables 1–3.

We also extracted the means and SDs of SOD, CAT, GSH, GPx, and MDA level in liver and MDA level in plasma from the animal studies for both intervention group (defined as animals with induced disease supplemented with artichoke) and comparison group (defined as animals with induced disease). For articles with missing SDs for outcome values, SDs were calculated from standard error.

We used final values of outcomes only if quantitative data were provided or could be estimated from graphs. When two or more doses of artichoke were evaluated in the same study, each dose was compared independently with comparison group.

2.3 | Quality assessment

The assessment of risk of bias was undertaken using the Cochrane collaboration's tool (Higgins et al., 2011) for randomized clinical trials and SYRCLE's risk of bias tool (Hooijmans et al., 2014) for animal studies. The SYRCLE's risk of bias tool is an adapted version of the Cochran risk of bias tool for animal intervention studies. Both tools cover six domains of bias: selection bias, performance bias, attrition bias, detection bias, reporting bias, and other sources of bias. Risk of bias is judged as low, unclear, or high in each domain. The risk of bias of

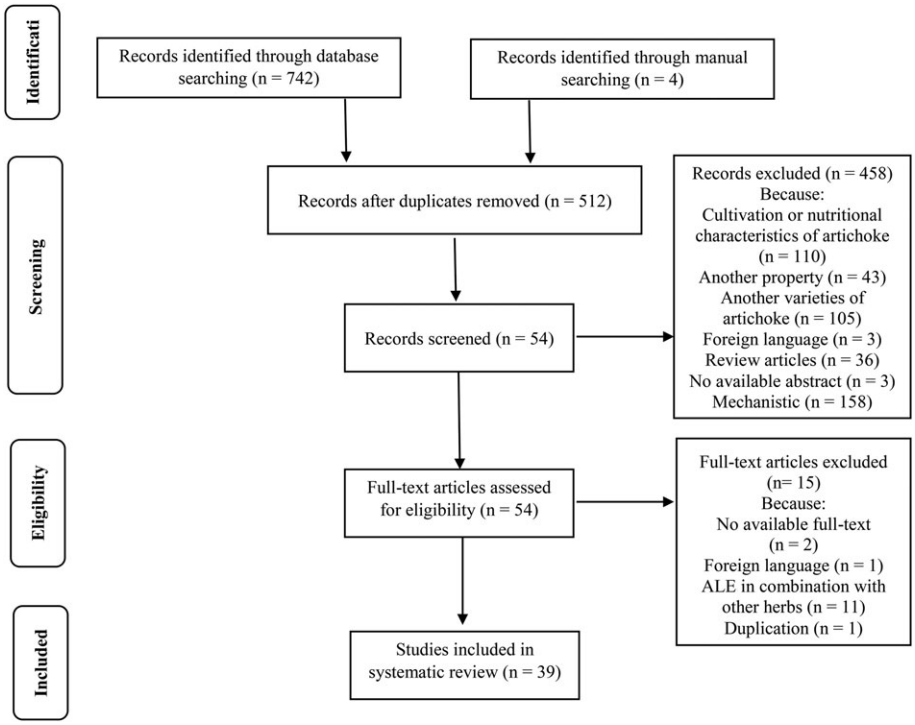

FIGURE 1 Flowchart of screening and choosing eligible articles

TABLE 1 Characteristic of human studies regarding the effect of artichoke on antioxidant parameters

Author (date)	Subjects	Intervention	Dosage	Duration	Results
Rezazadeh et al. (2017)	Patients with metabolic syndrome (*n* = 40 per group)	Hydroalcoholic extract of artichoke leaf	1800 mg/day	12 weeks	↓ox-LDL, nonsignificant changes of MDA, SOD, GPx, and TAC concentrations in intervention group compared with placebo
Skarpanska-Stejnborn et al. (2008)	Members of the rowing team (*n* = 12 per artichoke group and *n* = 10 per placebo group)	Artichoke leaf extract	1200 mg/day	5 weeks	↑TAC during restitution, nonsignificant changes of SOD, GPx, GR, GSH, TBARS in supplemented group versus placebo group

Note. GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; MDA: malondialdehyde; ox-LDL: oxidized low density lipoprotein; SOD: superoxide dismutase; TAC: total antioxidant capacity; TBARS: thiobarbituric-acid-reactive substances.

in vitro studies were not assessed, as no validated tool was available (Krithikadatta, Gopikrishna, & Datta, 2014).

The risk of bias in the eligible studies was evaluated independently by three authors and disagreements on scores were resolved through discussion.

2.4 | Data analysis

Although we aimed to perform meta-analysis for human, animal, and in vitro studies, a reliable meta-analysis was not possible for human and in vitro studies due to restriction in number and comparable outcomes. For animal studies, effect estimates were calculated using standardized mean differences (SMD; Hedges's g) and a 95% confidence interval (CI) to report the size of artichoke effect on oxidant/antioxidant indices by accounting the differences in the units of measurements in different studies. Data were pooled using a random effects model to account for anticipated heterogeneity.

Heterogeneity was examined using I-squared statistic (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). Meta-regression and subgroup analysis were implemented to identify potential sources of between-study heterogeneity, including study duration, dosage of supplement, and induced disease. Publication bias was assessed by visual evaluation for funnel plot asymmetry and Egger's linear regression test. Sensitivity analyses were also performed to examine the effect of each studies on overall pooled estimates and heterogeneity. The sensitivity analysis was conducted to identify the impact of each study on the pooled effect size. All data analysis was conducted using Stata 12.0 software (StataCorp LP, College Station, TX).

3 | RESULTS

3.1 | Study characteristics

The included studies were categorized into human, animal, and in vitro studies. Characteristics of included studies are summarized in Table 1–3.

TABLE 2 Characteristic of animal studies regarding the effect of artichoke on antioxidant parameters

Author (date)	Subjects	Intervention	Dosage	Duration	Results
Ben Salem et al. (2017)	Diabetes rats induced by alloxan	Ethanol extract of artichoke leaf	200 and 400 mg/kg	4 weeks	↑CAT, SOD, and GSH activities; ↓MDA and AOPP in liver, kidney, and pancreas; and improved histological findings versus diabetic rats
El-Boshy et al. (2017)	Rats with Cd-induced toxicity	Hydroalcoholic extract of artichoke leaf	300 mg/kg	4 weeks	↓liver MDA, nonsignificant changes of kidney MDA, liver, and kidney SOD, GPx, CAT, and GSH versus Cd-intoxicated group
Kaymaz et al. (2017)	Rats with alpha-amanitine induced hepatotoxicity	Aqueous extract of artichoke leaf	1,500 mg/kg	2 weeks	↓MDA, ↑SOD, CAT, and GPx; improved histopathological findings versus alpha-amanitine-intoxicated group
Tang et al. (2017)	Mice with acute alcohol-induced liver injury	Ethanol extract of artichoke	400,800 and 1,600 mg/kg	10 days	↑SOD, GSH, ↓MDA versus alcohol-intoxicated group
Colak et al. (2016)	Rats with CCl4-induced hepatotoxicity	Ethanol extract of artichoke leaf	1,500 mg/kg	2 weeks	↓MDA ↑CAT and SOD versus CCL4-intoxicated group
Jaleel et al. (2016)	Rats with ethylene glycol-induced urolithiasis	Artichoke leaf extract	125, 250 and 500 mg/kg	4 weeks	↓MDA and GSH versus ethylene glycol treated group
Khattab et al. (2016)	Rats with GM-induced nephrotoxicity	Aqueous extract of artichoke leaf	200, 400, and 600 mg/kg	10 days	↓MDA versus GM-intoxicated group
Magied et al. (2016)	Hypercholesterolemic rats fed HCD	Aqueous methanolic extracts of artichoke leaves and heads	1,500 and 3,000 mg/kg	42 days	↑liver, heart, and blood GPx ↓liver, heart, and serum MDA versus hypercholesterolemic group
Mocelin et al. (2016)	Hypercholesterolemic rats fed HCD	Aqueous extract of artichoke leaf	150, 300, and 600 mg/kg	30 days	↓ox-LDL and antioxidized-LDL versus control group
El Morsy and Kamel (2015)	Rats with paracetamol-induced liver injury	Aqueous artichoke leaf extract	1,500 mg/kg	2 weeks	↓MDA ↑SOD, GSH, GR, and GST activity versus paracetamol-intoxicated group
Najim et al. (2015)	Rats with 5-Flurouracil (5-FU) induced cardiotoxicity	Ethyl acetate and methanol artichoke extracts	200 mg/kg	30 days	↑TAC versus 5-FU-intoxicated group
Abdel-Kader et al. (2014)	Rats treated with CCl4	Artichoke leaves	20% or 40% of diets	4 weeks	↑SOD and CAT level in a dose dependent manner versus CCl4 group
Al-Ahdab (2014)	Rats with CCl4-induced acute hepatotoxicity	Aqueous extracts of artichoke leaves and pulp	200 and 400 mg/kg	6 weeks	↑SOD, GPx, and CAT activity in tissue, partial mitigation of histopathological lesions induced by CCl4 in the liver versus CCL4-intoxicated rats
Magielse et al. (2014)	Diabetes rats induced by streptozotocin	Aqueous artichoke leaf extract	200 and 1,000 mg/kg	3 weeks	In 200 mg/kg group: ↓MDA and 8-OHdG, ↑GSH, In 1,000 mg/kg group: ↓8-OHdG, nonsignificant change of MDA and GSH versus diabetics rats
Heidarian and Rafieian-Kopaei (2013)	Rats fed with lead-containing diet	Hydroethanolic extract of artichoke	300 mg/kg	6 weeks	↓MDA, ↑FRAP versus lead-intoxicated rats
Song et al. (2012)	D-galactose induced aging rats	Hydroalcoholic extract of artichoke leaf	20, 40, and 80 mg/kg	36 days	↑SOD in brain and liver, GPx in brain, and CAT in liver ↓MDA versus aging model

(Continues)

TABLE 2 (Continued)

Author (date)	Subjects	Intervention	Dosage	Duration	Results
Heidarian et al. (2011)	Hyperlipidemic rats fed lipogenic diet	Artichoke	10% of diets	45 days	↓MDA and ↑FRAP versus control and lipogenic diet group
Heidarian and Soofiniya (2011)	Diabetic rats induced by streptozotocin	Aqueous artichoke leaf extract	200 and 400 mg/kg	21 days	↑SOD, FRAP ↓MDA versus diabetic group
Kucukgergin et al. (2010)	Hypercholesterolemic rats fed HCD	Artichoke leaf extract	1,500 mg/kg	2 weeks	↓MDA and DC level in liver and heart ↑GPx, GST, and vitamin E in liver, nonsignificant changes of SOD, GSH, and vitamin C in liver and heart versus hypercholesterolemic rats
Kusku-Kiraz et al. (2010)	Hypercholesterolemic rats fed HCD	Artichoke leaf extract	1,500 mg/kg	2 weeks	↓MDA, DC level, and ↑FRAP versus hypercholesterolemic rats
Mehmetcik et al. (2008)	Rats with CCl4-induced hepatotoxicity	Artichoke leaf extract	1,500 mg/kg	2 weeks	↓MDA and DC level in liver, ↑GPx activity, GSH level in liver, and nonsignificant changes of SOD activity, vitamin E, and vitamin C level versus CCl4 treated rats
Goñi et al. (2005)	Normal rats	Artichoke head	14% of diets	3 weeks	↑FRAP and free-radical scavenging capacity versus control rats (fiber-free diet supplemented with cellulose)
Jimenez-Escrig et al. (2003)	Normal rats	Artichoke head	14% of diets	3 weeks	↑GPx activity, ↓2-Aminoadipic semialdehyde, nonsignificant changes of SOD, GR, CAT, FRAP, and free-radical scavenging capacity versus control rats

Note. AOPP: advanced oxidation protein product; CAT: catalase; Cd: cadmium; DC: diene conjugate; FRAP: ferric reducing/antioxidant power; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; GST: glutathione-S-transferase; HCD: high-cholesterol diet; MDA: malondialdehyde; SOD: superoxide dismutase; TAC: total antioxidant capacity; 8-OHdG: 8-hydroxydeoxyguanosine.

TABLE 3 Characteristic of in vitro studies regarding the effect of artichoke on antioxidant parameters

Author (date)	Subjects	Treatment	Dosage	Duration	Results
Miláčková et al. (2017)	Human monocytic leukemia cell line THP-1 exposed to LPS	Artichoke leaf extract, caffeic acid, chlorogenic acid, and quinic acid	50 μg/mL, 100 μM	2 hr	↓ROS
D'Antuono et al. (2015)	Human low density lipoprotein system	Hydroalcoholic extract of artichoke, caffeic acid, and chlorogenic acid	0.18–1.44 μg/mL	1–4 hr	Inhibition of LDL oxidation
Mileo et al. (2015)	Human breast cancer cell line MDA-MB231	Artichoke head extract	10 and 30 μM	10 days	↑ROS
Takei et al. (2015)	NHEKs−−UVB treated	Cynaropicrin	1 μM	18 hr	Inhibition of ROS generation
Garbetta et al. (2014)	Human intestinal cell line (HT-29) exposed to H_2O_2	Artichoke head extract, chlorogenic acid, and 3,5-O-, 1,5-O-dicaffeoylquinic acids	0.75, 1.5, 3, 6, 12, and 24 μg/ml	30 min	↓induced ROS level
Löhr et al. (2009)	Human liver cells HepG2-ethanol-induced cell toxicity	Artichoke leaf extract	1, 10, 100 μg/mL	48 hr	Inhibition of gene expression of GPx and GR and inhibition of GST activity
Juzyszyn et al. (2008)	Cultured HUVECs exposed to LPS and ox-LDL	Artichoke extract	25–100 μg/mL	24 hr	Suppression of ROS formation induced by LPS and ox-LDL
Miccadei et al. (2008)	Cultured rat hepatocytes and human hepatoma HepG2 cells exposed to glucose oxidase	Artichoke head extract and chlorogenic acid	400, 800, and 1200 μM	24 hr	Prevention of the loss of total GSH and the accumulation of MDA
Rahimuddin et al. (2007)	Human skin fibroblasts exposed to UVA (250 and 500 kJ/m2)	Luteolin, luteolin-7-O-glucoside	30 μM	18 hr	Prevention of increase in lipid peroxides in 250 kJ/m2 but not in 500 kJ/m2, prevention of increase in MDA level in 250 and 500 kJ/m2 by luteolin, and not by luteolin-7-O-glucoside versus flavonoid treated non-irradiated cells
Zapolska-Downar et al. (2002)	Endothelial cells and monocytes exposed to TNFα, LPS and ox-LDL	Aqueous and ethanolic extracts from artichoke	25, 50, and 100 μg/ml	24 h	Inhibition of basal and stimulated ROS production in endothelial cells and monocytes in dose dependent manner
Perez-Garcia et al. (2000)	Human leukocytes exposed to hydrogen peroxide, PMA, and FMLP	Artichoke leaf extract, cynarin, caffeic acid, chlorogenic acid, and luteolin,	100 μg/ml and 1 ng/ml	-	↓ROS production in a concentration-dependent manner
Brown and Rice-Evans (1998)	LDL isolated from blood of healthy volunteers	Artichoke leaf extract, luteolin, and Luteolin-7-O-glucoside	1–20 μg/ml and 1–0.1 μM	-	Retarded LDL oxidation in a dose dependent manner, luteolin-7-O-glucoside was less effective than luteolin
Gebhardt (1997)	Cultured rat hepatocytes exposed to tert-butyl hydroperoxide (t-BHP)	Aqueous artichoke leaf extract, caffeic acid, chlorogenic acid, cynarin and cynarosid	0.001, 0.01, 0.1, and 1.0 mg/ml	40 min	Prevention of the loss of intracellular GSH caused by t-BHP, ↓MDA production and LDH leakage dose dependently
Gebhardt and Fausel (1997)	Cultured rat hepatocytes exposed to hydroperoxide	Artichoke leaf extract	0.005 and 0.5 mg/ml	40 min	Prevention of increase of MDA formation caused by hydroperoxide in dose-dependent manner, ↓the loss of total GSH and the cellular leakage of GSSG resulting from exposure to hydroperoxide

Note. FMLP: N-formyl-methionyl-leucyl-phenylalanine; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; GST: glutathione-S-transferase; HUVEC: human umbilical endothelial cell; LPS: lipopolysaccharide; MDA: malondialdehyde; NHEK: human epidermal keratinocyte; ox-LDL: oxidized-LDL; PMA: phorboM2-myristate-13-acerate; ROS: reactive oxygen species; UVA: ultraviolet-A; UVB: ultraviolet-B

3.1.1 | Human studies

The antioxidant effects of artichoke were reported just in two human studies (Rezazadeh, Aliashrafi, et al., 2018; Skarpanska-Stejnborn et al., 2008). Skarpanska-Stejnborn et al. (2008) evaluated the effects of supplementation with artichoke leaf extract (1,200 mg/day) on antioxidant defense system in 22 members of the Polish rowing team for 5 weeks. The subjects performed a 2,000-meter rowing exercise test before and after the study. The redox parameters were measured before each test, 1 min after the test finished, and after a 24-hr restitution period. The supplementation resulted in significant increase of total antioxidant capacity after restitution in intervention group compared with placebo group. However, the activity of SOD, GPx and glutathione reductase (GR) as well as reduced glutathione levels (GSSG) and thiobarbituric-acid-reactive-substances concentrations did not change significantly during experimental period. Our recent double-blind, randomized controlled trial on 80 patients with metabolic syndrome indicated that supplementation with hydroalchoholic extract of artichoke leaf (1800 mg/day) decreased significantly oxidized-LDL (ox-LDL) level compared with placebo after 12 weeks. But, there were no significant differences in MDA, SOD, GPx, and total antioxidant capacity levels between and within groups (Rezazadeh, Aliashrafi, et al., 2018).

3.1.2 | Animal studies

The effect of artichoke on the improvement of antioxidant defense system is supported by finding from different animal studies as shown in Table 2. Based on inclusion criteria, 23 animal studies were included in this systematic review.

Several animal studies have been demonstrated the efficacy of artichoke leaves and extract of artichoke leaves in improvement of antioxidant–oxidant balance in rats with hepatotoxicity. Kaymaz et al. (2017) reported that in rats with hepatotoxicity induced by alpha-amanitine, supplementation with aqueous extract of artichoke leaf caused significant decrease of MDA level and significant increase of activity of SOD, GPx, and CAT in treatment group (receiving alpha-amanitine and artichoke leaf extract) compared with control group (receiving alpha-amanitine). Also, administration of artichoke leaf extract (Al-Ahdab, 2014; Colak et al., 2016) or artichoke leaves (Abdel-Kader et al., 2014) in rats with hepatotoxicity induced by carbon tetrachloride (CCl4) decreased MDA and diene conjugate (DC) levels and improved antioxidant parameters (i.e., activity of SOD, GPx, GSHm and CAT) and histopathological findings of hepatocytes compared with CCL4 treated rats. The artichoke leaf extract consumption in rats with paracetamol-induced hepatotoxicity (El Morsy & Kamel, 2015), and in mice with acute alcohol-induced liver injury (Tang et al., 2017) showed similar results favor to protect liver from toxicity induced by paracetamol and alcohol. But, Mehmetcik et al. (2008) observed that MDA and DC levels decreased and GPx activity and GSH level increased, whereas SOD activity and levels of vitamin E and vitamin C did not change significantly in liver tissue of rats with carbon tetrachloride-induced hepatic injury after administration of artichoke leaf extract (1.5 mg/kg) for 2 weeks.

El-Boshy et al. (2017) assessed the effects of hydroalcoholic extract of artichoke leaf (300 mg/kg) against cadmium (Cd) toxicity in rats. In Cd- and artichoke leaf extract-treated group, liver MDA significantly decreased compared with Cd-treated group, whereas the kidney peroxidation (MDA) and the liver and kidney antioxidant markers, SOD, GPx, CAT, and GSH did not change significantly compared with intoxicated rats.

The beneficial antioxidant effects of artichoke leaf extract have also been indicated in other organ toxicity such as nephrotoxicity (Khattab et al., 2016) and cardiotoxicity (Najim et al., 2015). Moreover, artichoke leaf extract was effective in attenuation of elevated level of MDA and reduced level of GSH in kidney of rats with ethylene glycol-induced urolithiasis (Jaleel et al., 2016). Also, supplementation with artichoke leaf extract in rats fed with lead-containing diet decreased their MDA level and increased FRAP level (Heidarian & Rafieian-Kopaei, 2013). In ageing rats model induced by d-galactose, reduced level of MDA and elevated activity of SOD, GPx and, CAT were shown after artichoke leaf extract consumption (Song et al., 2012).

Furthermore, antioxidant properties of artichoke leaf extract have been revealed in diabetic rats. Supplementation with extract of artichoke leaf resulted in significant reduction of MDA and advanced oxidation protein product (AOPP) level and significant increase in the activity of CAT and SOD and level of GSH and ferric reducing/antioxidant power (FRAP) in supplemented group compared with the nonsupplemented group (Ben Salem et al., 2017; Heidarian & Soofiniya, 2011). In another study, Magielse et al. (2014) assessed the effects of two doses of aqueous artichoke leaf extract (200 mg/kg and 1,000 mg/kg) on oxidant and antioxidant markers in streptozotocin-induced diabetic rat model. They showed that artichoke leaf extract in 200 mg/kg dose decreased the significant MDA and 8-hydroxydeoxyguanosine (8-OHdG) level and increased the erythrocyte GSH level, whereas, artichoke leaf extract in 1,000 mg/kg dose only decreased 8-OHdG and did not show any significant effects on MDA and Glutathione-S-transferase (GST) levels relative to diabetic rats.

Studies on hypercholesterolemic rats found that artichoke leaf extract supplementation (Heidarian, Jafari-Dehkordi, & Seidkhani-Nahal, 2011b) or artichoke consumption (Kusku-Kiraz et al., 2010) decreased MDA and DC level and increased FRAP level. Aqueous methanolic extracts of green globe and violet artichoke leaves and heads supplementation led to increase of GPx level in liver, heart, and blood and to decrease of MDA level in liver, heart, and blood in hypercholesterolemic rats (Magied, Hussien, Zaki, & Said, 2016). In addition, another study reported that administration of aqueous extract of artichoke leaf to hypercholesterolemic rats resulted in a significant decrease of ox-LDL and antioxidized-LDL level (Mocelin et al., 2016). However, Kucukgergin et al. (2010) showed that artichoke leaf extract decreased MDA and DC level in liver and heart and increased GPx, GST, and vitamin E in liver but did not change SOD, GSH, and vitamin C in liver and heart of hypercholesterolemic rats.

Studies on normal rats showed that consumption of the edible portion of artichoke (~14% of diet) resulted in more favorable antioxidant status (Goñi et al., 2005; Jiménez-Escrig et al., 2003). In Goñi et al.'s (2005) study, FRAP and free-radical scavenging capacity increased significantly in cecal contents of artichoke group compared with control group. Also, Jiménez-Escrig et al. (2003) reported the increase of GPx in erythrocyte and decrease of 2-aminoadipic semialdehyde, a protein oxidation biomarker in plasma proteins, whereas the

serum level of FRAP and free-radical scavenging capacity and erythrocyte level of SOD, GR, and CAT showed no differences between artichoke group and control group.

3.1.3 | In vitro studies

Previous in vitro studies on normal cell lines that were exposed to inflammatory mediators, oxidase, ultraviolet B (UVB), and hydrogen peroxide (H_2O_2) indicated the favorable effects of artichoke leaf extract or its pure constituents in prevention or inhibition of ROS production (Garbetta et al., 2014; Juzyszyn et al., 2008; Perez-Garcia et al., 2000; Takei et al., 2015; Zapolska-Downar et al., 2002). Moreover, in cell toxicity induced by ethanol in human liver cells HepG2, artichoke head extract inhibited GST activity and gene expression of GPx and GR in a dose-dependent manner (Löhr et al., 2009). Rahimuddin et al. (2007) reported that in ultraviolet A-treated human skin fibroblast, luteolin, and luteolin-7-O-glucoside (both present in artichoke leaves) prevented the increase of lipid peroxides and MDA level. Luteolin was more effective in reduction of MDA level than luteolin-7-O-glucoside.

Treatment with artichoke leaf extract and its three compounds (caffeic acid, chlorogenic acid, and quinic acid) in lipopolysaccharide-intoxicated human leukemic cells reduced intracellular ROS significantly (Miláčková et al., 2017). Furthermore, low doses of artichoke head extract for 10 days in MDA-MB231 human breast cancer cell line resulted in increased level of ROS production and suppression of cell growth (Mileo et al., 2015).

Studies on rat hepatocytes supported the antioxidant properties of artichoke leaf or head extract and its constituents against stress oxidative induced by oxidase through inhibition of increase of MDA and loss of GSH and cellular leakage of reduced glutathione levels caused by oxidase (Gebhardt, 1997; Gebhardt & Fausel, 1997; Miccadei et al., 2008). In addition, artichoke leaf extract protected low-density lipoprotein-cholesterol from Cu^{2+}-mediated oxidation in vitro (Brown & Rice-Evans, 1998; D'antuono, Garbetta, Linsalata, Minervini, & Cardinali, 2015).

3.2 | Risk of bias

The results of assessment of risk of bias for randomized clinical trial and animal studies are presented in Figure 2. The unclear risk of bias was detected in selection bias (n = 22, because of the lack of knowledge on the method of randomization), performance bias (n = 3, because of absence of knowledge on blinding of participants or caregivers), and detection bias (n = 22, because of absence of information on blinding of outcome assessors). The risk of bias in reporting bias and attrition bias was low. The risk of performance bias in the 19 animal studies of the 23 studies showed a high risk of bias because they did not blind caregivers or researchers from information of which intervention each animal received.

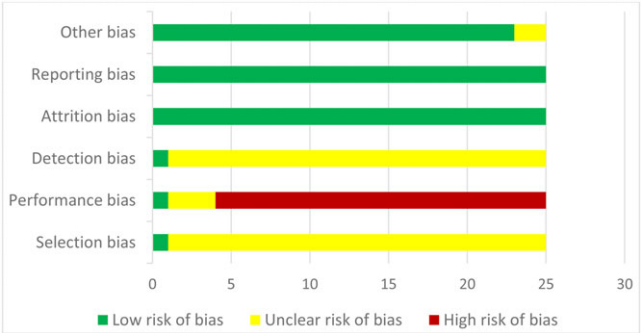

FIGURE 2 Risk of bias assessment across the studies (n = 25) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Quantitative synthesis

3.3.1 | Liver SOD

The present meta-analysis was performed on 14 datasets of the eight included studies. Two studies assessed the effects of different dosage of artichoke leaf extract (two doses [200 and 400 mg/kg] in study of Ben Salem et al. [2017] and three doses [20, 40, and 80 mg/kg] in study of Song et al. [2012]) and one study evaluated two doses of aqueous extracts of artichoke leaves and pulp (200 and 400 mg/kg; Al-Ahdab, 2014).

The pooled SMD for the effects of extract of artichoke leaves or pulp on liver SOD in intervention group compared with comparison group was 1.16 (95%CI: 0.52, 1.80, p < 0.001). Between-study heterogeneity was high (I2 = 77.2%; Figure 3). Subgroup analysis indicated that both of animals who received less than 1,000 mg/kg (SMD: 1.08, 95%CI: 0.31, 1.84, p = 0.006) and equal or more than 1,000 mg/kg artichoke extract (SMD: 1.41, 95%CI: 0.06, 2.77, p = 0.041) had significant increase of liver SOD. There was high residual heterogeneity in subgroups. Meta-regression analysis showed that dosage and study duration did not influence pooled estimates (p > 0.05). However, induced disease (hepatotoxicity and other induced diseases) significantly affected the effect size (p < 0.001). A significant increase in liver SOD was shown in animals with hepatotoxicity (1.54, 95%CI: 0.94, 2.14; I2 = 40.9%) but not in animals with other induced diseases (0.78, 95%CI: -0.24, 1.80; I2 = 84.0%).

The sensitivity analysis indicated that removal of each study did not greatly affect overall meta-analysis estimates. Even after excluding the study of Song et al. (2012) with very low dose of supplement, the overall effect size did not change significantly (SMD: 1.31, 95% CI: 0.59, 2.03).

3.3.2 | Liver CAT

The quantitative analysis of liver CAT (nine datasets) indicated a significant improvement in intervention group compared with comparison group (SMD: 2.51, 95%CI: 1.21, 3.81, I2 = 85.4%; Figure 4). This improvement was significant in animals with less than 1,000 mg/kg supplementation of artichoke extract (SMD: 2.36, 95%CI: 0.86, 3.86, p = 0.002). On the contrary, in animals with equal or more than 1,000 mg/kg, no significant effect of artichoke extract supplementation was observed (SMD: 3.23, 95%CI: -0.37, 6.83, p = 0.079). Heterogeneity in subgroups was also high.

Based on the results of meta-regression analysis, dosage, study duration, and induced disease did not affect pooled estimates. The sensitivity analysis showed that the pooled SMD and 95% CIs were not changed by excluding each study.

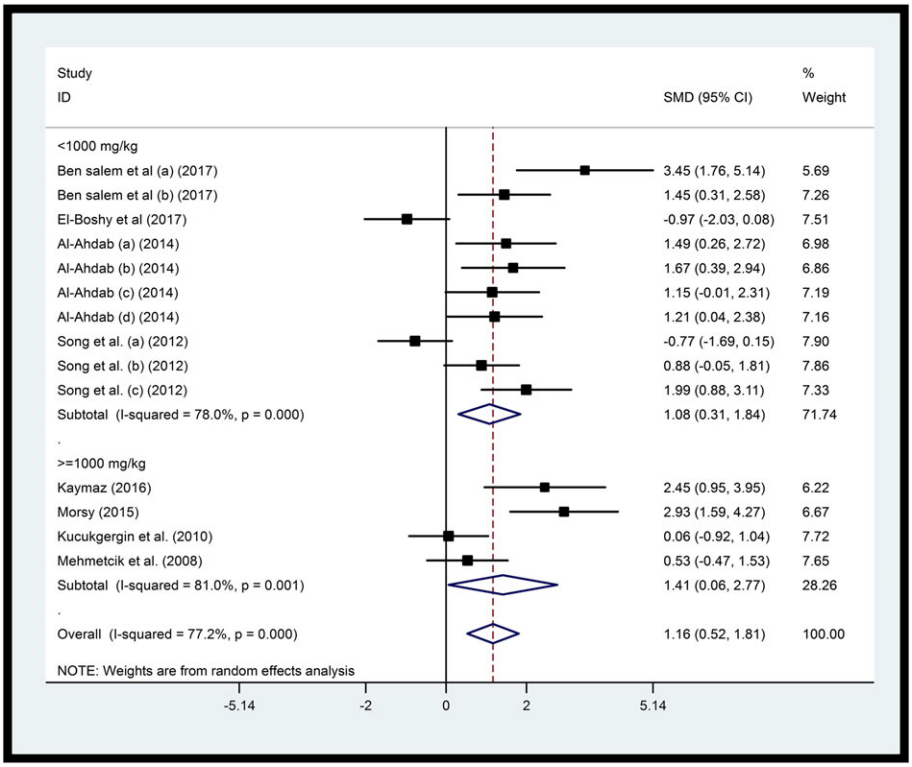

FIGURE 3 Forest plot of standardized mean difference (SMD) in liver superoxide dismutase (SOD) between intervention and comparison group in deferent dosage (<1,000 mg/kg, ≥1,000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

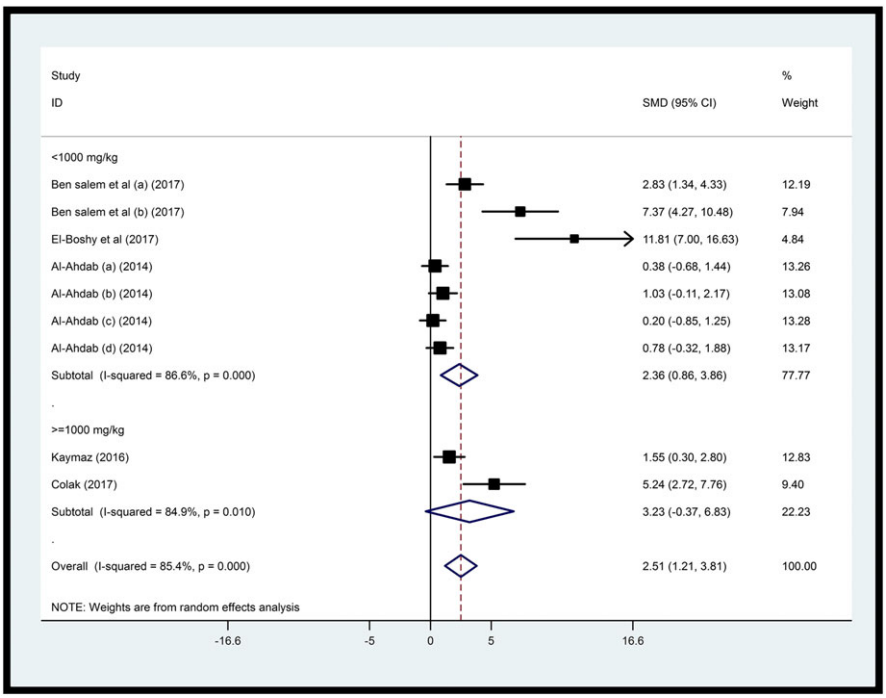

FIGURE 4 Forest plot of standardized mean difference (SMD) in liver catalase (CAT) between intervention and comparison group in deferent dosage (<1,000 mg/kg and ≥1,000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3.3 | Liver GSH

A forest plot of ten datasets indicated significant increase in liver GSH in animals with induced disease supplemented with artichoke extract compared with animals with induced disease (SMD: 3.4, 95% CI: 2.04, 4.76, I2 = 87.1%; Figure 5). In subgroup analysis, animals with less than 1,000 mg/kg supplementation of artichoke extract had more increase of liver GSH (SMD: 4.98, 95%CI: 2.83, 7.12, $p < 0.001$) compared with animals with equal or more than 1,000 mg/kg supplementation (SMD: 2.10, 95%CI: 0.55, 3.66, $p = 0.008$). Dosage subgroups showed high level of heterogeneity.

To identify the source of heterogeneity, meta-regression analysis conducted on duration, dosage, and type of induced disease. Based on results of meta-regression, none of mentioned variables accounted for a significant proportion of heterogeneity.

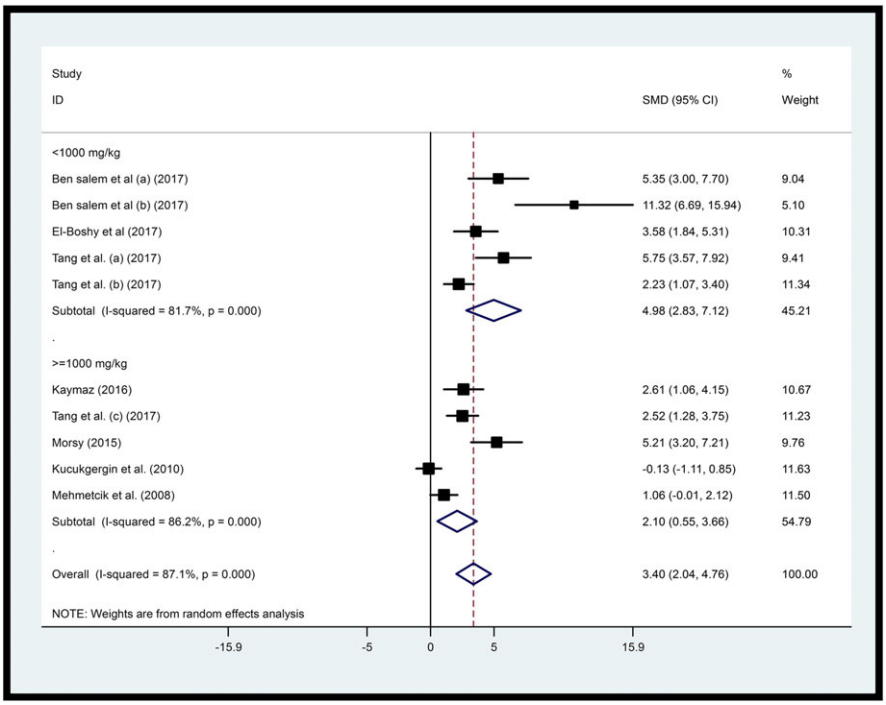

FIGURE 5 Forest plot of standardized mean difference (SMD) in liver glutathione (GSH) between intervention and comparison group in deferent dosage (< 1000 mg/kg and ≥ 1000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3.4 | Liver GPx

Ten datasets of six studies reported liver GPx concentration at endpoint. There was a significant increase in liver GPx in intervention group compared with comparison group (SMD: 2.23, 95% CI: 1.22, 3.25, I2 = 81.7%) (Figure 6). Subgroup analysis based on dosage showed that liver GPx in dosage less than 1,000 mg/kg (SMD: 2.07, 95%CI: 0.81, 3.33, p = 0.001) and equal or more than 1000 mg/kg of artichoke extract (SMD: 2.65, 95%CI: 0.90, 4.40, p = 0.003) significantly increased. Heterogeneity for subgroups pooled estimates was high. This heterogeneity was not related to study duration and dosage based on metaregression analysis (p > 0.05); however, type of induced disease in animals affect the pooled effect size significantly. After subgroup analysis for type of induced disease, artichoke extract supplementation increased liver GPx in animals with hepatotoxicity (SMD: 3.25, 95% CI: 2.22, 5.42, I2 = 75.4%, p < 0.001) more than other organ toxicity (SMD: 0.62, 95% CI: 0.14, 1.10, I2 = 0%, p = 0.011). Subgroup of induced disease also decreased heterogeneity more than other subgroups.

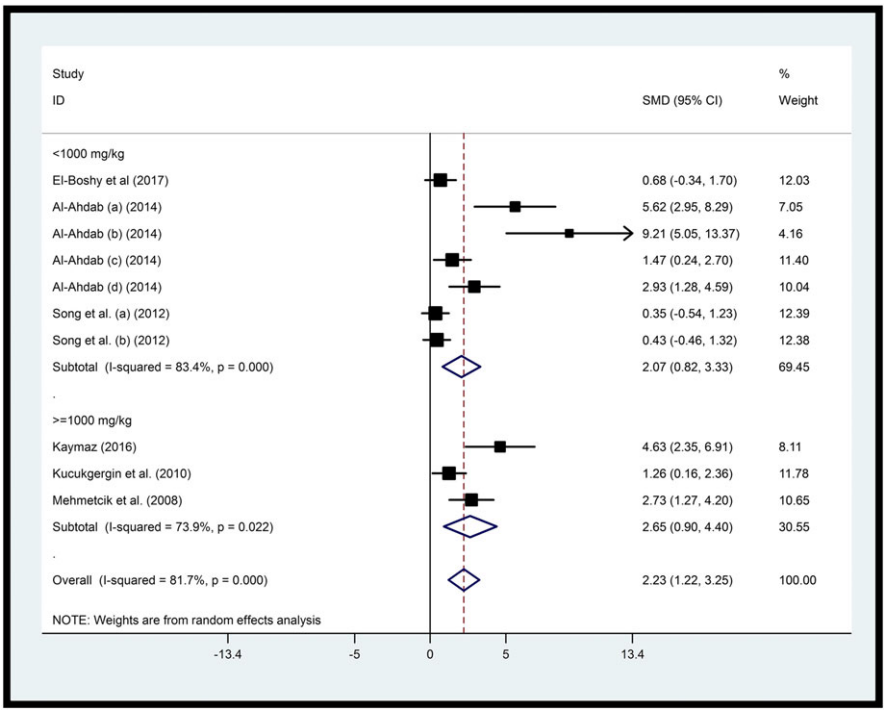

FIGURE 6 Forest plot of standardized mean difference (SMD) in liver glutathione peroxidase (GPx) between intervention and comparison group in deferent dosage (<1,000 mg/kg and ≥1,000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3.5 | Liver MDA

Twelve datasets demonstrated that liver MDA decreased significantly in intervention animals compared with comparison animals (SMD: -2.21, 95% CI: -3.16, −1.25, I2 = 87.1%) (Figure 7). Animals that received equal or more than 1,000 mg/kg artichoke extract had more reduction of liver MDA than those animals received less than 1,000 mg/kg (SMD: −2.86 vs. −1.59, respectively).

Metaregression analysis indicated that dosage of supplement did not significantly affect the effect size of intervention (p > 0.05). However, study duration (p = 0.014) and type of induced disease (p = 0.033) significantly influenced pooled estimates. Subgroup analysis according to study duration (≤20 days, >20 days) showed a significant reduction of liver MDA in studies of up to 20 days duration (SMD: −3.09, 95% CI: −4.26, −1.92, I2 = 79.7%, p < 0.001), but not in studies of more than 21 days duration (SMD: −0.58, 95% CI: −1.45, 0.29, I2 = 68.7%, p = 0.192). Similarly, subgroup analysis on type of induced disease indicated that liver MDA significantly decreased in animals with hepatotoxicity (SMD: −3.38, 95% CI: −4.73, −2.03, I2 = 81.0%, p < 0.001); however, reduction of liver MDA was not significant in animals with other induced disease (SMD: −0.76, 95% CI: −1.56, 0.04, I2 = 68.4%, p = 0.063).

3.3.6 | Plasma MDA

The meta-analysis on 12 datasets revealed that artichoke extract slightly decreased plasma MDA level in intervention group compared with comparison group (SMD: −1.03, 95% CI: −1.95, −0.10, I2 = 84.7%; Figure 8). However, reduction of plasma MDA was not significant, neither in which animals that consumed less than 1,000 mg/kg (SMD: −1.17, 95% CI: −2.35, 0.01, p = 0.051) nor in animals that received equal or more than 1,000 mg/kg artichoke extract (SMD: −0.73, 95% CI: −1.51, 0.04, p = 0.063).

The finding of metaregression analysis showed that duration, dosage, and type of induced disease were not source of heterogeneity of plasma MDA.

3.4 | Publication bias

The funnel plot for the effects of artichoke extract on liver SOD, liver GSH, liver GPx, and liver MDA indicated an asymmetry (Figures 9a, 9b, 9c, 9d, 9e). The Egger's regression also confirmed the publication bias (p < 0.05). However, when these publication biases were corrected using trim and fill method by adding theoretically missing studies, the results did not change significantly (data not shown).

On the basis of a funnel plot (Figure 9f) and Egger's statistical test, there was no publication bias for plasma MDA.

4 | DISSCUSION

In the present study, we systematically reviewed the antioxidant activity of artichoke leaf or head and their extract in in vitro, animal, and human studies. In vitro studies indicated the favorable effect of artichoke on prevention or elimination of ROS formation and improvement of antioxidant status. Quantitative analysis in animal studies demonstrated that supplementation with artichoke extract can increase SOD, CAT, GSH, and GPx level in liver as well as decrease MDA level in liver and plasma of animals with induced disease compared with comparison animals. However, no change or a slight improvement of antioxidant status was reported in limited clinical trials.

The inconsistency in results between clinical trials and experimental studies might be due to the methodological differences in measures of oxidative and antioxidative parameters in vivo or in vitro and to severity and type of stimulators of oxidative stress.

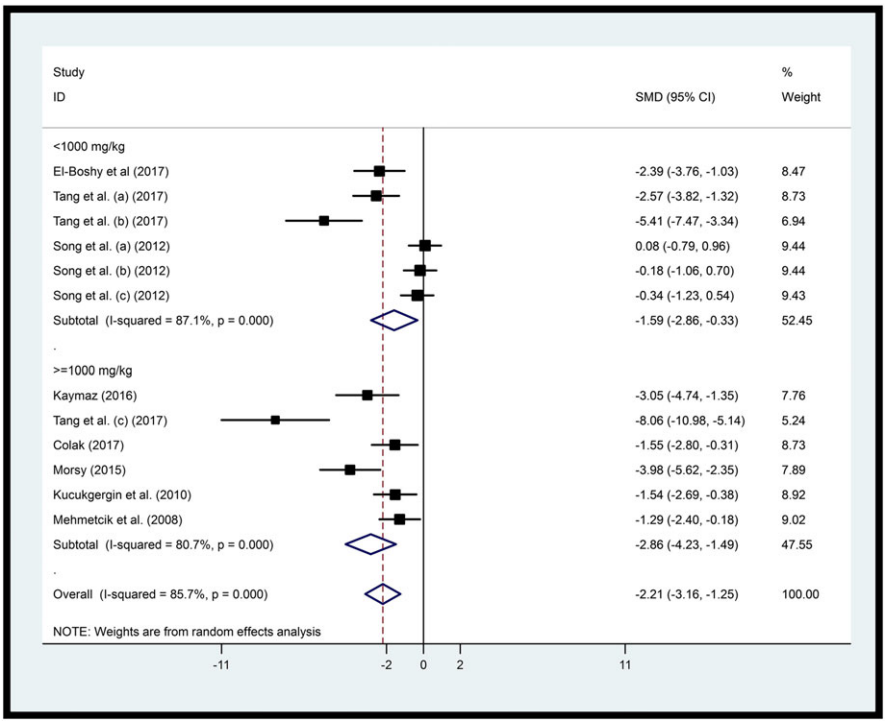

FIGURE 7 Forest plot of standardized mean difference (SMD) in liver malondialdehyde (MDA) between intervention and comparison group in deferent dosage (<1,000 mg/kg and ≥1,000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

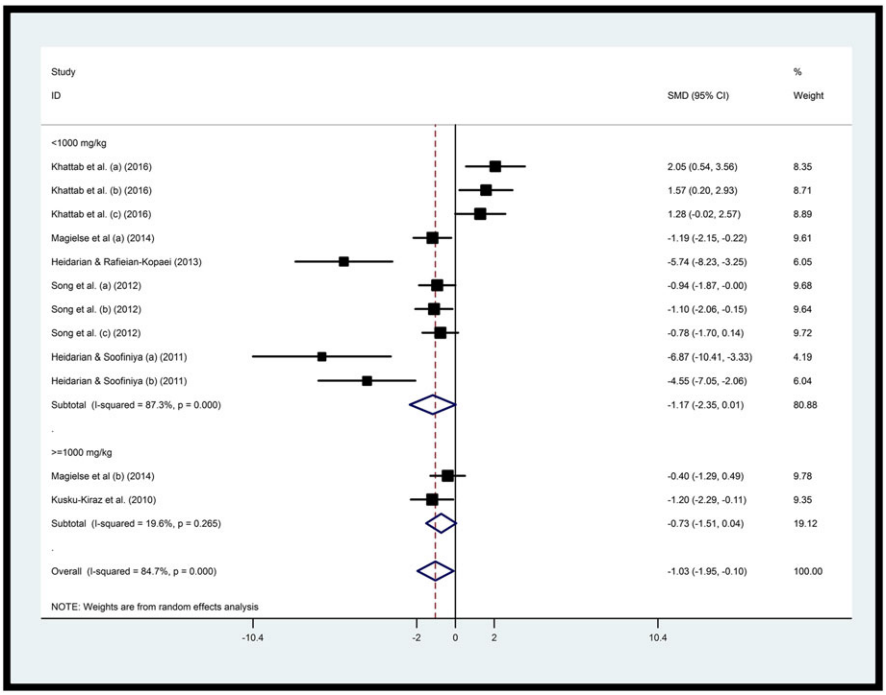

FIGURE 8 Forest plot of standardized mean difference (SMD) in plasma malondialdehyde (MDA) between intervention and comparison group in deferent dosage (<1,000 mg/kg and ≥1,000 mg/kg) [Colour figure can be viewed at wileyonlinelibrary.com]

This meta-analysis indicated that animals with hepatotoxicity may benefit more from artichoke extract compared with animals with other diseases. Meanwhile, the measurement of antioxidant indices in liver tissues in many studies may account for this finding. Differences in dosage of artichoke extract did not affect significantly the results of the present meta-analysis. Based on our finding, artichoke extract in low dosage (<1000 mg/kg) for a short duration (<20 days) are suggested as potent antioxidant in animals, mostly rats with hepatotoxicity. However, due to insufficient number of studies in many of the subgroup analysis and highly heterogeneous data, probably resulting of differences in design and quality, we cannot draw a conclusion for recommending dosage of artichoke extract and duration of study for human studies.

Free radicals and ROS at moderate concentrations play an important role in control of cell function; however, at high concentrations, they can be an important mediator to injure all major cell structures, including proteins, lipids, and DNA. Antioxidant defense system, existing in most living organisms, can scavenge free radicals and be classified into two major groups: enzymatic antioxidants (SOD, CAT, GPx, and GSH) and nonenzymatic antioxidants (vitamin E, vitamin C, carotenoids, flavonoids, polyphenols, and others). The "redox homeostasis" is determined by balance between the production of free radicals and ROS and their elimination by various antioxidants (Fang, Yang, & Wu, 2002). Antioxidants found in some herbs could help enhance the body's innate defense system and maintain redox balance (Rubió et al., 2013).

The in vitro assessment of antioxidant activity by various methods such as DDPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,20-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt), FRAP (ferric reducing ability of plasma), and beta-carotene bleaching test indicated that aqueous and ethanolic extract of artichoke possess high radical scavenging capacity (Ben Salem & Affes, 2017; da Silva Oliveira et al., 2014; Kollia, Markaki, Zoumpoulakis, & Proestos, 2017a; Kollia, Markaki, Zoumpoulakis, & Proestos, 2017b). Moreover, artichoke is categorized as an antioxidant rich vegetable, based on the comprehensive Antioxidant Food Database (Carlsen et al., 2010). Furthermore, even artichoke byproducts extract indicated high content of phenolic compounds that could be used as antioxidant in meat products (Ergezer & Serdaroğlu, 2018).

There are several methods for determination of bioactive compounds of artichoke. Recently, fingerprinting *C. scolymus* was performed by a high-performance liquid chromatography-photodiode array detection method that is an efficient and green method for the desired separation and save environmental resources (Souza, Carneiro, Vieira, Funari, & Rinaldo, 2018). The pharmacokinetics assessment of artichoke extract (Wittemer et al., 2005) and cooked edible artichoke (Azzini et al., 2007) in human subjects confirmed the bioavailability of metabolites derived from caffeoylquinic acids and flavoniods not as free but as conjugated to sulfuric or glucuronic acid in plasma and urine after consumption.

It is hypothesized that the antioxidant activity of artichoke might be related to following compounds: (a) polyphenolics (caffeoylquinic acids and flavonoids) and (b) Sesquiterpenes (Ben Salem & Affes, 2017; Brown & Rice-Evans, 1998; Gebhardt, 1997; Miccadei et al., 2008; Miláčková et al., 2017; Perez-Garcia et al., 2000; Rahimuddin et al., 2007; Takei et al., 2015).

- 1. Polyphenolic compounds:
- (a) Caffeoylquinic acids: The chemical structure of caffeoylquinic acids is composed of one or two caffeic acid moieties and one quinic acid molecule. It is reported that cynarin (1,3-O-dicaffeoylquinic acid) and chlorogenic acid (5-O-caffeoylquinic acid), the most important caffeoylquinic derivatives in artichoke, would be partly responsible for antioxidant activity of artichoke (Gebhardt & Fausel, 1997; Miccadei et al., 2008; Miláčková et al., 2017; Pandino, Lombardo, Mauromicale, & Williamson,

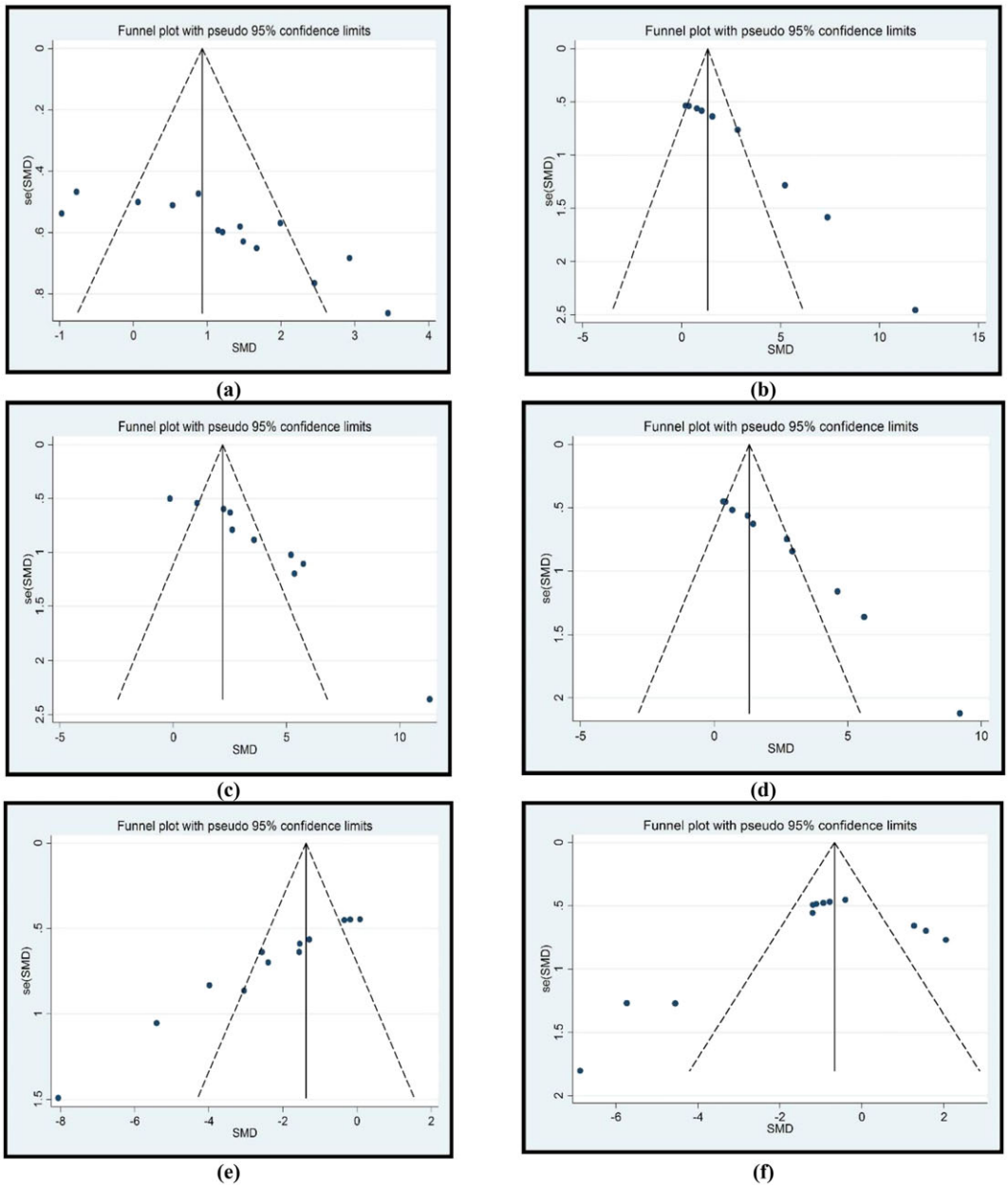

FIGURE 9 Funnel plot for (a) liver superoxide dismutase (SOD), (b) liver catalase (CAT), (c) liver glutathione (GSH), (d) liver glutathione peroxidase (GPx), (e) liver malondialdehyde (MDA), and (f) plasma MDA. The horizontal axis indicated the standardized mean difference (SMD). The vertical axis indicated the standard error (SE) of the SMD. Results of each study are represented by black circles. The vertical line in each plot represents the overall effect size [Colour figure can be viewed at wileyonlinelibrary.com]

2011; Perez-Garcia et al., 2000). Recently, the antioxidant activity of chloregenic acid and cynarin was shown using various in vito antioxidant assays (Sato et al., 2011; Topal et al., 2016). Within the caffeoylquinic acid derivatives of artichoke, the content of cynarin and chlorogenic acid is about 1.5% and 39%, respectively, which is highly varied in different part of plant (i.e., leaves, outer bracts, inner bracets, and head) and different regions (Lattanzio, Kroon, Linsalata, & Cardinali, 2009).

- (b) Flavonoids: Flavonoids are comprised of two benzene rings linked through a three carbon chain, which usually make an oxygenated heterocycle. The main flavonoids present in artichoke are the flavones (luteolin and apigenin), anthocyanidins (cyanidin, pelphinidin, and peonidin), and their glycosides and rutinosides derivatives (Wang et al., 2003). The flavones are found in leaves and head of artichoke; however, the anthocyanin pigments have been identified only in head of plant (de Falco et al., 2015; Lattanzio et al., 2009). Schutz et al. (2006) characterized and quantified the artichoke anthocyanin profile. Cyanidin 3,5-diglucoside, cyanidin 3-glucoside, cyanidin 3,5-malonyldiglucoside, cyanidin 3-(3-malonyl) glucoside, and cyanidin 3-(6-malonyl) glucoside were identified, followed by several minor compounds as peonidin and delphinidin derivatives. Despite low concentration of flavonoids in artichoke (approximately 10% or less of phenolic compounds), they possess very powerful antioxidant activity. Luteolin and luteolin-7-*O*-glucoside have been shown protective and antioxidative properties against ultraviolet A-induced oxidative stress in

human skin fibroblasts (Rahimuddin et al., 2007) and also against in vitro oxidation of LDL isolated from healthy volunteers (Brown & Rice-Evans, 1998).

The antioxidant capacity of polyphenolics (caffeoylquinic acids and flavonoids) is ascribed to their specific structural features including the number and arrangement of H-donating hydroxyl groups about the nuclear structure (Lattanzio, Cicco, & Linsalata, 2005).

- 2. Sesquiterpenes: Sesquiterpene lactones consists of three isoprene units and one lactone ring that are mainly found in the leaves and rarely in the head of artichoke (Ramos et al., 2013). Cyanoropicrin and grosheimin are main predominant sesquiterpenes in artichoke. It has been revealed that cyanoropicrin could inhibit ROS production in ultraviolet B-irradiated keratinocytes by induction of nuclear translocation of aryl hydrocarbon receptor, as well as by upregulation of transcription of the genes encoding nuclear factor E2–related factor 2 (Nrf2) and NAD(P)H: quinone oxidoreductase 1 (Nqo1). AhR is an activator of Nrf2/Nqo1 in a ligand-depend manner and Nrf2 is a transcription factor that upregulates antioxidative enzymes such as Nqo1 (Takei et al., 2015).

Several potential mechanisms are suggested for antioxidant activity of bioactive compounds of artichoke as follows: lipid peroxidation inhibiting and free radicals scavenging by acting as reducing agents, hydrogen donors, and singlet-oxygen quenchers and metal chelators (Valko et al., 2007), as well as modulating of ROS-dependent cell functional signaling at several key sites. The modulation effects could be attributed to intercepting free radicals and ROS at the level of critical signaling pathways involving various protein kinases, phosphatases, and transcription factors (Leonarduzzi, Sottero, & Poli, 2010).

Literature review indicated that artichoke and its extracts could be effective as an antioxidant in prevention and treatment of disease associated with oxidative stress. From a prevention standpoint, artichoke may improve the antioxidative defense system in healthy condition and may protect low-density lipoprotein-cholesterol from oxidation (Brown & Rice-Evans, 1998; Goñi et al., 2005; Jiménez-Escrig et al., 2003; Rezazadeh, Rahmati-Yamchi, et al., 2018; Skarpanska-Stejnborn et al., 2008). Moreover, in a treatment perspective, artichoke extracts could inhibit oxidative stress when animals are exposed to toxins and when human or animal cells are stimulated by agents that generate reactive oxygen species (Abdel-Kader et al., 2014; Al-Ahdab, 2014; Ben Salem & Affes, 2017; Brown & Rice-Evans, 1998; Colak et al., 2016; El Morsy & Kamel, 2015; El-Boshy et al., 2017; Gebhardt, 1997; Gebhardt & Fausel, 1997; Heidarian & Rafieian-Kopaei, 2013; Jaleel et al., 2016; Juzyszyn et al., 2008; Kaymaz et al., 2017; Khattab et al., 2016; Löhr et al., 2009; Mehmetcik et al., 2008; Miccadei et al., 2008; Miláčková et al., 2017; Najim et al., 2015; Perez-Garcia et al., 2000; Rahimuddin et al., 2007; Zapolska-Downar et al., 2002). In addition, artichoke head extract exhibited apoptosis and chemopreventive properties in breast cancer cells and hepatoma cells by increased ROS production (Mileo et al., 2015; Mileo, Di Venere, Linsalata, Fraioli, & Miccadei, 2012).

The present study had several limitations. Due to insufficient clinical trials and incomparable in vitro data, we could not perform meta-analysis on human and in vitro studies. In animal studies, there was high heterogeneity between the studies regarding study design, induced disease, type of intervention (artichoke leaf, hydroalcoholic, or aqueous extract of artichoke leaf or head), dosage, duration of study, and oxidative/antioxidative indices measured. Furthermore, in the majority of experimental studies, details on randomization, allocation concealment, and blinding of outcome assessment were not reported, leading to unclear risk of bias in selection bias and detection bias. The risk of performance bias also was high in most of the experimental studies because of lack of blinding participants and researchers. Because the results of animal researches are often translated into clinical practice, the improvement of the methodological quality of animal intervention studies is necessary to lessen the risk of bias.

The strength of the current study was to systematically review all of the relevant human, animal, and in vitro studies. Moreover, meta-analysis of animal studies and subsequent subgroup analysis was conducted to identify the effects of dosage of artichoke extract, study duration, and type of induced disease on the overall effect sizes.

5 | CONCLUSION

Artichoke is a vegetable that is consumed as a food around the world and indicated health- promoting properties in different disease. The preset meta-analysis provided convincing evidence for antioxidant activity of artichoke in animal models by re-establishment of "redox homeostasis." The antioxidant activity of artichoke extract was not different in low dosage (<1,000 mg/kg) and high dosage (≥1,000 mg/kg). This study suggested the beneficial antioxidant effects of artichoke extract in animals with hepatotoxicity. It should be noted that because of high heterogeneity between animal studies, we could not suggest the best dosage and duration for both animal and human subjects. Therefore, more double-blind placebo-controlled randomized clinical trials are warranted to evaluate antioxidant activity of artichoke and to clarify effective dose, duration, and type (head or leaf) of artichoke and its extract in health or disease.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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