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Evaluation of mangosteen (*Garcinia mangostana*) antioxidant activity in clinical trials and *in vivo* animal studies: A systematic review

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ABSTRACT

Mangosteen (*Garcinia mangostana*), a tropical fruit highly studied because of its potent antioxidant activity, has been utilized as supplements to alleviate chronic diseases related to oxidative stress, such as cardiovascular diseases, neurodegenerative diseases, diabetes, and others. Regardless, previous studies evaluating mangosteen antioxidant activity *in vivo* showed conflicting results toward oxidant-related diseases, and an extensive review summarizing its antioxidant effect on oxidant-related diseases was not available. Based on these, our study aimed to systematically evaluate scientific evidence of mangosteen antioxidant activity on animal models and clinical trials regarding its role in improving oxidant-related diseases. Results showed that the administration of either mangosteen extract, isolated compound, or commercialized product was able to increase antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, as well as reduce oxidative stress markers such as malondialdehyde. They were also shown to improve disease-related parameters in type II diabetes models, cardiovascular models, neurological disorder models, liver and kidney injury models, and stress-induced models. However, in clinical trials, most of the studies used commercialized mangosteen-based products that contain additional antioxidant compounds. Therefore, the results were deemed inconclusive and more clinical studies of mangosteen antioxidant activity in oxidant-related diseases are needed.

INTRODUCTION

Free radicals, atoms, or molecules that are reactive due to the possession of unpaired electrons exist in the human body as by-products of adenosine triphosphate (ATP) production in the form of reactive oxygen species (ROS) and reactive nitrogen species (Liguori *et al*., 2018; Pham-Huy *et al*., 2008). The existence of the highly unstable reactive oxygen and nitrogen species (RONS) not only comes as a result of ATP production but also comes from external sources, such as water pollution, air pollution, alcohol, tobacco, food, and radiation (Liguori *et al*., 2018). It was well-known that a moderate amount of RONS is useful for a cellular response, such as reduction–oxidation regulation, for protein activation (Dröge, 2002; Kim *et al*., 2002); however, a high amount of RONS is known to cause oxidative stress. This oxidative stress could result in cellular damage by oxidizing lipid in the membrane, thus disrupting the cellular structure (Pham-Huy *et al*., 2008), as well as inducing abstraction and addition reaction to the DNA structure, which alters the gene expression (Dizdaroglu *et al*., 2002; Kumar *et al*., 2012).

Oxidative stress could cause oxidative modification which results in the damage of cellular macromolecules, such as DNA, proteins, lipids, and carbohydrates (Liguori *et al*., 2018). Prolongation of the damage could increase the risk of several chronic diseases, such as cancer, autoimmune diseases, cardiovascular diseases, neurodegenerative diseases, mental disorders, and skin aging (Pham-Huy *et al*., 2008). In order to minimize the damage, antioxidants are needed.

Antioxidants are compounds that are able to stabilize free radicals by a mechanism of hydrogen atoms donation, inhibition of low-density lipoprotein (LDL) oxidation, and chelation of metal ions. Stabilization of free radicals by antioxidants could prevent and repair DNA damage (Pham-Huy *et al*., 2008; Santos-Sánchez *et al*., 2019). In a state of oxidative stress, the body is

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incapable of producing an adequate amount of antioxidants to neutralize free radicals; therefore, exogenous antioxidants are needed to overcome oxidative stress. One of the sources for antioxidants is from the consumption of plants containing antioxidant compounds. Phenolic and flavonoids compounds that are easily found in vegetables, fruits, and legumes are some of the phytochemicals that are known for their antioxidant activity (Santos-Sánchez *et al*., 2019).

Mangosteen (*Garcinia mangostana*) is a tropical fruit whose biological activities, such as antimicrobial activity (Chomnawang *et al*., 2005), antidiabetic activity (Taher *et al*., 2016), antitumor activity (Nakagawa *et al*., 2007), anti-inflammatory activity (Chen *et al*., 2008), and antioxidant activity (Weecharangsan *et al*., 2006), have been extensively studied. Among these studies, its antioxidant activity is the one receiving prominent interest. Several studies have confirmed that the administration of the mangosteen extract could help in improving the condition of oxidant-related diseases, such as diabetes, hyperlipidemia, neurological disorders, skin aging, acne, and others (Huang *et al*., 2014; Im *et al*., 2017; Leontowicz *et al*., 2006; Nelli and Kilari, 2013). Due to these findings, patents and commercialization of several mangosteen-based products, such as Verve®, Vemma®, and Mastin®, have recently progressed. However, despite the commercialization, conflicting results of the study about their antioxidant effect in various disease models are still discovered. In addition, an extensive review that summarizes the antioxidant effect of mangosteen products toward oxidant-related diseases was not available. Due to these factors, a systematic review is needed to properly assess the effectiveness of mangosteen antioxidant activity in alleviating oxidant-related diseases in various clinical and *in vivo* study models. Hence, this study aimed to carry out a systematic review to evaluate scientific evidence regarding the antioxidant activity of mangosteen on animal models and clinical trials in relation to its role in improving the pathology of the related diseases.

MATERIALS AND METHODS

The protocol of this study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Moher *et al*., 2009).

Search strategies

Databases that were used were PubMed, PubMed Central (PMC), Cochrane Library, ScienceDirect, and Google Scholar up to 30th June 2020. Keywords that were used for searching the studies were "mangosteen", "manggis", "*Garcinia mangostana*", "oxidative stress", "antioxidant", "oxidant-related disease", "cardiovascular disease", "atherosclerosis", "diabetes", "neurological disorder", "cancer", "acne", and "skin aging". The search was restricted to articles that were published in English and Indonesian.

Inclusion and exclusion criteria

Screening and selection of included studies were carried out by two investigators (BE and PH) independently based on the inclusion and exclusion criteria. Studies that were included in this review were clinical and animal studies published in a peer-reviewed journal and indexed in either SCOPUS or Web of Science and which evaluated the mangosteen fruit antioxidant activity with an outcome related to the antioxidant power, including but not limited to the changes in the level of total antioxidant capacity, catalase (CAT), superoxide dismutase (SOD), and others. *In vitro* studies and review papers were excluded from this study but manual screening of related review papers references was carried out for additional studies. The titles and abstracts of the studies were screened first before screening the full articles. Any disagreements were resolved through discussion between the reviewers.

Data extraction

Extracted information from the included studies was the author's name, year of publication, type of study, subjects or disease model, sample size, intervention and comparator, treatment duration, intervention and comparator dose, route of administration, and outcomes of the study.

Quality assessment

Quality of the clinical trial studies was assessed using Downs and Black's (1998) checklist with evaluated parameters including reporting, external validity, internal validity (bias), internal validity (confounding), and power. For *in vivo* studies, the quality assessment was carried out using ToxRTool with evaluated parameters including test intervention identification, test organism characterization, study design description, study results documentation, and plausibility of study design and results (Schneider *et al*., 2009). Quality assessment was carried out independently by two investigators (BE and PH). Any disagreements were resolved through discussion between the reviewers.

RESULTS AND DISCUSSION

Study selection

The total amount of related articles that was obtained from PubMed, PMC, Cochrane Library, ScienceDirect, and Google Scholar searches was 251 articles, 968 articles, 25 articles, 1,786 articles, and 5,982 articles, respectively. The checking of article duplications was conducted using Mendeley, while the abstract and full-text screening based on the inclusion and exclusion criteria was carried out by both the authors individually and manually. The final screening of articles resulted in a total of 47 included articles (41 articles for *in vivo* studies and 6 articles for clinical trials). The process of study screening and selection is detailed in Figure 1.

Quality assessment

Clinical trial studies' quality was assessed using Downs and Black's checklist (Supplementary Data Table 1). Two of them showed poor quality (Suthammarak *et al*., 2016; Kondo *et al*., 2009), while two others showed fair quality (Xie et *al*., 2015a, 2015b), and the rest showed good quality (Baroroh *et al*., 2018; Sutono, 2013). The poor quality score of the studies was due to insufficient information regarding the characteristics of patients who dropped out of the trials and lack of external validity of the subject population. The qualities of *in vivo* studies were assessed using ToxRTool and all studies showed reliable quality without restriction needed (Supplementary Data Table 2).

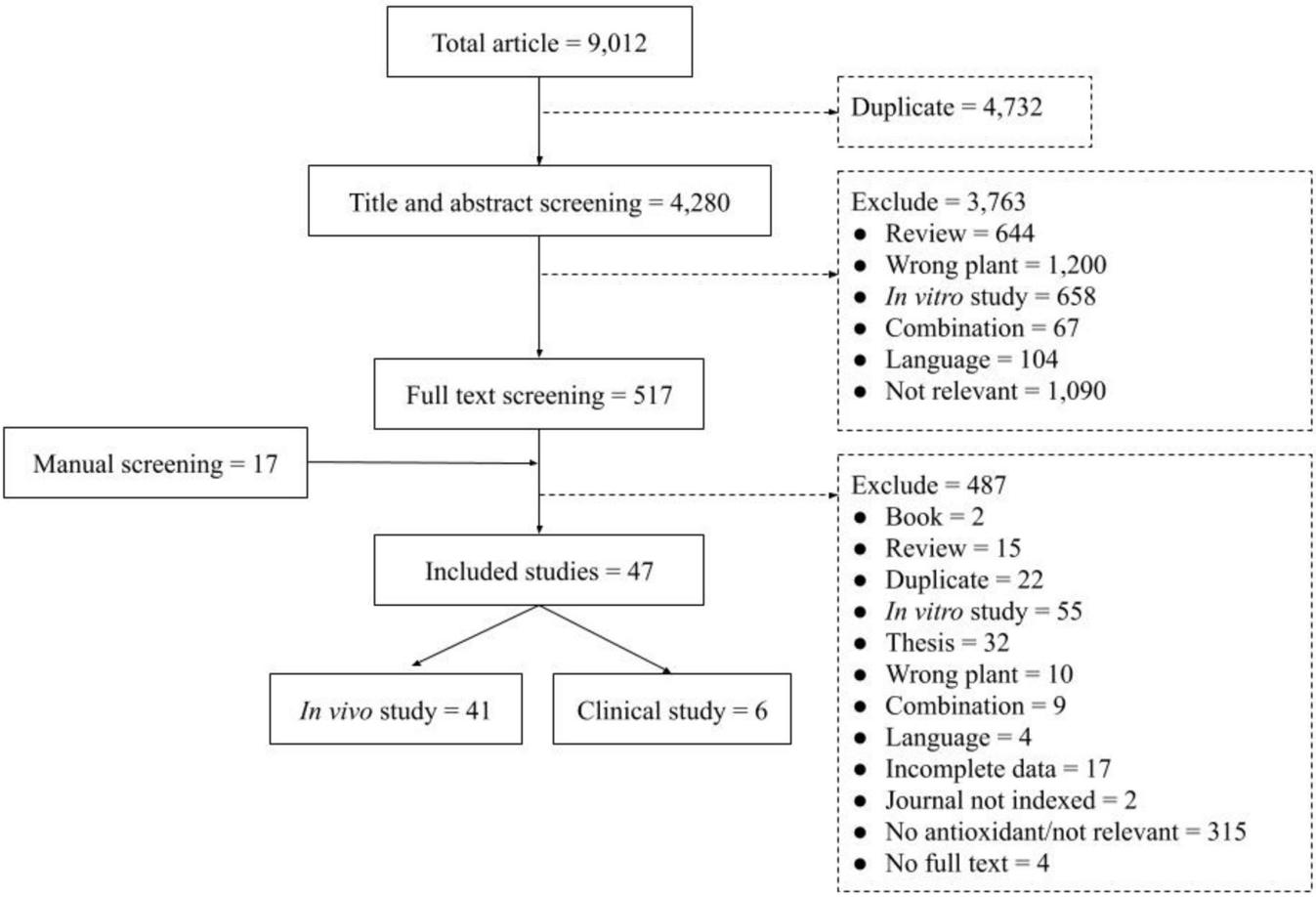

Figure 1. Flowchart of studies' screening and selection.

Clinical trials

A total of six studies were conducted using human subjects to evaluate the antioxidant activity of mangosteen through the oral route (Table 1). Among the six studies, two studies used mangosteen pericarp extract as the intervention (Baroroh *et al*., 2018; Suthammarak *et al*., 2016), while the other four studies used commercial mangosteen supplement as the intervention (Kondo *et al*., 2009; Sutono, 2013; Xie *et al*., 2015a; 2015b). The result of the intervention showed that antioxidant capacity in plasma and red blood cells (RBC) increased after the administration of mangosteen extract or products (Kondo *et al*., 2009; Suthammarak *et al*., 2016; Xie *et al*., 2015a; 2015b). However, unfortunately, two of the studies did not carry out adequate statistical analysis, wherein the result from the treated group was not statistically compared to the placebo group (Kondo *et al*., 2009; Xie *et al*., 2015a).

Malondialdehyde (MDA) is one of the products of lipid peroxidation and also one of the markers of oxidative stress. A high amount of MDA indicates a high level of reaction between oxygen and unsaturated lipids in the body (Ayala *et al*., 2014). Among the six studies, two studies evaluated the MDA level of the subjects after the intervention (Sutono, 2013; Baroroh *et al*., 2018). Both of them showed a decrease in MDA level; however, it was not statistically significant when compared to the control group. These results showed that either the mangosteen extract or products could not reduce the MDA level or the dose administered was not enough to show a significant effect on the MDA level.

Mangosteen products that were used in the studies were Verve®, Vemma®, and mangosteen rind extract capsule from PT and Sido Muncul (Kondo *et al*., 2009; Sutono, 2013; Xie *et al*., 2015a, 2015b). All products showed antioxidant activity in human subjects by increasing plasma antioxidant capacity and reducing the MDA level. However, ingredients contained in the products, such as vitamin C, vitamin E, and green tea extracts, might also contribute to the antioxidant activity, implying that the antioxidant activity did not solely come from mangosteen.

Table 1. Data extraction of clinical studies.

Author (year)	Type of study	Subject (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Suthammarak *et al*. (2016)	Quasiexperiment	Healthy subjects (n = 11)	I: mangosteen pericarp ethanolic extract capsule (maceration spray-drying). C0: no comparator.	24 weeks	220 or 280 mg daily	Oral	RBCs antioxidant capacity: ↑ versus C0. Protein in RBC and whole blood cells oxidative damage: ↓ versus C0. No significant changes in blood and urine samples.
Xie *et al*. (2015b)	RCT	Healthy subjects (n = 60)	I: Verve® (containing mostly mangosteen fruit, Vemma Nutrition Co., Arizona). C0: placebo (fructose liquid).	30 days	245 ml/days	Oral	Plasma antioxidant capacity (ORAC): ↑ versus C0; plasma CRP: ↓ versus C0. No significant changes in body weight. Heart rate, immunoglobulins, interleukins, creatinine, ALT, and AST.
Xie *et al*. (2015a)	RCT	Healthy subjects (n = 20)	I: Verve® (containing mostly mangosteen fruit, Vemma Nutrition Co., Arizona). C0: placebo.	6 hours	245 ml	Oral	↑ versus C0 plasma antioxidant capacity up to 60% after 1-hour consumption, then gradually reduce and remain stable after 4 to 6 hours with 10% higher compared to 0 hour. Statistical analysis is not done.
Sutono (2013)	RCT	Subject with mild-to-moderate acne vulgaris (n = 94)	I: mangosteen rind extract capsule (PT Sido Muncul, Indonesia). C0: placebo.	3 weeks	3 × 400 mg	Oral	Reduction of MDA level but not statistically significant. Total acne lesions: ↓ versus C0.
Kondo *et al*. (2009)	RCT	Healthy male and female (n = 20)	I: Vemma® (Mangosteen Plus™ with essential minerals®, Vemma Nutrition Co., Arizona). C0: placebo.	24 hours	59 ml	Oral	↑ versus C0 antioxidant capacity up to 16% after 1 hour and 18% after 2 hours of consumption, then remain stable until 6 hours of consumption. No changes in placebo group but not statistically compared to treatment group.
Baroroh *et al*. (2018)	Pretest and posttest design	COPD patients with acute exacerbation (n = 34)	I: mangosteen pericarp extract. C0: placebo.	Until patient health improves and is allowed to go home by the doctor (4–5 days)	2 × 1,100 mg	Oral	No significant difference in MDA level compared to pretest and placebo group. COPD assessment test and IL-6: ↓ versus pretest result, = versus C0.

↑ = statistically significant increase versus C0; ↓ = statistically significant decrease versus C0; ORAC = oxygen radical absorbance capacity; MDA = malondialdehyde; CRP = C-reactive protein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IL-6 = interleukin-6.

In vivo animal studies

A total of 41 articles studied the antioxidant activity of mangosteen in *in vivo* animal models (listed in Table 2). Most of the studies used mangosteen pericarp as the intervention where 15 used the extracts, two used the dried and ground pericarp, and 17 used the isolated compounds, such as xanthone, α-mangostin (AM), or γ-mangostin. In addition to mangosteen pericarp, five studies used mangosteen flesh as the intervention and two studies used commercial products from Lord Duke Biotechnology Company.

Nearly all the 22 studies that evaluated the MDA level as one of the oxidative stress markers showed a significant decrease after the subjects were treated with mangosteen extract or products. Out of the 22 studies, only three of them showed no significant decrease in MDA level (Herrera-Aco *et al*., 2019; Oberholzer *et al*., 2018; Subani, 2014). The negative results could be due to either different routes of administration used (Subani, 2014) or insufficient dose of mangosteen extract (Herrera-Aco *et al*., 2019; Oberholzer *et al*., 2018).

SOD is an antioxidant enzyme that is known as one of the first-line defenses in our body against oxidative stress along with CAT and glutathione (GSH) peroxidase (GPx) (Ighodaro and Akinloye, 2018). It was explained that SOD worked by dismutating the superoxide radicals into hydrogen peroxide and an oxygen molecule. The excess hydrogen peroxide was then broken down further by CAT and GPx into water and oxygen molecules in the peroxisome and mitochondria, respectively. Additionally, GPx is also responsible for converting lipid peroxides into their corresponding alcohol forms (Ighodaro and Akinloye, 2018), and it also acts as the catalyst of GSH reaction with radicals to form oxidized glutathione or glutathione disulfide before being excreted from the cells (Lushchak, 2012).

Table 2. Data extraction of *in vivo* animal studies.

Author (year)	Subject-disease model (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Nelli and Kilari (2013)	Wistar rats induced by STZ, type II diabetic model ($n = 30$)	I: AM (benzene maceration column fractionation). C1: gliclazide. C0: no treatment.	55 days	I: 25 and 50 mg/kg C1: 1 mg/kg	Oral	Testis and epididymis lipid peroxidation: ↓ versus C0, = versus C1. Testis and epididymis SOD, CAT, and GPx level: ↑ versus C0, = versus C1. Blood glucose level: ↓ versus C0 and C1; body weight: ↑ versus C0, = versus C1; testis, epididymis, seminal vesicle, and prostate gland weight: ↑ versus C0, = versus C1; serum testosterone: ↑ versus C0, = versus C1.
Jariyapongskul *et al.* (2015)	Sprague Dawley rats induced by STZ, type II diabetic model ($n = 56$)	I: AM (ethyl alcohol maceration column fractionation). C0: no treatment.	8 weeks	200 mg/kg	Oral	MDA level: ↓ versus C0. Blood glucose level, arterial blood pressure, HbA1C, serum insulin, HOMA-IR, cholesterol, triglyceride, blood-retinal barrier leakage, AGE, RAGE, TNF-a, and VEGF: ↓ versus C0. Ocular blood flow: ↓ versus C0. SOD and GSH level: ↑ versus C0, = versus C1; LPO: ↓ versus C0, = versus C1.
Kumar *et al.* (2016)	Wistar albino rats induced by STZ, type II diabetic model ($n = 96$)	I: AM (AIMIL Pharmaceutical, New Delhi). C1: glibenclamide. C0: no treatment.	56 days	I: 25, 50, and 100 mg/kg C1: 10 mg/kg	Oral	Blood glucose level, fructose-1-6-biphosphatase, total cholesterol, triglyceride, LDL, atherogenic index, and coronary risk index: ↓ versus C0, = versus C1. Bodyweight and plasma insulin: ↑ versus C0, = versus C1. Hemoglobin (A1c), glucose-6-phosphatase, and VLDL: ↓ versus C0, = versus C1. CAT level: ↑ versus C0, = versus C1 for 50 and 100 mg/kg dose.
Wahjuni *et al.* (2017)	Wistar rats induced by alloxan and high glucose diet, hyperglycemia model ($n = 25$)	I: mangosteen peel ethanolic extract (maceration evaporation). C0: no treatment.	21 days	50, 100, and 150 mg/kg	Oral	SOD level: ↑ versus C0. Repair pancreas histology: ↑ versus C0.
Karim *et al.* (2018)	Mice induced by STZ, type II diabetic model ($n = 30$)	I: mangosteen vinegar rind (Asia & Pacific Quality Trade Co., Ltd., Bangkok)). C1: glibenclamide. C0: no treatment.	1 week	I: 100 and 200 mg/kg BW C1: 60 mg/kg BW	Oral	Plasma and liver tissue MDA level, glucose level, and triglyceride level: ↓ versus C0, ↑ versus C1. Liver tissue CAT, SOD, glycogen, and HDL: ↑ versus C0, ↓ versus C1. Total cholesterol and LDL level: ↓ versus C0, ↑ versus C1 for 200 mg/kg dose.
Karim *et al.* (2019a)	ICR mice induced by STZ and high-fat diet, type II diabetic model ($n = 36$)	I: mangosteen pericarp aqueous extract (maceration freeze-drying). C1: glibenclamide. C0: no treatment.	1 week	I: 100 and 200 mg/kg C1: 60 mg/kg	Oral	Kidney MDA level and blood glucose level: ↓ versus C0, ↑ versus C1. BUN: ↓ versus C0, = versus C1 for both doses. Kidney SOD level, insulin, and HOMA-IR: ↑ versus C0, ↓ versus C1 for 200 mg/kg dose.
Karim *et al.* (2019b)	ICR mice induced by STZ and high-fat diet, type II diabetic model ($n = 36$)	I: xanthone from mangosteen pericarp (Asia & Pacific Quality Trand Co., Ltd., Thailand). C1: glibenclamide. C0: no treatment.	1 week	I: 100, 200, and 400 mg/kg C1: 60 mg/kg	Oral	Liver MDA, triglyceride, AST, and ALT: ↓ versus C0, = versus C1. Liver CAT level: ↑ versus C0, ↓ versus C1 for all doses. Kidney and liver SOD: ↑ versus C0, = versus C1. Plasma insulin: ↑ versus C0, ↓ versus C1. Total cholesterol, LDL, and the number of apoptotic cells/kidney: ↓ versus C0, ↑ versus C1 for 200 and 400 mg/kg doses. Kidney CAT level: ↑ versus C0, = versus C1 for 400 mg/kg dose.
Husen *et al.* (2017a)	Balb/c mice induced by STZ and high-fat diet, type II diabetic model ($n = 30$)	I: mangosteen pericarp fraction (Maceration freeze-drying): n-hexane (nonpolar), chloroform (semipolar), and ethanol (polar). C1: metformin. C0: no treatment.	14 days	I: 100 mg/kg C1: 100 mg/kg	Oral	MDA level: ↓ versus C0 and C1 for polar fraction and↓ versus C0, = versus C1for nonpolar fraction. Cholesterol: ↓ versus C0, = versus C1 for polar fraction.

Continued

Author (year)	Subject-disease model (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Husen *et al*. (2017b)	BALB/C mice induced by lard and STZ, type II diabetic model (n = 24)	I: mangosteen pericarp ethanolic extract (maceration freeze-drying) C1: metformin. C0: no treatment.	14 days	I: 50, 100, and 200 mg/kg BW C1: 100 mg/kg BW	Oral	Serum MDA and cholesterol: ↓ versus C0, = versus C1 level for 100 and 200 mg/kg dose. Bodyweight: ↑ versus C0 and C1 for all doses.
Leontowicz *et al*. (2006)	Wistar rats fed with nonoxidized cholesterol, cholesterol model (n = 20)	I: freeze-dried mangosteen. C0: no treatment.	4 weeks	5%	Oral	Antioxidant activity through ABTS assay: ↑ versus C0. Total cholesterol, LDL, and triglyceride: ↓ versus C0. No significant difference in weight gain, food consumption and efficiency, and HDL.
Leontowicz *et al*. (2007)	Wistar rats fed with nonoxidized cholesterol, cholesterol model (n = 20)	I: freeze-dried mangosteen. C0: no treatment.	4 weeks	5%	Oral	Plasma antioxidant activity: ↑ versus C0. Total cholesterol, LDL, and triglyceride: ↓ versus C0. No significant difference in HDL.
Haruenkit *et al*. (2007)	Wistar rats fed with nonoxidized cholesterol, cholesterol model (n = 25)	I: freeze-dried mangosteen flesh. C0: no treatment.	26 days	50 g/kg	Oral	No significant increase in plasma antioxidant activity versus C0. No significant difference in protein content, feed intake, body gain, feed efficiency ratio, protein efficiency ratio, total cholesterol, LDL, HDL, and triglyceride versus C0.
Devi Sampath and Vijayaraghavan (2007)	Wistar albino rats induced by isoproterenol, myocardial infarction model (n = 24)	I: AM (methanol maceration chromatography). C0: no treatment.	8 days	200 mg/kg BW	Oral	GSH, GST, GPx, SOD, and CAT level: ↑ versus C0. Lipid peroxides (nmoles of TBARS/g of protein), GOT, GPT, CPK, and LDH: ↓ versus C0.
Sampath and Kannan (2009)	Wistar albino rats induced by isoproterenol, myocardial infarction model (n = 24)	I: AM (methanol maceration chromatography) C0: no treatment.	8 days	200 mg/kg	Oral	GSH, GPx, GST, SOD, and CAT level: ↑ versus C0. LPO level: ↓ versus C0. Isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, a-ketoglutarate dehydrogenase, NADH dehydrogenase, cytochrome c, cytochrome c1, cytochrome b, cytochrome aa3, ATP, and nitrate/nitrite: ↑ versus C0.
Hafisalevi *et al*. (2012)	Wistar rats fed with atherosclerosis diet, atherosclerosis model (n = 30)	I: mangosteen pericarp extract. C0: no treatment.	90 days	200, 400, and 800 mg/kg	Oral	Serum SOD level: ↑ versus C0. Serum MDA level: ↓ versus C0.
Boonprom *et al*. (2017)	Sprague Dawley rats induced by L-NAME, hypertension model (n = 32)	I: mangosteen pericarp aqueous extract (maceration spray-drying). C0: no treatment.	5 weeks	200 mg/kg	Intragastric	Vascular superoxide production and plasma MDA: ↓ versus C0. SBP, MAP, DBP, PP, HR, HVR, heart weight, left ventricular weight, wall thickness (left ventricular, aorta, mesenteric artery), cross-sectional area (left ventricular, aorta, mesenteric artery), lumen diameter (mesenteric artery), and TNF-a: ↓ versus C0. Left ventricular luminal area, plasma nitrate/nitrite, and HBF: ↑ versus C0.
Huang *et al*. (2014)	B6 and 3 × Tg-AD mice, Alzheimer's model (n = 68)	I: mangosteen pericarp supplement (Lord Duke Biotechnology Company, Taiwan). C0: no treatment.	8 months	5,000 ppm	Oral	Serum GSH level: ↑ versus C0. Spatial learning ability, short-term memory, Neun, calbindin, BDNF, ChAT, TH, and 5-HT: ↑ versus C0. Aβ42, Tau pSer202, IL-6, and p38/p38: ↓ versus C0. No significant difference in swimming velocity.
Avinash *et al*. (2016)	Swiss albino mice induced by STZ, Alzheimer's model (n = 24)	I: mangosteen pericarp ethanolic extract (maceration rotary evaporation). C0: no treatment.	28 days	200 and 400 mg/kg	Oral	SOD, CAT, GPx, and GSH level: ↑ versus C0. Spontaneous alteration (Y-maze test), number of line crossing, and head dipping (open field habituation memory): ↑ versus C0. AChE: ↓ versus C0. Striatum sample MDA level: ↓ versus C0.
Parkhe *et al*. (2020)	Sprague Dawley mice induced by rotenone, Parkinson's disease model (n = 15)	I: AM (Chemical Biology laboratory, NIPER Ahmedabad, India). C0: no treatment.	21 days	10 mg/kg	Intraperitoneal	No significant difference in striatum sample GSH level. Time latency to fall, forced required in muscle strength grip, % alteration in memory impairment: ↑ versus C0. α-Synuclein/GAPDH and TH-expression: ↑ versus C0.

Continued

Author (year)	Subject-disease model (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Oberholzer *et al.* (2018)	FSL rats, depression model ($n = 66$)	I: grinded mangosteen pericarp powder (Industrial Analytical, South Africa). C1: imipramine hydrochloride (IMI). C0: no treatment.	14 days	I: 50 mg/kg C1: 20 mg/kg	Oral	Hippocampus MDA level: ↓ versus C0, = versus C1. No significant difference in MDA level in frontal cortex. Discrimination index (novel object recognition): ↑ versus C0, = versus C1. Immobility time: ↓ versus C0, = versus C1. Swimming time: ↑ versus C0 and C1 (forced swim test). 5-HIAA/5-HT: ↑ versus C0 and C1. No significant effect in distance move and locomotor performance (open field test).
Sattayasai *et al.* (2013)	ICR mice induced by scopolamine, memory impairment model ($n = 10$)	I: mangosteen pericarp ethanolic extract (maceration rotary evaporation). C0: water/no treatment.	17 days	100 mg/kg BW	Oral gavage	ROS and caspase level in scopolamine induce mice brain extract: ↓ versus C0. Time for escaping the maze (spatial memory test): ↓ versus C0. Latency time (fear memory test): ↑ versus C0.
Phyu and Tangpong (2014)	ICR mice induced by lead acetate, cognitive impairment model ($n = 42$)	I: xanthone from mangosteen aqueous extract (Sigma-Aldrich, USA). C1: vitamin E. C0: no treatment.	38 days	I: 100 and 200 mg/kg BW C1: 100 mg/kg BW	Oral	RBC and brain tissue MDA level: ↓ versus C0, = versus C1. RBC and brain tissue AChE level: ↑ versus C0, = versus C1. Immobility time (forced swim test) and latency time (water maze swimming test): ↓ versus C0, = versus C1. Frontal cortical MDA level: ↓ versus C0, = versus C1 for AM-treated group.
Lotter *et al.* (2020)	SD mice induced by lipopolysaccharide, schizophrenia immune-inflammatory model ($n = 80$)	I: GML or AM (Sigma-Aldrich, Australia). C1: haloperidol (Hal). C0: no treatment.	16 days	GML: 50 mg/kg AM: 20 mg/kg Hal: 2 mg/kg	Oral	Startle amplitude: ↓ versus C0, = versus C1. Treatment × startle block interaction: ↑ versus C0, = versus C1 (prepulse inhibition). Total distance moved (open field test): ↓ versus C0 and C1 for AM treated group. Immobility: ↓ versus C0 and C1 (GML, hal + GML, hal + AM group), = versus C1 (AM group). Struggling: ↑ versus C0 and C1(hal + GML, hal + AM group). Swimming behavior: ↑ versus C0 and C1 (GML and AM group) (forced swim test). IL-6: ↓ versus C0, = versus C1 (GML, AM, and hal + GML). TNF-a: ↓ versus C0 and C1 (GML, hal + GML).
Indharty *et al.* (2019)	Sprague Dawley rats induced with unilateral focal brain injury, close head injury model ($n = 20$)	I: mangosteen pericarp ethanolic extract (maceration rotary evaporation). C0: no treatment.	7 days	100 mg/kg	Oral	MDA level, caspase 8, caspase 9, AIF, and apoptosis: ↓ versus C0. SOD level: ↑ versus C0.
Wang *et al.* (2018)	C57BL/6 mice induced by CCL4, acute liver injured model ($n = 50$)	I: ɣ-mangostin from mangosteen pericarp (ethanol maceration HPLC). C0: no treatment.	7 days	5 and 10 mg/kg BW	Intraperitoneal	SOD, NRF2, SIRT1, HO-1, and SOD2 level: ↑ versus C0. Liver GSH content: ↑ versus C0 for 10 mg/kg dose. ALT and AST level, necrosis, and inflamed hepatocytes: ↓ versus C0.
Yan *et al.* (2018)	ICR mice induced by acetaminophen, acute liver injury model ($n = 32$)	I: AM (ethanol smashing tissue extraction HPLC). C0: no treatment.	7 days	100 and 200 mg/kg	Intragastric	Serum MDA level: ↓ versus C0. GSH level: ↑ versus C0. Necrosis score, TUNEL positive cells, ALT, AST, TNF-a, IL-1β, LC3, BNIP3, and Bax cleaved caspase 3: ↓ versus C0; Bcl-2, p-Akt, p-mTOR, p62: ↑ versus C0.
Wang *et al.* (2019)	C57BL/6 mice induced by CCl_4, chronic liver injury model ($n = 50$)	I: ɣ-mangostin from mangosteen pericarp (ethanol maceration HPLC). C0: no treatment.	1 month	5 and 10 mg/kg	Intraperitoneal	SOD and liver GSH level: ↑ versus C0. ALT, AST, HMGB1, collagen I, and a-SMA: ↓ versus C0. SIRT3: ↑ versus C0.
Tsai *et al.* (2016)	SD rats fed with high-fat diet (modified AIN93M diet), hepatic steatosis model ($n = 24$)	I: mangosteen pericarp extract (Shinn Nan World Trade Co., Ltd., Taiwan). C0: no treatment.	11 weeks	25 mg/days	Oral	TBARS level, body weight, free fatty acid, and triglyceride: ↓ versus C0. GSH, GPx, GRd, SOD, and CAT level: ↑ versus C0.

Continued

Author (year)	Subject-disease model (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Pérez-Rojas *et al.* (2009)	Wistar rats induced by cisplatin, nephrotoxicity model ($n = 34$)	I: AM (DNP International Inc. Co., USA). C0: no treatment.	10 days	12.5 mg/kg	Oral	MDA level: ↓ versus C0. Serum GPx and CAT level: ↑ versus C0. Creatinine, BUN, urinary volume, FeNa, urinary protein, urinary N-acetyl Beta-D-glucosaminidase, kidney damage area, and renal protein carbonyl: ↓ versus C0. Osmolality and GSH: ↑ versus C0.
Rana *et al.* (2020)	ICR mice induced by lead acetate, chronic kidney disease model ($n = 42$)	I: xanthone from mangosteen pericarp (Research Excellent Center for Innovation and Health Products, Walailak University, Thailand). C1: vitamin E. C0: no treatment.	38 days	I: 100 and 200 mg/kg C1: 100 mg/kg	Oral	Plasma and RBC MDA level: ↓ versus C0, = versus C1. Tissue MDA and CAT level: ↓ versus C0, = versus C1 for 200 mg/kg dose. Body weight, kidney weight, BUN, creatinine, TNF-a, COX-2/beta-actin, and iNOX/beta-actin: ↓ versus C0, = versus C1. No significant difference in SOD level and lead in blood and kidney.
Febriane *et al.* (2015)	Sprague Dawley mice fed with oxidized palm oil, unhealthy diet model ($n = 25$)	I: mangosteen pericarp methanolic extract with and without microencapsulation (maceration freeze-drying). C0: no treatment.	50 days	Microcapsule: 100 and 200 mg/kg Extract: 100 mg/kg	Oral	MDA level: ↓ versus C0 (microcapsule > extract). No significant difference in body weight, food intake, and liver weight.
Wihastuti *et al.* (2015)	Wistar rats induced by dichlorvos as organophosphate, toxicology model ($n = 25$)	I: mangosteen pericarp ethanolic extract (xanthone) (maceration rotary evaporation). C0: no treatment.	21 days	400, 800, and 1,200 mg/kg BB/days	Subcutaneous	ox-LDL level and PON-1 level: ↓ versus C0. AChE level: ↑ versus C0.
Zhang *et al.* (2016)	Kunming mice induced by 52% ethanol, alcohol metabolism model ($n = 236$)	I: mangosteen edible part juice (grinder). C0: distilled water.	6 hours	I and C: equal to 100 g fruit for a person of 60 kg	Oral	MDA level: ↓ versus C0. No significant difference in SOD level, alcohol concentration, acetaldehyde level, ADH, and ALDH level.
Im *et al.* (2017)	Hairless mice induced by UVB, UVB radiation model ($n = 15$)	I: AM (ethanol maceration chromatography). C0: no treatment.	12 weeks	100 mg/kg	Oral	CAT and SOD level: ↑ versus C0. Skin wrinkle, IL-1b, IL-6, TNF-a, MMP-1, MMP-2, ERK, p38, and JNK: ↓ versus C0.
Chang *et al.* (2020)	SD rats given treadmill running test, exercise model ($n = 40$)	I: mangosteen concentrate drink (LordDuke Biotechnology Co., Taiwan). C0: no treatment.	6 weeks	0.9 mL, 4.5 mL, or 9 mL	Oral	Serum and hepatic MDA level, hepatic SOD level, and hepatic CAT level: ↓ versus C0. Muscular GPx level: ↑ versus C0 for 4.5- and 9-mL dose. Muscular SOD, triglyceride, and total cholesterol level: ↓ versus C0. Muscular CAT level: ↑ versus C0 for 9 mL dose. No significant changes in plasma glucose and plasma lactate.
Subani (2014)	Balb/c mice induced with 2-ME, infertility model ($n = 30$)	I: mangosteen pericarp ethanolic extract (maceration freeze-drying). C0: no treatment.	35 days	25, 50, and 100 mg/kg	Subcutaneous	No significant decrease in MDA level in mice spermatozoa. Spermatozoa motility, normal morphology (except 10 mg/kg dose), viability, and membrane integration: ↑ versus C0.
Herrera-Aco *et al.* (2019)	DBA/1J mice induced by collagen solution, arthritis model ($n = 30$)	I: AM (maceration chromatography). C1: methotrexate. C0: no treatment.	33 days	I: 10 and 40 mg/kg C1: 0.5 mg/kg	Oral	Joint MDA level: ↓ versus C0, = versus C1 for both doses. Joint GSH level: ↑ versus C0, = versus C1 for 10 mg/kg dose. No significant difference in joint GPx, GST, and CAT level. No significant difference in liver and kidney MDA, GSH, GPx, GST, SOD, GRd, and CAT level. Arthritis score in day 18, histology score, IgG2a, IL-6, LIX, and IP-10: ↓ versus C0 and C1; RANTES, IL-33: ↓ versus C0, = versus C1.
Tjahjani *et al.* (2019)	DDY mice inoculated with *P. berghei*, malaria-infected model ($n = 24$)	I: ethyl acetate mangosteen peel fraction (alcohol maceration evaporation). C1: artemisinin. C0: no treatment.	3 days	I: 100, 20, and 4 mg/kg BW C1: 50 mg/kg BW	Oral	Total antioxidant level: ↑ versus C0 and C1. Parasitemia level: ↓ versus C0, ↑ versus C1.

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Author (year)	Subject-disease model (sample size)	Intervention (I) and comparator (C)	Treatment duration	Dose	Route of administration	Outcome
Tsai *et al.* (2020)	F344 rats induced with DMAB and high-fat diet, prostatic hyperplasia model (n = 24)	I: dried mangosteen pericarp (First Canned Food, Thailand).	24 weeks	2.5 % and 5%	Oral	MDA level, final weight, prostate weight, liver weight, epididymis fat, perirenal fat, DHT, testosterone, triglyceride, total cholesterol, LDL, and HDL level: ↓ versus C0.
		C0: no treatment.				GPx level: ↑ versus C0.
		I: mangosteen pericarp ethanolic extract (binary solvent extraction system freeze-drying).				% lipid peroxidation inhibition and reduced GSH: ↑ versus C0, = versus C1 and C2 (30-day treatment > 14 days).
Samuagam *et al.* (2015)	Healthy Sprague Dawley rats (n = 36)	C1: silymarin.	14 and 30 days	I: 100 mg/kg C1: 50 mg/kg	Oral	SOD and CAT level: ↑ versus C0, = versus C1 and C2 (30-day treatment = 14 days).
		C2: a-tocopherol.		C2: 100 mg/kg		Total protein: ↑ versus C0, = versus C1 and C2. Total bilirubin, ALP, SGPT, and SGOT: ↓ versus C0, = versus C1 and C2.
		C0: no treatment.				TAC and GPx level: ↑ versus C0.
Adyab *et al.* (2019)	Sprague Dawley rats induced by STZ and high-fat diet, obese model (n = 40)	I: freeze-dried mangosteen flesh.	7 weeks	200, 400, and 600 mg/kg	Oral	No significant difference in SOD and glucose levels.
		C0: no treatment.				Food intake, energy intake, body weight, total cholesterol, TNF-a, and IL-6 level: ↓ versus C0.

↑ = statistically significant increase versus C0 or greater than versus C1; ↓ = statistically significant decrease versus C0 or lesser than versus C1; = = equal versus C1; SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GSH = glutathione; GRd = glutathione reductase; GST = glutathione s-transferase; MDA = malondialdehyde; HbA1C = hemoglobin A1C; HOMA-IR = homeostatic model assessment of insulin resistance; AGE = advance glycation end products; RAGE = receptor of advance glycation end products; TNF-a = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor; VLDL = very low-density lipoprotein; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TBARS = thiobarbituric acid reactive substances; GOT/SGOT = glutamate oxaloacetate transaminase; GPT/SGPT = glutamate pyruvate transaminase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; LPO = lipid peroxide; SBP = systolic blood pressure; MAP = mean arterial blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate; HBF = hind limb blood flow; HVR = hind limb vascular resistance; BDNF = brain-derived neurotropic factor; ChAT = choline acetyltransferase; TH = tyrosine hydroxylase; 5-HT = serotonin/5-hydroxytryptamine; IL = interleukin; AChE = acetylcholinesterase; 5-HIAA/5-HT = 5-hydroxyindoleacetatic acid/5-hydroxytryptamine; AIF = apoptosis-inducing factor; NRF2 = nuclear factor erythroid 2-related factor-2; SIRT = sirtuin, HO-1, heme oxygenase 1; SOD2 = superoxide dismutase-2; HMGB1 = high motility group box-1; α-SMA = α-smooth muscle actin; LC3 = light chain 3; BNIP3 = BCL/2adenovirus E1B protein-interacting protein-3; FeNa = fractional excretion of sodium; ox-LDL = oxidized LDL; ALDH = aldehyde dehydrogenase; ADH = alcohol dehydrogenase; MMP = matrix metalloproteinase; ERK = extracellular signal regulated kinase; JNK = c-Jun N-terminal kinase; LIX = LPS-induced CXC chemokine; RANTES = regulated on activation normal T expressed and secreted; DHT = dihydrotestosterone; ALP = alkaline phosphatase.

Among 20 studies that evaluated SOD level, three of them showed no significant difference in SOD level (Adyab *et al*., 2019; Herrera-Aco *et al*., 2019; Zhang *et al*., 2016), one of them showed a significant decrease in SOD level (Chang *et al*., 2020), and the rest showed a significant increase in SOD level signifying increased antioxidant activity. Many studies have evaluated the antioxidant activity of different parts of the mangosteen fruit and showed that mangosteen pericarp exhibits the highest antioxidant capacity compared to mangosteen flesh and seed (Lim *et al*. 2013), thus explaining its low SOD level (Adyab *et al*., 2019; Zhang *et al*., 2016). A significant increase in SOD levels showed that mangosteen extract or products promote the activity of SOD enzyme in neutralizing oxidative stress. A significant decrease in the SOD level could be due to the direct activity of mangosteen extract or products in neutralizing ROS which reduces the need for an antioxidant enzyme such as SOD (Ismail *et al*., 2018). All studies with evaluated CAT (n = 13) and GPx (n = 10) levels showed a significant increase in both enzyme levels after the subjects were treated with mangosteen extract or product. A total of 12 studies evaluated the GSH level after administration of mangosteen extract or product and one of the studies showed no significant difference in the GSH level (Parkhe *et al*., 2020), while the rest showed a significant increase in GSH level.

Mangosteen antioxidant activity in type II diabetes model

Out of 41 *in vivo* studies, seven of them studied mangosteen antioxidant activity in the type II diabetes model obtained by either inducing the subjects (mice or rats) with streptozotocin (STZ) or STZ accompanied with a high glucose diet. Among the seven studies, five of them showed a positive correlation between the increase in mangosteen antioxidant activity and the decrease in blood glucose level (Jariyapongskul *et al*., 2015; Karim *et al*., 2018, 2019a; Kumar *et al*., 2016; Nelli and Kilari, 2013), one study showed a positive correlation with the increase in plasma insulin level (Karim *et al*., 2019b), and the other study showed improvement in pancreatic histology (Wahjuni *et al*., 2017).

Based on the result, the administration of mangosteen extracts showed an increase in antioxidant enzyme (SOD, CAT, or GPx) or a decrease in oxidative marker (MDA), which also correlates with a reduction in the blood glucose level, an increase in insulin level, and improvement of pancreatic histology. Induction of STZ and high glucose diet is known to cause oxidative stress and hepatotoxicity (Karim *et al*., 2018). Prolongation of these could damage the DNA, proteins, lipids, and other macromolecules of beta cells which then cause a reduction in insulin production, thus resulting in type II diabetes (Oberley, 1988). Phytochemicals, such as xanthone, that are contained in mangosteen are known for their antioxidant and free-radical scavenging activities (Gondokesumo *et al*., 2019; Sinaga and Siregar, 2016). They are capable of donating their hydrogen atoms to stabilize the free radicals and inhibit lipid peroxidation which minimizes the beta cells injury and improves their functions in regulating blood glucose level. Therefore, administration of mangosteen extracts that possess antioxidant activity could improve type II diabetes subjects' condition.

Mangosteen antioxidant activity and cholesterol

A total of five studies evaluated mangosteen antioxidant activity and correlated them with total cholesterol levels. Two of them were tested in a type II diabetic model induced with STZ and a high-fat diet (Husen *et al*., 2017a, 2017b), and the rest of them were tested in an animal models fed with nonoxidized cholesterol (Haruenkit *et al*., 2007; Leontowicz *et al*., 2006, 2007). Cholesterol is often divided into high-density lipoprotein (HDL) and LDL (Elshourbagy *et al*., 2014). It was explained that HDL's function is to deliver free cholesterol from peripheral cells to the liver for it to be removed, while LDL's function is to transport cholesterol from the liver to the peripheral tissue. Around 60%–70% of the total cholesterol consists of LDL, and a high level of LDL is susceptible to oxidation and is associated with cardiovascular disease through the formation of atherosclerotic plaque (Elshourbagy *et al*., 2014). Administration of the mangosteen extract was able to decrease the cholesterol level by increasing antioxidant capacity which inhibits LDL oxidation, thus resulting in a low level of MDA (Husen *et al*., 2017a, 2017b; Leontowicz *et al*., 2006, 2007). However, one study showed that the administration of lyophilized mangosteen flesh did not cause a significant increase in antioxidant capacity; hence, it also did not show a significant effect on total cholesterol level (Haruenkit *et al*., 2007).

Mangosteen antioxidant activity in cardiovascular disease

A total of four studies evaluated mangosteen antioxidant activity in cardiovascular disease models which were myocardial infarction model (Devi Sampath and Vijayaraghavan, 2007; Sampath and Kannan, 2009), atherosclerosis model (Hafisalevi *et al*., 2012), and hypertension model (Boonprom *et al*., 2017). The results showed that the administration of AM from the mangosteen pericarp extract improved the antioxidant level [SOD, CAT, GPx, glutathione s-transferase (GST), and GSH]. It also improved the condition of myocardial infarction subjects by decreasing the lipid peroxidation level and marker enzymes [such as lactate dehydrogenase (LDH), creatine phosphokinase (CPK), glutamate pyruvate transaminase (GPT), and glutamate oxaloacetate transaminase (GOT)] and increasing respiratory chain enzyme, tricarboxylic acid cycle enzymes, and mitochondrial cytochromes (Devi Sampath and Vijayaraghavan, 2007; Sampath and Kannan, 2009).

In the atherosclerosis model, oxidation of LDL could cause atherosclerosis plaque which is one of the primary causes of cardiovascular diseases (Cervantes Gracia *et al*., 2017). Based on the results in Hafisalevi *et al*.'s (2012) study, the administration of mangosteen pericarp extract showed a significant increase in SOD antioxidants which then reduced the lipid peroxidation level (showed as MDA level), thus alleviating the atherosclerosis subjects' condition.

For the hypertension model, subjects were induced with L-NAME that is capable of causing hypertension and cardiovascular remodeling through oxidative stress and inflammation (Boonprom *et al*., 2017). L-NAME is a known synthase inhibitor of nitric oxide (NO). It was explained that the inhibition of NO will induce inflammation, oxidative stress, and high blood pressure (Boonprom *et al*., 2017). Results showed that the administration of mangosteen pericarp aqueous extract was able to counteract the L-NAME effects by decreasing the production of superoxide radicals and plasma MDA level in L-NAME-induced mice. These decreases contributed to reducing systolic blood pressure, increasing tumor necrosis factor alpha (TNF-α) level, improving hemodynamic status, increasing nitrate or nitrite production, and improving cardiovascular morphology of the subjects (Boonprom *et al*., 2017).

Mangosteen antioxidant activity in neurological disorder

A total of eight studies tested mangosteen antioxidant activity in an animal model related to a neurological disorder. Among these, two studies used Alzheimer's model (Avinash *et al*., 2016; Huang *et al*., 2014), while others used Parkinson's model (Parkhe *et al*., 2020), depression model (Oberholzer *et al*., 2018), memory impairment model (Sattayasai *et al*., 2013), cognitive impairment model (Phyu and Tangpong, 2014), schizophrenia immune-inflammatory model (Lotter *et al*., 2020), and closed head injury model (Indharty *et al*., 2019). There are two neurological disorders that commonly occur in elderly patients, i.e., Alzheimer's and Parkinson's. Alzheimer's is a condition wherein the brain structure degenerates severely enough, thus resulting in memory and cognitive impairment that interfere with daily life (Avinash *et al*., 2016). The hallmark of this disease is the accumulation of β-sheet aggregated amyloid peptides (Aβ) plaque in the brain parenchyma (Huang *et al*., 2014). Based on the results, it was shown that the administration of mangosteen extract or supplement helps in increasing antioxidant level (SOD, GSH, CAT, and GPx) and improving several Alzheimer's parameters, such as increasing spatial learning ability, short-term memory, habituation memory, cognitive function, neurotransmission antibody [5-hydroxytryptamine (5-HT), calbindin, choline acetyltransferase (ChAT), NeuN, and tyrosine hydroxylase (TH)], and decreasing amyloid-β antibody and acetylcholinesterase (AChE) level (Avinash *et al*., 2016; Huang *et al*., 2014). Furthermore, other studies have shown that treatment with mangosteen reduced brain ROS level, as well as MDA level in brain tissue and RBC, thus improving the condition of the memory impairment model, increasing AChE level, and inhibiting neurobehavioral defects in the cognitive impairment model (Phyu and Tangpong, 2014; Sattayasai *et al*., 2013).

The difference between Parkinson's and Alzheimer's is that Parkinson's mostly affects memory and behavioral problems, such as movement, tremor, and balance disturbance, while Alzheimer's mostly affects memory, language, and cognitive function, such as problem-solving function and speed of thinking (Han *et al*., 2018). The hallmark of Parkinson's disease is the loss of dopaminergic neurons related to the inhibition of TH activity and the presence of Lewy bodies that are made of phosphorylated a-synuclein aggregates (Parkhe *et al*., 2020). It was shown that treatment with AM resulted in an increase in GSH antioxidant enzyme and decrease in MDA level, which helps improve

locomotor activity, memory deficiency, and TH activity and decreases phosphorylated α-synuclein.

Depression is a psychiatric disorder that is difficult to treat due to its complex pathophysiologies, such as dysregulated levels of monoamine, inflammation, and oxidative stress (Oberholzer *et al*., 2018). It was stated that treatment with mangosteen pericarp powder showed a decrease in lipid peroxidation or MDA level, as well as improvement of hippocampal tissue damage, memory recognition, and serotonergic effects. Other than depression, schizophrenia is also another type of psychiatric disorder that causes hallucination and cognitive impairment with symptoms such as low working memory, attention, and altered information processing (Lotter *et al*., 2020). It was explained that the pathophysiology of schizophrenia is still unclear. However, the hypothesis suggests that the interaction between genetic predisposition and stress in early life such as malnutrition and trauma could cause schizophrenia. Trauma induces inflammation and oxidative stress which causes a delay in the brain and cognitive development, thus increasing the risk of schizophrenia. Based on these, the study by Lotter *et al*. (2020) showed that the administration of dried ground mangosteen pericarp (GML) and AM improved parameters related to schizophrenia. The result showed no reversal observed in sensorimotor gating (psychosis-like behavior). However, it was shown that GML and AM alone or in combination with haloperidol as the standard treatment were capable of inhibiting depressive-like behavior. Also, GML and AM were shown to decrease proinflammatory cytokines [TNF-α and interleukin-6 (IL-6)], while AM alone was able to decrease the MDA level, thus exhibiting their anti-inflammatory and antioxidant capabilities.

In a closed head injury model, the injury was carried out using Feeney's weight-drop procedure by dropping a metal mass on the opened scalp on the right frontal area of a rat (Indharty *et al*., 2019). It was explained that traumatic brain injury causes two kinds of damage, which are the initial damage due to the physical force and the secondary damage that occurs hours or days after the initial damage due to neuroinflammatory response and oxidative stress. Results showed that mangosteen pericarp ethanolic extract improved traumatic brain injury subjects by significantly increasing the SOD antioxidant level and reducing neuronal apoptosis based on the downregulation of apoptosis-inducing factor (AIF), caspase-8, caspase-9, and MDA level (Indharty *et al*., 2019).

Mangosteen antioxidant activity toward liver and kidney

A total of four studies tested the mangosteen antioxidant activity toward liver in the acute liver injury model (Wang *et al*., 2018; Yan *et al*., 2018), chronic liver injury model (Wang *et al*., 2019), and hepatic steatosis model (Tsai *et al*., 2016). The acute and chronic liver injury could occur when the liver is exposed to chemical stresses, such as alcohol and drug consumption, and the difference between the two is the duration of stress exposure (Wang *et al*., 2018). In acute liver injury, the liver is exposed to the stress in a shorter duration compared to chronic injury. Similar to other injuries, acute and chronic liver injury induces inflammation and oxidative stress (Cichoż-Lach and Michalak, 2014). In acute liver injury, the administration of ɣ-mangostin showed an increase in SOD and GSH antioxidant levels. It also showed an improved liver condition through increasing nuclear factor erythroid 2-related factor-2 (NRF2) and sirtuin 1 (SIRT1) level (Wang *et al*., 2018). Meanwhile, the administration of AM increased GSH antioxidant level and inhibited inflammation, apoptosis, and autophagy (Yan *et al*., 2018). In chronic liver injury, the administration of ɣ-mangostin showed an increase in SOD and GSH antioxidant levels, as well as an improved liver condition through an increase in sirtuin 3 (SIRT3) level and a decrease in high mobility group box 1 (HMGB1) level, reducing the accumulation of collagen I and α-smooth muscle actin (α-SMA) in a chronic liver injury model (Wang *et al*., 2019).

Hepatic steatosis is a condition wherein there is an accumulation of triglyceride in the hepatocytes which usually occur due to disrupted lipid metabolism by hepatocytes that cause lipid peroxidation and inflammation. It is also known as a hallmark for non-alcohol fatty liver disease. The administration of mangosteen pericarp showed that it was able to reverse hepatic steatosis by increasing the level of antioxidants (GSH, GPx, SOD, and CAT) and decreasing lipid peroxidation levels, plasma-free fatty acids, and hepatic triglyceride levels (Tsai *et al*., 2016).

A total of two studies evaluated mangosteen antioxidant activity toward the kidneys in the chronic kidney disease model induced with lead acetate (Rana *et al*., 2020) and nephrotoxicity model induced with cisplatin (Pérez-Rojas *et al*., 2009). In the chronic kidney disease model, the administration of xanthones from mangosteen pericarp showed an increase in SOD antioxidant levels and inhibited inflammation and apoptosis (Rana *et al*., 2020). In the nephrotoxicity model, the administration of AM increased GPx, GSH, and CAT antioxidant levels which were known to inhibit oxidative stress, nitrosative stress, inflammation, and fibrotic pathway (Pérez-Rojas *et al*., 2009).

Mangosteen antioxidant activity toward a stress-induced model

A total of five studies evaluated mangosteen antioxidant activity in animal models that were exposed to stress inducers, which include organophosphate (Wihastuti *et al*., 2015), alcohol (Zhang *et al*., 2016), exercise (Chang *et al*., 2020), ultraviolet B (UVB), radiation (Im *et al*., 2017), and oxidized palm oil as an unhealthy diet model (Febriane *et al*., 2015). Organophosphate is a common pesticide used for crops and accumulation of organophosphate could cause toxicity through inflammation, oxidative stress, and increase in lipid peroxidation. Additionally, organophosphate toxicity is also capable of inhibiting AChE activity which causes headache, nausea, and muscle spasm, and therefore could lead to paralysis (Wihastuti *et al*., 2015). In the study, the administration of mangosteen pericarp ethanolic extract showed an increased in the level of AChE and a decreased level of oxidized LDL.

High consumption of alcohol is known to cause liver injury because most of the alcohol is metabolized in the liver with several responsible enzymes, such as alcohol dehydrogenase (ADH), which convert alcohol into acetaldehyde and aldehyde dehydrogenase (ALDH) that in turn converts acetaldehyde into acetate (Zhang *et al*., 2016). It was explained that alcohol and acetaldehyde itself could result in a decrease in antioxidant activity with symptoms such as nausea, vomiting, rapid pulse, and lightheadedness. Administration of mangosteen flesh juice did not show any significant difference in alcohol, acetaldehyde, ADH, ADLH, and SOD antioxidant concentration; however, it did show a significant decrease in MDA level (Zhang *et al*., 2016). The ineffective result of this study might be due to the antioxidant amount in the mangosteen flesh that is not high enough to show a significant result compared to the other parts of the fruit, such as the pericarp (Lim *et al*. 2013).

Extensive exercise for a long duration could also significant muscle damage, oxidative stress, and fatigue (Chang *et al*., 2020). It was stated that the administration of mangosteen supplements showed the ability to alleviate muscle fatigue by decreasing the MDA level, increasing antioxidant level, and lactate clearance. UVB radiation is common stress especially for people who enjoy outdoor activity. Exposure to UVB radiation is known to cause oxidative stress and inflammation which increases skin degeneration (Im *et al*., 2017). It was observed that the administration of AM could inhibit UVB-induced skin wrinkles, increase the antioxidant level, and decrease proinflammatory cytokines.

Meanwhile, in the unhealthy diet model, the animals were fed with oxidized palm oil and treated with mangosteen pericarp methanolic extract, with or without microencapsulation to mask the extract taste (Febriane *et al*., 2015). The result showed that the administration of mangosteen extract significantly reduced the MDA level, with higher reduction observed in the group treated with microencapsulated mangosteen extract.

Mangosteen antioxidant activity toward other disease models

Several studies have also evaluated mangosteen antioxidant activity in a malarial model (Tjahjani *et al*., 2019), prostatic hyperplasia model (Tsai *et al*., 2020), infertility model (Subani, 2014), arthritis model (Herrera-Aco *et al*., 2019), obese model (Adyab *et al*., 2019), and as a supplement in healthy subjects (Samuagam *et al*., 2015). In the malarial model, mice were inoculated with *Plasmodium berghei* and treated with ethyl acetate fraction of mangosteen pericarp (Tjahjani *et al*., 2019). Results showed that mangosteen fraction significantly decreases the parasitemia level and increases the total antioxidant level. In the prostatic hyperplasia model, rats were induced with 3,2′-dimethyl-4-aminobiphenyl (DMAB) and a high-fat diet that was supplemented with dried mangosteen pericarp for the treatment group (Tsai *et al*., 2020). Results showed that mangosteen supplement could alleviate prostatic hyperplasia development by increasing GPx antioxidant and decreasing serum testosterone, dihydrotestosterone (DHT), lipid peroxidation level, prostate weight, and lipid profile. In the infertility model, mice were induced with 2-methoxyethanol (2-ME) and treated with mangosteen pericarp ethanolic extract (Subani, 2014). Results showed that mangosteen extract was able to increase spermatozoa motility, viability, normal morphology, and membrane integrity. However, it was also discovered that the treatment did not result in a significant decrease in MDA level. In the arthritis model, mice were induced with a collagen solution and treated with AM (Herrera-Aco *et al*., 2019). Results showed that treatment with AM reduced arthritic score in the first 18 days of the treatment, MDA level, and proinflammatory cytokines and increased GSH antioxidant. In the obese model, rats were induced with STZ and fed a high-fat diet that was supplemented with dried mangosteen flesh for the treatment group (Adyab *et al*., 2019). Results showed that supplementation of mangosteen flesh reduced subject body weight, total cholesterol, and proinflammatory cytokines and increased total antioxidant capacity.

CONCLUSION

Mangosteen extracts, products, and isolated compounds were shown to increase antioxidant levels through *in vivo* studies by either increasing antioxidant enzymes (such as SOD, CAT, GPx, and GSH) or by decreasing oxidative stress markers (such as MDA level). Mangosteen showed a positive effect in alleviating disease-related parameters in type II diabetes models, cardiovascular models, neurological disorder models, stress-induced models, and liver and kidney injury models. These results signified that mangosteen could be a promising adjuvant drug or supplement to oxidant-related diseases. However, in clinical trials, although mangosteen intervention significantly increased plasma antioxidant capacity, it did not show any significant effect toward other parameters, such as the MDA level. Moreover, interventions in clinical trials mostly used commercial products that contain other ingredients with antioxidant activity, such as vitamin C and green tea extract. Therefore, more clinical trial results measuring the antioxidant parameter (such as level of SOD, CAT, GPx, and GSH antioxidant enzymes) are needed to conclude whether mangosteen extract or their isolated compounds possess significant antioxidant activity capable of alleviating oxidant-related diseases.

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CONFLICT OF INTEREST

All the authors declare that they have no conflicts of interest for this work.

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SUPPLEMENTARY TABLES

Supplement Table 1. Included clinical trials quality assessment using Downs and Black's checklist.

Author (year)	Reporting	External validity	Internal validity–bias	Internal validity–confounding (selection bias)	Power	Score/total score (criteria)
Suthammarak *et al*. (2016)	8	1	4	1	0	14/28 (poor)
Baroroh *et al*. (2018)	10	1	6	5	0	22/28 (good)
Xie *et al*. (2015b)	9	1	6	3	0	19/28 (fair)
Xie *et al*. (2015a)	6	0	7	3	0	16/28 (fair)
Sutono (2013)	8	2	6	6	0	22/28 (good)
Kondo *et al*. (2009)	5	0	6	2	0	13/28 (poor)

Supplement Table 2. Included *in vivo* studies quality assessment using ToxRtool.

Author (year)	Test subtract identification	Test organism characterization	Study design description	Study result documentation	Plausibility of study design and result	Score/total score (criteria)
Wihastuti *et al*. (2015)	4	4	7	3	2	20/21 (Reliable without restriction)
Husen *et al*. (2017b)	3	5	7	3	2	20/21 (Reliable without restriction)
Karim *et al*. (2018)	4	5	7	3	2	21/21 (Reliable without restriction)
Zhang *et al*. (2016)	4	5	7	3	2	21/21 (Reliable without restriction)
Sattayasai *et al*. (2013)	4	5	7	3	2	21/21 (Reliable without restriction)
Tjahjani *et al*. (2019)	4	5	7	3	2	21/21 (Reliable without restriction)
Wang *et al*. (2018)	3	3	7	3	2	18/21 (Reliable without restriction)
Tsai *et al*. (2020)	4	5	7	3	2	21/21 (Reliable without restriction)
Lotter *et al*. (2020)	4	4	7	3	2	20/21 (Reliable without restriction)
Chang *et al*. (2020)	4	5	7	3	2	21/21 (Reliable without restriction)
Phyu and Tangpong (2014)	2	4	7	3	2	18/21 (Reliable without restriction)
Oberholzer *et al*. (2017)	4	4	7	3	2	20/21 (Reliable without restriction)
Karim *et al*. (2019a)	4	4	7	3	2	20/21 (Reliable without restriction)
Rana *et al*. (2020)	4	5	7	3	2	21/21 (Reliable without restriction)
Parkhe *et al*. (2019)	3	5	7	3	2	20/21 (Reliable without restriction)
Im *et al*. (2017)	3	5	7	3	2	20/21 (Reliable without restriction)
Karim *et al*. (2019b)	3	4	7	3	2	19/21 (Reliable without restriction)
Haruenkit *et al*. (2007)	4	5	7	3	2	21/21 (Reliable without restriction)
Leontowicz *et al*. (2006)	4	5	7	3	2	21/21 (Reliable without restriction)
Indharty *et al*. (2019)	4	4	7	3	2	20/21 (Reliable without restriction)
Leontowicz *et al*. (2007)	4	5	7	3	2	21/21 (Reliable without restriction)
Avinash *et al*. (2016)	4	5	7	3	2	21/21 (Reliable without restriction)
Nelli *et al*. (2013)	4	5	7	3	2	21/21 (Reliable without restriction)
Yan *et al*. (2018)	4	5	7	3	2	21/21 (Reliable without restriction)
Jariyapongskul *et al*. (2015)	4	5	7	3	2	21/21 (Reliable without restriction)
Huang *et al*. (2014)	3	5	7	3	2	20/21 (Reliable without restriction)
Febriane *et al*. (2015)	3	5	7	3	2	20/21 (Reliable without restriction)
Kumar *et al*. (2016)	3	5	7	3	2	20/21 (Reliable without restriction)
Subani (2014)	3	4	7	3	2	19/21 (Reliable without restriction)
Husen *et al*. (2017a)	3	5	7	3	2	20/21 (Reliable without restriction)
Tsai *et al*. (2016)	3	5	7	3	2	20/21 (Reliable without restriction)
Adyab *et al*. (2019)	4	5	7	3	2	21/21 (Reliable without restriction)
Hafisalevi *et al*. (2012)	2	5	7	3	2	19/21 (Reliable without restriction)
Perez-Rojas *et al*. (2009)	3	5	7	3	2	20/21 (Reliable without restriction)
Wahjuni *et al*. (2017)	4	5	7	2	2	20/21 (Reliable without restriction)
Herrera-Aco *et al*. (2018)	3	5	7	3	2	20/21 (Reliable without restriction)
Devi Sampath and Vijayaraghavan (2007)	3	5	7	3	2	20/21 (Reliable without restriction)
Boonprom *et al*. (2017)	4	5	7	3	2	21/21 (Reliable without restriction)
Sampath and Kannan (2009)	3	5	7	3	2	20/21 (Reliable without restriction)
Wang *et al*. (2019)	3	5	7	3	2	20/21 (Reliable without restriction)
Samuagam *et al*. (2015)	4	4	7	3	2	20/21 (Reliable without restriction)