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Anti-Inflammatory Potency of Mangosteen (*Garcinia mangostana* L.): A Systematic Review

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Abstract

BACKGROUND: Mangosteen (*Garcinia mangostana* L.) is a tropical fruit, widely used in Southeast Asia as a health food and supplement, because of its beneficial effects on the body. In many studies, mangosteen is described to have many health effects such as antimicrobial, antioxidant, anti-proliferative, anti-carcinogenic, and antiinflammatory. The anti-inflammatory effect is important because many diseases have pathophysiology associated with the inflammatory process.

AIM: This study aimed to assess and conclude the scientific database systematically to investigate the anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.).

METHODS: Cochrane handbook for systematic reviews and the guideline of preferred reporting items for systematic review and meta-analysis (PRISMA) were used as guidelines in this review.

RESULTS: The authors searched the study in electronic databases which met inclusion and exclusion criteria. The authors independently evaluated 412 studies in database finding, 24 studies fulfilled the criteria for this review.

CONCLUSION: Mangosteen (*Garcinia mangostana* L.) has anti-inflammatory potency (especially the component of xanthone and flavonoid) in various inflammatory conditions and diseases; such as obesity, skin disease, psychiatric disease, tooth disease, asthma, atherosclerosis, acetaminophen-induced hepatotoxicity, peritonitis, colitis, prostatic hyperplastic, arthritis, and soft-tissue inflammation.

Introduction

Mangosteen (*Garcinia mangostana* L.) is a tropical fruit, widely used in Southeast Asia as a health food and supplement, because of its beneficial effects on the body [1]. Xie *et al*. (2015) described that mangosteen had no adverse effect on the liver and kidney, so it is safe for the body [2]. Another research by Sunarjo *et al*. (2017) and Candra *et al*. (2016) reported the safety of mangosteen pericarp that mangosteen pericarp had a broad safety index and the use with dosage ≤ 5000 mg/kg in mice were not toxic [3], [4]. In many studies, mangosteen is described to have many health effects such as antimicrobial, antioxidant, anti-proliferative, anti-carcinogenic, and anti-inflammatory [5]. The anti-inflammatory effect is important because many diseases have pathophysiology associated with the inflammatory process. Inflammation is the part of the immune system and host defense that has a pivotal role in opposition to external agents such as infection or foreign things. External stimuli will activate signaling cascade including mitogen-activated protein kinases (MAPK), nuclear factor kappa-light-chain-enhancer of activated b cells (NF-kB), and activator protein (AP)-1; the increased of vascular permeability; and the damage of tissue through the arrival of leukocytes with the production of reactive oxygen species (ROS) and local inflammatory mediator [1], [6], [7]. The production of pro-inflammatory cytokines and mediators such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-α, nitric oxide (NO), cyclooxygenase (COX), and prostaglandin (PG); and anti-inflammatory cytokine such as IL-10 are the essential response to extra stimuli [7], [8], [9], [10].

The anti-inflammatory effect of mangosteen is found in the flesh and the pericarp of the fruit. *In vitro* studies by Lim *et al*. (2019) and Widowati *et al*. (2016) reported that *Garcinia mangostana* L. extract (GME) and *Garcinia mangostana* L. pericarp extract (GMPE) reduced the levels of COX-2, IL-1β, IL-6, IL-8, and NO [7], [11]. The effect of anti-inflammatory of mangosteen is associated with xanthones, particularly α-mangostin (α-MG) and γ-mangostin (γ-MG) [1], [5]. *In vitro* study by Bumrungpert *et al*. (2010) reported that α-MG and γ-MG reduced significantly the expression of MAPK, NF-kB, and AP-1 in human macrophages and adipocytes [1]. While Gutierrez-Orozco *et al*. (2013) reported that α-MG

reduced significantly TNF-α and IL-8 levels in human cells [5]. The possible mechanisms of anti-inflammatory effect of xanthone are the modulation of pro- and anti-inflammatory cytokines and mediators and the regulation of inflammation signaling cascade [6], [12].

The anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.) has been assessed in several studies, but systematic review about it was not available. This study aimed to assess and conclude the scientific database systematically to investigate the anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.).

Methods

Cochrane handbook for systematic reviews and the guideline of preferred reporting items for systematic review and meta-analysis (PRISMA) were used as method guidelines in this study [13], [14].

Inclusion and exclusion criteria

Inclusion criteria

Publication type:

- Full-text studies discussing anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.)
- Primary studies of every design: descriptive study (e.g., case report and case series), observational study (e.g., cross-sectional, case–control, and cohort), and experimental study (e.g., clinical trial)

Language of publication: English

Time of publication: January 2000–February 2021

Population: *in vivo* sample, animal study, and human study

Objective, methodology, and outcome measure: Studies must discuss the anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.)

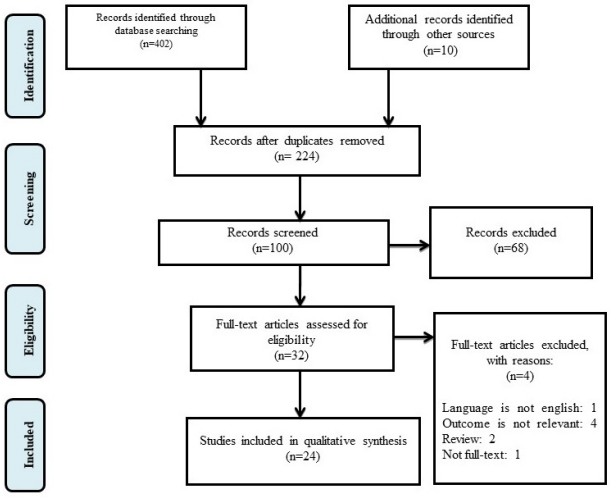
Exclusion criteria

The following criteria were excluded from the study:

- Publication: Review
- Population: *In silico* and *in vitro* sample
- Variables were associated with outcome in anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.)

Literature search

A systematic search study was applied in these electronic databases: Cambridge Core, Clinical Key, Cochrane, Ebsco, Embase, Emerald Insight, Google Scholar, JSTOR, Medline, Nature, Proquest, PubMed, Science Direct, Scopus, and Springer Link. The search was applied using the following keywords for the title and abstract: (anti-inflammatory OR anti-inflammatory OR inflammation) AND (mangosteen or *Garcinia mangostana*). The references from included studies were also checked in the context of search study strategy.



1: PRISMA flow diagram

Data collection and analysis

Selected articles underwent evaluation process after two authors (AAS and JB) had found titles and abstracts identified in the electronic database. The results were discussed by third authors (AP), and any differences of opinion were discussed. Full papers from potential studies were evaluated by the authors (AAS and JB). All studies selected for this systematic review were checked by two authors to confirm the results (AAS and JB). The data from all included studies were shown in a summary table featuring key points of each study. The key points of each study were: First author, year; study design; subject-disease model; intervention and comparator; treatment duration; outcome.

Quality assessment

The author independently assessed the quality assessment and risk of bias of each retrieved article and discussed them with other authors. Cochrane risk of bias was applied to assess randomized control trial study for human, whose results were either high risk or some concerns or low risk [14]. Risk of bias from systematic review center for laboratory animal experimentation (SYRCLE) was applied to assess risk of bias in animal study (low risk/high risk) [15].

Table 1: Cochrane risk of bias

Serial number	First author, year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
1	Lueangarun, 2018 [16]	Low risk	Low risk	Low risk	Low risk	Low risk
2	Romain, 2015 [17]	Low risk	Low risk	Low risk	Low risk	Low risk
3	Udani, 2009 [18]	Low risk	Low risk	Low risk	Low risk	Low risk
4	Xie, 2015 [2]	Low risk	Some concern	Low risk	Low risk	Low risk
5	Watanabe, 2018 [19]	Low risk	Low risk	Low risk	Low risk	Low risk

Domain 1: Risk of bias arising from the randomization process, Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention/effect of adhering to intervention), Domain 3: Missing outcome data, Domain 4: Risk of bias in measurement of the outcome, Domain 5: Risk of bias in selection of the reported result.

Results

Selection of articles for review

Figure 1 showed PRISMA flow diagram. Initially, 402 peer-reviewed studies were found from electronic databases and an additional ten studies were found through other sources (search engine). After deleting duplicates, 224 studies underwent title and abstract screening. Articles that did not fulfill the inclusion and exclusion criteria were not further screened. Thirty-two studies were screened for eligibility of which 24 studies fulfilled all the inclusion criteria.

Assessment of study validity (quality assessment and risk of bias)

All included studies were related with the anti-inflammatory potency of mangosteen. Table 1 showed quality scores for randomized control trial in human study, all studies were included in some concerns and low risk, while Table 2 provided risk of bias assessment in animal study and all of studies were low risk.

Study characteristic

The study characteristics for the included studies are shown in Table 3. All of the studies were randomized control trial (n: 24) with most of the subjects were mice (n: 13). One study reported the anti-inflammatory potency of mangosteen in healthy human; five studies in skin diseases; three studies in obesity; two studies in psychiatric diseases, arthritis, teeth diseases, and paw inflammation of animal; and the anti-inflammatory potency in atherosclerosis, asthma, acetaminophen-induced hepatotoxicity, peritonitis, colitis, prostatic hyperplastic, and soft-tissue inflammation was reported in one study (each disease).

Discussion

Anti-inflammatory potency of mangosteen (Garcinia mangostana L.)

The anti-inflammatory effect of mangosteen was described in 24 studies. Most of the studies (seven studies) used GMPE per oral (p.o.), six studies used GMPE topical, four studies used GME p.o., four studies used α-MG from GMPE, one study used GME topical, one study used α-MG from GME, and one study used α-MG and γ-MG from GMPE.

Five studies evaluated the anti-inflammatory potency of mangosteen in skin disorders [16], [27], [31], [33], [34]. The pathogenesis of skin disorders is mostly associated with the production of ROS and chronic inflammation, so antioxidant and anti-inflammatory products such as mangosteen are considered to be a potential treatment [12]. The mechanism action of mangosteen is related to the regulation of inflammatory cytokine; the modulation of NF-kB and MAPK signaling pathway (pro-inflammatory signaling pathways); and immune cell activation through the regulation of chemokines, activation, and infiltration [12], [16], [27], [31], [33], [34], [39]. Mokoagow

Table 2: Systematic review center for laboratory animal experimentation risk of bias

Serial number	First author, year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
1	Adyab, 2019 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Astuti, 2019 [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
3	Chae, 2017 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Chen, 2008 [23]	low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	Herrera-Aco, 2019 [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Huang, 2014 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7	Jang, 2012 [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	Im [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9	Kresnoadi, 2017 [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10	Lotter, 2020 [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
11	Mohan, 2018 [30]	Low risk	Low risk	Low risk	Low risk	low risk	Low risk
12	Mokoagow, 2020 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
13	Putri, 2017 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
14	Romain, 2015 [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
15	Sombolayuk, 2019 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
16	Tatiya-aphiradee, 2019 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
17	Tsai, 2020 [35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
18	Yan, 2018 [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
19	Yurista, 2012 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
20	Zuo, 2018 [38]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Domain 1: Selection bias (sequence generation, baseline characteristics, allocation concealment), Domain 2: Performance bias (random housing, blinding), Domain 3: Detection bias (random outcome assessment, blinding), Domain 4: Attrition bias (incomplete outcome data), Domain 5: Reporting bias (selective outcome reporting), Domain 6: Other (other sources of bias).

Table 3: Study characteristic

Serial number	First author, year	Study design	Subject-disease model	I and C	Treatment duration	Outcome
1	Adyab, 2019 [20anthocyanins and phenolic acids. Mangosteen pericarp extract showed inhibitory activity towards pancreatic lipase and may have potential use for obesity treatment. However, there is limited study on the beneficial effects of mangosteen flesh against obesity. This study aimed to investigate the effects of *Garcinia mangostana* flesh (GMF]	RCT	SD rats with obesity induced by high-fat diet (*n*: 40)	C1: Healthy C2: Placebo I1-3: GME 200, 400, 600 mg/kg p.o.	7 weeks	GME reduced significantly IL-6 and TNF-α in a dose-dependent manner
2	Astuti, 2019 [21]	RCT	ICR mice with paw inflammation induced by carrageenan (*n*: 40)	C1: Healthy C2: Placebo C3: Diclofenac sodium gel I1-3: GMPE gel 0.1%, 0.5%, 1% I4-5: GMPE Nanoemulgel 0.0625% and 0.0125%	360 min (measured every 30 min)	All intervention groups showed a significant reduction of inflammation from 90th minute. I4 and I5 showed better inflammation reduction compared to I1-I3 in 90th-minute, and a similar effect with C3 in 90th-minute, in a dose-dependent manner
3	Chae, 2017 [22]	RCT	ICR mice with colitis induced by DSS (n: 40)	C1: Healthy C2: Placebo C3: 5-aminosalicylic acid I1-2: GMPE 30 and 120 mg/kg p.o.	7 days	GMPE reduced significantly disease activity index score, histological inflammatory score, NF-kB pathway, and MPO activity in a dose-dependent manner; and the similar effect with 5-aminosalicylic acid
4	Chen, 2008 [23]	RCT	ICR mice with paw inflammation induced by carrageenan (*n*: 12)	C1: Placebo C2: Sulindac 20 mg/kg p.o. I: α-MG 20 mg/kg p.o. (from GME)	6 h (measured every 1 h)	α-MG reduced significantly paw edema from the first hour, faster than sulindac
5	Herrera-Aco, 2019 [24]	RCT	DBA/1J, BALB/c, and C57BL/6 mice with CIA induced by collagen type II injection (*n*: 30)	C1: healthy C2: placebo C3: MTX 0.5 mg/kg p.o. I1-2: α-MG 10 and 40 mg/kg p.o. (from GMPE)	33 days	α-MG reduced significantly clinical score in both doses, histopathological score in high dose, and anti-inflammatory marker in serum and joint; and had superior effect than MTX
6	Huang, 2014 [25]	RCT	RCT: Triple transgenic Alzheimer's disease mice (*n*: 15–17/group)	C: Placebo I: GMPE 5000 ppm p.o.	8 months	GMPE reduced significantly cognitive impairment and IL-6 level
7	Jang, 2012 [26]	RCT	BALB/c mice with asthma induced by OVA intraperitoneal injection	C1: Healthy C2: Placebo I1: Dexamethasone 3 mg/kg I2: Montelukast 30 mg/kg I3-4: α-MG 10 and 30 mg/kg p.o. (from GMPE) I5-6: γ-MG 10 and 30 mg/kg p.o. (from GMPE)	3 days	α-MG and γ-MG reduced significantly the number of leukocyte and inflammatory cells; NF-kB p65 expression in lung tissue; and TGF-1β level (dose-dependent manner)
8	Im, 2017 [27]	RCT	HR-1 hairless mice induced by UVB irradiation (*n*: 15)	C1: Healthy C2: Placebo I: α-MG 100 mg/kg p.o (from GMPE)	7 days	α-MG reduced significantly IL-1β, IL-6, and TNF-α mRNA levels
9	Kresnoadi, 2017 [28]	RCT	Tooth extraction socket of *Cavia cobayas* (*n*: 14)	C: Placebo I: GMPE topical in teeth 0.1 cc	7 and 30 days	GMPE reduced significantly NF-kB p65 expression and receptor activator of NF-kB
10	Lueangarun, 2018 [16]	RCT	Human with acne vulgaris	C: Clindamycin gel 1% twice daily I: GME nanoparticle gel 0.5% twice daily	12 weeks	GMPE gel reduced significantly inflammatory lesions compared to clindamycin gel after 12 weeks treatment
11	Lotter, 2020 [29]	RCT	SD rats with schizophrenia induced by LPS (*n*: 80)	C1: Placebo C2: Haloperidol 2 mg/kg p.o. I1: GMPE 50 mg/kg p.o. I2: α-MG 20 mg/kg p.o.	16 days	GME and α-MG reduced significantly IL-6 level and had a similar effect with haloperidol GME reduced significantly TNF-α level and had the superior effect than haloperidol, α-MG reduced insignificantly TNF-α level
12	Mohan, 2018 [30]	RCT	ICR mice with peritonitis induced by carrageenan (*n*: 54)	C1: Healthy C2: Placebo C3: Dexamethasone 0.5 mg/kg p.o. I1-6: α-MG 1–25 mg/kg p.o. (from GMPE)	6 h	α-MG reduced significantly TNF-α and IL-1β at 25 mg/kg, decreased significantly leukocyte infiltration (neutrophil) at 14 and 25 mg/kg, and had a similar effect with dexamethasone
13	Mokoagow, 2020 [31]	RCT	ICR mice with skin inflammation induced by TPA	C1: Healthy C2: Placebo C3-6: GMPE cream 2.5%, 5%, 10%, 20%	6 h	GMPE cream reduced significantly neutrophil infiltration in a dose-dependent manner and reduced significantly epidermal thickness with the best dose was 10%
14	Putri, 2017 [32]	RCT	Wistar rats with carrageenan-induced gingival inflammation (*n*: 28)	C1: Placebo C2: Chlorhexidine 0.2% topical I1-2: GMPE topical 12.5 and 25%	2, 4, 6 h	Inflammatory diameter in I1 was reduced significantly in comparison with C1 and C2, but didn't show a significant difference compared with I2 in all of the treatment durations
15	Romain, 2015 [17]	RCT (animal and human study)	Animal study: ICR mice with inflammation induced by LPS intraperitoneal injection (*n*: 24) Human study: Acute and chronic soft tissue inflammation (*n*: 24)	Animal study C: Placebo I: GME 60 mg/kg p.o. twice daily Human study C: Nimesulide 100 mg p.o. twice daily I: GME 600 mg p.o. twice daily	Animal study: 90 min Human study: 5 days	GME reduced significantly TNF-α level in an animal study and reduced significantly soft tissue pain in the human study, the effect in human study was lower than nimesulide

(Contd...)

Table 3: ***(Continued)***

Serial number	First author, year	Study design	Subject-disease model	I and C	Treatment duration	Outcome
16	Sombolayuk, 2019 [33]	RCT	ICR mice with wound (*n*: 32)	C: Placebo I1-6: GMPE cream 5%, 10%, 20% in skin, sacrificed after 3 and 8 days	3 and 8 days	GMPE cream reduced significantly number of inflammatory cells (particularly in 5% and 10% concentration) on days 3rd and 8th
17	Tatiya-aphiradee, 2019 [34]	RCT	ICR mice with superficial skin infection induced by methicillin-resistant *S. aureus* (*n*: 10–12/ group)	C1: Healthy C2: Placebo C3: Erythromycin topical 1.32% I1: GMPE topical 10% I2: α-MG topical 1.32%	1, 5, 8, and 10 days	GMPE and erythromycin reduced significantly the expression of TNF-α, IL-6, IL-1β, and TLR-2 mRNA from day 5th α-MG reduced significantly the expression of TNF-α, IL-6, IL-1β, and TLR-2 mRNA on day 10
18	Tsai, 2020 [35]	RCT	F344 rats with prostatic hyperplasia induced by DMAB intraperitoneal injection (*n*: 24)	C1: Healthy C2: Placebo I1: GMPE powder 2.5 and 5% p.o.	24 weeks	GMPE reduced significantly iNOS and COX-2 protein expressions in a dose-dependent manner
19	Udani, 2009 [18]	RCT	Obese human (*n*: 40)	C1: Placebo I1-3: GME juice 3, 6, 9 oz twice daily p.o.	8 weeks	GME juice 9 oz twice daily reduced significantly hsCRP level
20	Xie, 2015 [2]	RCT	Human (*n*: 60)	C: Placebo I: GME p.o.	30 days	GME reduced significantly CRP level
21	Watanabe, 2018 [19]	RCT	Obese human (*n*: 22)	I: placebo C: GME 400 mg p.o.	26 weeks	GME reduced significantly hsCRP and fibrinogen levels
22	Yan, 2018 [36]	RCT	ICR mice with hepatotoxicity induced by APAP (*n*: 32)	C1: Healthy C2: Placebo I1-2: α-MG 100 and 200 mg/kg p.o. (from GMPE)	7 days	α-MG reduced significantly TNF-α and IL-1β in a dose-dependent manner
23	Yurista, 2012 [37]	RCT	Wistar rats with atherosclerosis induced by high cholesterol diet (*n*: 30)	C1: Healthy C2: Placebo I1: GMPE 200 mg/kg p.o. I2: GMPE 400 mg/kg p.o. I3: GMPE 800 mg/kg p.o.	90 days	GMPE reduced significantly TNF-α, IL-1 levels; and the expression of NF-kB, ICAM-1, and IL-6; in a dose-dependent manner
24	Zuo, 2018 [38]	RCT	SD rats with CIA induced by collagen type II injection (*n*: 24)	C1: Healthy C2: Placebo C3: MTX 0.5 mg/kg p.o. I1: GMPE 0.5 g/kg/day p.o. I2: MTX 0.5 mg/kg + GMPE 0.5 g/kg/day p.o.	36 days	GMPE reduced significantly arthritis score, paw inflammation, and IL-17 level; and increased significantly IL-10 level

*Significantly: $p \leq 0.05$, insignificantly: $p > 0.05$. *G. mangostana: Garcinia mangostana, S. aureus*: *Staphylococcus aureus*, RCT: Randomized control trial, APAP: Acetaminophen, CIA: Collagen-induced arthritis, CRP: C-reactive protein, COX: Cyclooxygenase, DMAB: 3,2′-dimethyl-4-aminobiphenyl, DSS: Dextran sulfate sodium, GME: *G. mangostana* L. extract, GMPE: *G. mangostana* L. peel extract, hsCRP: High sensitivity CRP, ICAM: Intercellular adhesion molecule, ICR: Institute of cancer research, IL: Interleukin, iNOS: Inducible nitric oxide synthase, LPS: Lipopolysaccharide, MG: Mangostin, MPO: Myeloperoxidase, MTX: Methotrexate, NF-kB: Nuclear factor-kappaB, OVA: Ovalbumin, p.o.: Per oral, SD: Sprague-Dawley, TLR: Toll-like receptor, TNF: Tumor necrosis factor, TPA: 12-O-tetradecanoylphorbol-13-acetate, I: Intervention, C: Comparator, PG: Prostaglandin, N: Normal, NO: Nitric oxide, MAPK: Mitogen-activated protein kinases, GSH: Glutathione, DMPO: Dimethyl sulfoxide, AP: Activator protein.

et al. (2020) reported that GMPE cream reduced inflammation (neutrophil infiltration and epidermal thickness) in TPA-induced inflammation because mangosteen inhibits COX enzyme in the arachidonic acid pathway and NF-kB signaling cascade (because inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) cyclase in vascular endothelial cells due to absence of prostanoid production) [31]. Tatiya-aphiradee *et al*. (2019) reported that GMPE topical had an anti-bacterial effect; improved wound healing; and reduced the expression of TNF-α, IL-6, IL-1β, and TLR-2 mRNA in mice with superficial skin infection induced by methicillin-resistant *Staphylococcus aureus* [34]. Sombolayuk *et al*. (2019) reported that GMPE cream reduced the number of inflammatory cells and increased wound healing by improved granulation tissue production and re-epithelialization [33]. Im *et al*. (2017) reported that α-MG from GMPE reduced pro-inflammatory cytokines level (IL-1β, IL-6, and TNF-α mRNA), acted as an antioxidant (improved superoxide dismutase and catalase activities, and decreased skin wrinkles and MMP expression (a marker of skin aging) in UVB radiation-induced hairless mice [27]. Im A-R's study is supported with Djawad *et al*. (2020) reported that xanthones and flavonoid in mangosteen play an important role in antioxidant and anti-inflammatory function [27], [40]. Lueangarun *et al*. (2018) reported that GMPE gel reduced inflammatory lesions and comedones in acne patients with no serious side effects because of the antimicrobial, anti-inflammatory, and antioxidant properties [16].

Five articles in this systematic review reported the topic in the rheumatoid field (two studies in collagen-induced arthritis/CIA, two studies in paw inflammation of animal subjects, and one study in soft-tissue inflammation) [17], [21], [23], [24], [38]. Two animal models with collagen type II injection-induced CIA showed that GMPE reduced arthritis score and paw inflammation, anti-cyclic citrullinated peptide antibody (biomarker that indicates the severity of arthritis), and IL-17 level (cytokine that is implicated in the initiation of arthritis); repaired synovial hyperplasia and cartilage degradation in joints; increased anti-inflammatory cytokine level (IL-10); had a synergistic effect with methotrexate (a drug for arthritis) and also had anti-inflammatory potency [24], [38], [41], [42], [43]. Paw inflammation in mice used in two studies showed that GMPE and GME reduced inflammation volume of paw edema and the level of NO and PG-E2 through the suppression of COX-2 activity and NO generation [21], [23], [43]. Romain *et al*. (2015) described that GME reduced TNF-α level in an animal study and soft-tissue pain in human study [17].

A total of four studies discussed the anti-inflammatory effect of mangosteen in metabolic syndrome, three studies in obese subjects, and one study in atherosclerosis induced by high cholesterol diet [18], [19], [20], [37]. Atherosclerosis, the result of dyslipidemia and lipid peroxidation, is a chronic condition in which arteries harden through the build-up of plaques [44], [45]. Yurista *et al*. (2012) reported that GMPE reduced the level of pro-inflammatory cytokines (TNF-α, IL-1, and the expression of NF-kB, ICAM-1, and IL-6 in aorta) in high cholesterol-induced atherosclerosis rats that prevent the generation of atherosclerosis. The inhibition of central signaling from NF-kB activation is the possible mechanism of xanthone anti-inflammatory potency in GMPE [37]. Obesity is an abnormal or excessive accumulation of body fat that may have a harmful effect on health [46], [47]. One study in high-fat diet-induced obese rat reported that GME reduced pro-inflammatory cytokines level (IL-6 and TNF-α) and body weight; attenuated metabolic abnormalities (improved lipid profile and enhanced antioxidant level) and structural changes (reduced hepatic fat and ameliorated renal abnormalities) due to high-fat diet because the high level of fiber in GME; and bioactive compounds such as xanthones, anthocyanin, and phenolic acids act as antioxidant and anti-inflammatory [20], [48]. Two studies used obese human as subject and reported that GME reduced body weight, high sensitivity C reactive protein (hsCRP) level, fibrinogen level; and improve insulin sensitivity with no side effect because of the inhibition of the conversion of arachidonic acid to PG-E2 by COX and blocking of inhibitor kappa-B kinase [18], [19], [49].

The anti-inflammatory potency of mangosteen was also explained in the abdomen and urological disorders [22], [30], [35], [36]. Tsai *et al*. (2020) reported that GMPE reduced prostate weight, serum testosterone and dihydrotestosterone concentrations, protein expression of proliferating cell nuclear antigen, prostatic tissue inflammation (iNOS and COX-2 protein expressions), and malondialdehyde levels in rats with prostatic hyperplasia induced by DMAB intraperitoneal injection because had many xanthones which can be antioxidant, anti-inflammatory, and anti-proliferative agents [35]. Mohan *et al*. (2018) reported that α-MG from GMPE reduced the levels of TNF-α, IL-1β, and leukocyte infiltration in mice with peritonitis induced by carrageenan because the inhibition of inflammation (inhibit the translocation of NF-kB together with decreasing COX-2 enzymes) [30]. Chae *et al*. (2017) reported that GMPE reduced disease activity index score, histological inflammatory score, NF-kB pathway, and myeloperoxidase activity in mice with colitis induced by dextrane sulfate sodium because of the role of mangosteen as antioxidant and anti-inflammatory [22]. Yan *et al*. (2018) reported that α-MG from GMPE reduced pro-inflammatory cytokine level (TNF-α and IL-1β) and had a protective effect against acetaminophen-induced hepatotoxicity, because MG maintained the balance of apoptosis, resulting in the avoidance of mitochondrial dysfunction due to acetaminophen, beside the effect of anti-oxidant and anti-inflammatory [36].

Two kinds of research were conducted to test the anti-inflammatory effect of mangosteen in psychiatric diseases (alzheimer and schizophrenia) [25], [29]. Alzheimer is a neurodegenerative disease (associated with chronic inflammatory and oxidative process) that cause dementia (progressive cognitive disorder and memory loss), with the pathogenesis is associated with the deposition of amyloid β (Aβ) and intra-neuronal neurofibrillary tangles (formed by tau proteins) in the brain parenchyma [25], [50], [51], [52]. Huang *et al*. (2014) reported that GMPE reduced Aβ deposition and tau protein levels in the hippocampus; attenuated the cognitive disorder; increased brain-derive neurotrophic factor and antioxidant level of glutathione; and reduced pro-inflammatory level (IL-6) and inflammatory-related signaling pathways (phosphorylated p38 MAPK and COX-2) of triple transgenic Alzheimer's mice [25]. Schizophrenia is a neuropsychiatric disorder associated with inflammatory and oxidative alteration with psychosis symptoms [29], [53], [54], [55]. Lotter *et al*. (2020) described that GME and α-MG reduced plasma pro-inflammatory level (IL-6 and TNF- α), cortical lipid peroxidation, and psychosis symptoms [29].

The anti-inflammatory effect of mangosteen was reported in tooth and gingiva disorder. Putri *et al*. (2017) reported that GMPE topical reduced inflammatory diameter of gingiva and Kresnoadi *et al*. (2017) reported that GMPE topical reduced pro-inflammatory cytokine expression (NF-kB), because the component of xanthone and flavonoid (tannin and catechin) in GMPE [28], [32]. Xanthone suppresses the cyclooxygenase and lipoxygenase enzymes and resulting in the release of prostaglandins, prostacyclins, thromboxanes, and leukotrienes that are also inhibiting the inflammation processes. The mechanism of flavonoids in suppressing the inflammatory process is by inhibiting the release of arachidonic acid, the secretion of lysosomal enzymes from neutrophil cells and endothelial cells, and inhibits the exudation phase of the inflammation process and the release of cyclooxygenase enzyme irreversibly (prostaglandin synthetase), which catalyzes the converting of arachidonic acid into endoperoxide compounds, which will decrease the formation of prostaglandins and suppress the inflammatory process [11], [28], [32], [56], [57].

The effect of anti-inflammatory from mangosteen was also described in asthma [26]. Asthma is a chronic inflammatory disorder identified by the accumulation of inflammatory cells and mediators in the airway inducing airway hyper-responsiveness (AHR), and remodeling of the airway [26], [58], [59]. Jang *et al*. (2012) reported that α-MG and γ-MG from GMPE reduced the number of leukocyte and inflammatory cells and cytokines, AHR, and elevated levels of Th2 cytokines [26]. The research about mangosteen and its anti-inflammatory effect in the healthy human was reported by Xie *et al*.

(2015) [2]. GME decreased C-reactive protein (CRP) level and increased antioxidant capacity with no harmful impact on immune, hepatic, and renal functions for 30-days consumption. CRP is an acute inflammatory protein that elevates in the condition of infection or inflammation [2], [60].

Strength and limitation of the study

This systematic review consisted of 24 studies discussing the anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.). All studies were RCT and majority of the studies discussed the anti-inflammatory potency of mangosteen in skin diseases.

The limitation of the study was the studies that used human as a subject were limited, the variance of the demography in the human study, confounding variables in each study (especially in human study), limited follow-up time, and the minimum sample.

Future implication

This systematic review can be a scientific reading and material to physician, researcher, and all of the readers related to anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.). Further research is needed for the application of the anti-inflammatory potency of mangosteen (*Garcinia mangostana* L.) in various inflammatory diseases, the comparison of anti-inflammatory potency in pericarp and fruit, and the clinical study with various subject characteristics (demography variance) and larger sample size.

Conclusion

Mangosteen (*Garcinia mangostana* L.) has anti-inflammatory potency (especially the component of xanthone and flavonoid) in various inflammatory conditions and diseases; such as obesity, skin disease, psychiatric disease, tooth disease, asthma, atherosclerosis, acetaminophen-induced hepatotoxicity, peritonitis, colitis, prostatic hyperplastic, arthritis, and soft-tissue inflammation.

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