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

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**ARTICLE INFO**

Received on: 18/08/2020
Accepted on: 21/10/2020
Available online: 05/12/2020

**Key words:** Mangosteen, *Garcinia mangostana*, antioxidant, oxidative stress, clinical trials, *in vivo* study.

**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
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 (Weecharangsang 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).
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; Sutono, 2013; 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 | RBC’s antioxidant capacity: ↑ versus C0. |
| Xie et al. (2015b)    | RCT           | Healthy subjects (n = 60) | I: Verve® (containing mostly mangosteen fruit, Venma Nutrition Co., Arizona). C0: placebo (fructose liquid). | 30 days | 245 ml/days | Oral | No significant changes in body weight, Heart rate, immunoglobulins, interleukins, creatinine, ALT, and AST. |
| Xie et al. (2015a)    | RCT           | Healthy subjects (n = 20) | I: mangosteen rind extract capsule (PT Sido Muncul, Indonesia). C0: placebo. | 6 hours | 245 ml | Oral | Reduction of MDA level but not statistically significant. |
| Sutono (2013)         | RCT           | Subject with mild-to-moderate acne vulgaris (n = 94) | I: Vemna® (Mangosteen Plus™ with essential minerals®, Vemna Nutrition Co., Arizona). C0: placebo. | 3 weeks | 3 × 400 mg | Oral | Total acne lesions: ↓ versus C0. |
| Kondo et al. (2009)   | RCT           | Healthy male and female (n = 20) | I: Vemna® (Mangosteen Plus™ with essential minerals®, Vemna Nutrition Co., Arizona). C0: placebo. | 24 hours | 59 ml | Oral | No significant changes in MDA level compared to pretest and placebo 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 | 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 | SOD and GSH level: ↑ versus C0, = versus C1; LPO: ↓ versus C0, = versus C1. 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. Plasma and liver tissue MDA level, glucose level, and triglyceride level: ↓ versus C0 and C1; ↑ 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. 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. (2018) | Mice induced by STZ, type II diabetic model (*n* = 30) | I: mangosteen vinegar rind (Asia & Pacific Quality Trade Co., Ltd., Bangkok)). C0: no treatment. | 1 week | I: 100 and 200 mg/kg BW C1: 60 mg/kg BW | 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. 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. |
| 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). 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. 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 vinegar rind (Asia & Pacific Quality Trade Co., Ltd., Bangkok)). 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 C1 for nonpolar fraction. Cholesterol: ↓ versus C0, = versus C1 for polar fraction. |

Continued
| Author (year) | Subject-disease model | 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: freeze-dried mangosteen. C0: no treatment. | 14 days | 1: 50, 100, and 200 mg/kg BW C1: metformin. C0: no treatment. | 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. |
| 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 | No significant difference in weight gain, food consumption and efficiency, and HDL. |
| Hausenkit 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 | Plasma antioxidant activity: ↑ versus C0. Total cholesterol, LDL, 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 | No significant increase in plasma antioxidant activity 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 | No significant difference in protein content, feed intake, body gain, feed efficiency ratio, protein efficiency ratio, total cholesterol, LDL, HDL, and triglyceride versus C0. |
| Hafsielevi 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. |
| 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 | 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. SOD, CAT, GSH: ↑ versus C0. |
| 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 | 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 | 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: ground 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                                      | NMDA 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). |
|                                    |                                     |                                                                                                      |                    |                        |                          | ROS and caspase level in scopolamine induce mice brain extract: ↓ versus C0. |
| Sattayasai et al. (2015)            | 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                      | Time for escaping the maze (spatial memory test): ↓ versus C0.         |
|                                    |                                     |                                                                                                      |                    |                        |                          | Latency time (fear memory test): ↑ versus C0.                           |
|                                    |                                     |                                                                                                      |                    |                        |                          | 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. |
|                                    |                                     |                                                                                                      |                    |                        |                          | 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. |
| 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                                      | No significant effect in distance move and locomotor performance (open field test).               |
|                                    |                                     |                                                                                                      |                    |                        |                          | MDA level, caspase 8, caspase 9, AIF, and apoptosis: ↓ versus C0.        |
|                                    |                                     |                                                                                                      |                    |                        |                          | SOD level: ↑ versus C0.                                                  |
|                                    |                                     |                                                                                                      |                    |                        |                          | 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.     |
|                                    |                                     |                                                                                                      |                    |                        |                          | Seram MDA level: ↓ versus C0.                                          |
|                                    |                                     |                                                                                                      |                    |                        |                          | NMDA hippocampus MDA level: ↓ versus C0.                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Neerosis score, TUNEL positive cells, ALT, AST, TNF-a, IL-1β, LC3, BNP3, and Bax cleaved caspase 5: ↓ versus C0, Bel-2, p-Akt, p-mTOR, p62: ↑ versus C0. |
|                                    |                                     |                                                                                                      |                    |                        |                          | SOD, liver GSH level: ↑ versus C0.                                       |
|                                    |                                     |                                                                                                      |                    |                        |                          | ALT, AST, HMGB1, collagen I, and a-SMA: ↓ versus C0, SIRT3: ↑ versus C0. |
|                                    |                                     |                                                                                                      |                    |                        |                          | TBARS level, body weight, free fatty acid, and triglyceride: ↓ versus C0. |
|                                    |                                     |                                                                                                      |                    |                        |                          | GSH, Gpx, Grd, sod, and CAT level: ↑ versus C0.                          |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
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|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
|                                    |                                     |                                                                                                      |                    |                        |                          | Continued                                                                 |
| Author(s) | Subject-disease model (sample size) | Intervention (I) and comparator (C) | Treatment duration | Route of administration | Disc | Outcome |
|----------|-----------------------------------|------------------------------------|-------------------|------------------------|------|---------|
| Pérez-Rojas et al. (2009) | Wistar rats induced by cisplatin, nephrotoxicity model (n = 34) | I: mangosteen pericarp ethanolic extract | 30 days | Subcutaneous | Creatinine, BUN, urinary volume, FeNa, urinary protein, urinary N-acetyl creatinine, creatinine clearance, BUN clearance | No significant difference in MDA level, kidney damage area, and renal protein carbonyl: ↓ versus C0. | No significant difference in body weight, food intake, and liver weight. |
| Rana et al. (2019) | Sprague-Dawley mice fed with oxidized palm oil, unhealthy diet model (n = 30) | I: mangosteen pericarp ethanolic extract | 50 days | Oral | SOD level: ↓ versus C0. MDA level: ↓ versus C0 (microcapsule > extract). | No significant decrease in MDA level in mice spermatozoa. |
| Febriane et al. (2015) | ICR mice induced by lead acetate, chronic kidney disease model (n = 25) | I: mangosteen pericarp methanolic extract | 38 days | Oral | Osmolality and GSH: ↑ versus C0. | No significant decrease in MDA level in mice spermatozoa. |
| Im et al. (2017) | Kunming mice induced by UVB, UVB radiation model (n = 35) | I: mangosteen edible part juice (grinder) | 6 months | Oral | No significant difference in plasma glucose and plasma lactate. | No significant difference in plasma glucose and plasma lactate. |
| Zhang et al. (2020) | BDII mice induced with microencapsulation model (n = 20) | I: mangosteen pericarp ethanolic extract | 3 days | Oral | No significant difference in joint GPx, GST, and CAT level. | No significant difference in plasma glucose and plasma lactate. |
| Diez-Campos et al. (2020) | I: mangosteen pericarp ethanolic extract | 100 mg/kg BB/days | 3 days | Oral | Body weight, kidney weight, BUN, creatinine, TNF-a, COX-2/beta-actin, and iNOX/beta-actin: ↓ versus C0. | No significant decrease in plasma glucose and plasma lactate. |
Oral). They are capable of donating... One study showed a positive correlation with...

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 nontoxic 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 HDL 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 (Indharti 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 pathophysiology, 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 ethanol extract improved traumatic brain injury subjects by significantly decreasing proinflammatory cytokines including TNF-α and interleukin-6, while AM alone was able to decrease the MDA level, thus exhibiting their anti-inflammatory and antioxidant activities.

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 (Cichoñ-Lach and Michalak, 2014). In acute liver injury, the administration of γ-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 γ-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 (HMG1) level, reducing the accumulation of collagen I and a-smooth muscle actin (a-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 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 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 ethanol 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 spermatogenesis 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 trials 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.

**ACKNOWLEDGMENT**

The authors would like to express gratitude to Agnes Anania Triavika Sahamastuti, and Audrey Amira Crystalia who are involved in the proofreading process.

**CONFLICT OF INTEREST**

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

**FUNDING**

None.
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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 | 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)              |
| Kendo et al. (2009) | 5         | 0                 | 6                      | 2                             | 0    | 13/28 (poor)              |

How to cite this article:
Elmund B, Hartrianti P. Evaluation of mangosteen (Garcinia mangostana) antioxidant activity in clinical trials and in vivo animal studies: A systematic review. J Appl Pharm Sci, 2020; 10(12):114–129.

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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) |
| Sattayasa 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                                      | 21/21 (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) |
| Wahjani 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) |