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[Masoumeh Naserkheil, Farzad Ghafouri, Sonia Zakizadeh, Nasrollah Pirany et al. "Multi-Omics Integration and Network Analysis Reveal Potential Hub Genes and Genetic Mechanisms Regulating Bovine Mastitis", Current Issues in Molecular Biology, 2022](#)

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[Ribeiro, Daniela, Marisa Freitas, José L. F. C. Lima, and Eduarda Fernandes. "Proinflammatory Pathways: The Modulation by Flavonoids : PROINFLAMMATORY PATHWAYS AND FLAVONOIDS", Medicinal Research Reviews, 2015.](#)

The Thai Journal of Pharmaceutical Sciences Volume 47 Issue 1 Article 10 January 2023 [Effects of Quercetin and Its Derivatives](#) on miRNAs and Inflammatory Mediators in Inflammation: A Systematic Review Benediktus Wastu Paramabodhi Eva Annisaa Widyandani Sasikirana widyandani.sasikirana@live.undip.ac.id Wimzy Rizqy Prabhata Follow this and additional works at: <https://digital.car.chula.ac.th/tjps> Recommended Citation Paramabodhi, Benediktus Wastu; Annisaa, Eva; Sasikirana, Widyandani; and Prabhata, Wimzy Rizqy (2023) "Effects of Quercetin and Its Derivatives on miRNAs and Inflammatory Mediators in Inflammation: A Systematic Review," The Thai Journal of Pharmaceutical Sciences: Vol. 47: Iss. 1, Article 10. DOI: <https://doi.org/10.56808/3027-7922.2785> Available at:

<https://digital.car.chula.ac.th/tjps/vol47/iss1/10> This Article is brought to you for free and open access by the Chulalongkorn Journal Online (CUJO) at Chula Digital Collections. It has been accepted for inclusion in The Thai Journal of Pharmaceutical Sciences by an authorized editor of Chula Digital Collections. For more information, please contact ChulaDC@car.chula.ac.th. Original Article Thai Journal of Pharmaceutical Sciences [Effects of quercetin and its derivatives](#) on MicroRNAs and inflammatory mediators in inflammation: A systematic review Benediktus Wastu Paramabodhi, Eva Annisaa, Widyandani Sasikirana, Wimzy Rizqy Prabhata, Intan Rahmania Eka Dini Study Program of Pharmacy, Diponegoro University, Jl. Prof. H. Soedarto S.H., Semarang 50275, Indonesia Corresponding Author: Widyandani Sasikirana, ABSTRACT Study Program of Pharmacy, Diponegoro University, Quercetin has been known to have anti-inflammatory effects. Information regarding the anti- Jl. Prof. H. Soedarto S.H., inflammatory effects of quercetin or its derivatives on inflammatory mediators and microRNAs Semarang 50275, Indonesia. (miRNAs) is abundant and varied. However, a comprehensive understanding of its pharmacological E-mail: widyandani. actions at the cellular and molecular levels needs to be studied. Therefore, quercetin and its sasikirana@live.undip.ac.id derivatives were studied in this systematic review to investigate how they affect the expressions Received: January 06, 2022 of miRNAs and inflammatory mediators and their respective roles in the mechanisms of anti- Accepted: July 16, 2022 inflammatory actions. A literature search in PubMed and Scopus databases was carried out Published: March 29, 2023 based on the preferred reporting items for systematic reviews and meta-analysis protocol. Out of 2964 articles identified, 47 eligible articles were reviewed. Quercetin, isorhamnetin, rutin, hyperoside, quercitrin, and quercetin pivaloyl ester had anti-inflammatory activity by down- regulating the expressions of tumor necrosis factor-alpha, Interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, cyclooxygenase 2, or prostaglandin E2. [Quercetin-3-glucuronide and quercetin-3-O-β- glucuronide](#) did not affect the expressions of inflammatory mediators. Quercetin, isorhamnetin, and tamarixetin had anti-inflammatory activities through miRNAs modulation pathways, causing down-regulation of pro-inflammatory cytokines or upregulation of anti-inflammatory cytokines. It remained unclear how quercetin and its derivatives affect IL-10, miR-146a, and miR-155. [In conclusion, quercetin and its derivatives have](#) anti-inflammatory effects by regulating miRNAs and inflammatory mediators. MiRNAs regulate inflammatory mediators in either a positive or negative manner. Keywords: Cytokine, inflammation, microRNAs, quercetin, systematic review INTRODUCTION I nflammation is part of the complex response from self-protection mechanisms against noxious stimuli.[1] Vascular permeability alterations, leukocyte recruitment and accumulation, and inflammatory mediators release are important microcirculatory events during the inflammatory phase.[2] Inflammatory mediators are divided into various groups based on their biochemical properties: Vasoactive amines and peptides, inflammatory cytokines, proteolytic enzymes, lipid mediators, reactive oxygen species, nitric oxide, and complement components.[3] Although inflammation is a vital mechanism for removing toxic stimuli and healing, it can also lead to certain disorders.[4] Anti-inflammatory compounds can be a helpful therapeutic approach in managing inflammatory diseases.[5] It is known that natural compounds have been commonly used as complementary therapies in chronic diseases. For instance, propolis has been used as a complementary treatment for infection due to its antibacterial and anti-fungal effects.[6] Nigella sativa can be used as adjunct therapies for cardiovascular disease, Type 2 diabetes, and rheumatoid arthritis through its molecular mechanism by activating AMPK, inhibiting the NF-κB pathway, and increasing Interleukin (IL)-10 expression.[7] Another biological compound that has been known to have Paramabodhi, [et al.:Effects of quercetin and its](#)

derivatives [on](#) MicroRNAs beneficial effects on chronic diseases is quercetin. [8] Quercetin (3,3,4,5,7-pentahydroxyflavone) is a flavonol, one of the six flavonoid subclasses.[9] [Quercetin can exist in its natural state as an aglycone or](#) in the form of its derivatives, such as quercetin glycosides (e.g., isoquercetin, hyperoside, quercitrin, and rutin), prenylated quercetins (e.g., solophenol D and uralenol), quercetin methyl ethers (e.g., isorhamnetin and rhamnazin), and quercetin sulfates (e.g., quercetin 3,7, 3',4'-tetra sulfate). [10] Quercetin can be found in many natural products, such as Apium graveolens, Allium cepa, Moringa oleifera, Brassica oleracea, Nasturtium officinale, and Malus domestica.[11] Both quercetin and its derivatives have been known to have anti-inflammatory action through modulating microRNAs (miRNAs) or inflammatory mediators.[3,12,13] MiRNAs are single-stranded RNA, non-coding, and have a length of about 22 nucleotides which act as the negative regulator of genes with regulatory mechanisms affecting the stability of messenger RNAs (mRNAs).[14,15] One of the main characteristics of miRNAs is multi-regulatory, meaning that one miRNA can affect more than one target mRNA. Oppositely, one target mRNA or a specific target molecule can be regulated by more than one kind of miRNA.[12,16] In general, miRNAs will control the expression of a gene by binding to the target mRNAs, causing mRNAs degradation or inhibiting mRNAs translation.[17] Under the inflammatory condition, miRNAs expressions can be altered by being upregulated or downregulated. Cytokines, as the inflammatory mediator, contribute to the occurrence of acute or chronic inflammatory responses. MiRNAs can regulate genes related to cytokine secretion. Several miRNA-regulated cytokines are tumor necrosis factor-alpha (TNF- α), IL-1, IL-6, IL-17, IL-23, and TGF- β . [18] [Inflammation is progressed by the action of pro-inflammatory cytokines, including IL-1, TNF, IFN- \$\gamma\$, and IL-6, and is resolved by anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, IFN- \$\alpha\$, and TGF- \$\beta\$](#) . [19] The information regarding the involvement of miRNAs and inflammatory mediators is abundant, with varied results. Therefore, [there exists a need for a systematic and critical evaluation of the literature to](#) comprehensively [understand](#) the pharmacological [mechanisms of](#) quercetin and its derivatives at cellular and molecular levels. Carullo et al. discussed [the anti-inflammatory effects of quercetin in the inflammatory model](#) through different biological pathways.[3] Kordkheyli et al. discussed the effects of quercetin on miRNAs in different conditions, especially in cancer diseases.[12] However, to the authors' knowledge, no studies have comprehensively observed the expressions of miRNAs and inflammatory mediators under quercetin or its derivatives administration in specific inflammatory conditions. Moreover, the relationship between miRNAs and inflammatory mediators under quercetin administration has not been presented in any literature review. This article systematically reviews the evidence for quercetin's effects on miRNAs and inflammatory mediators from both in vitro and in vivo studies. Moreover, this systematic review intends to give information on the involvement of miRNAs in the regulation of inflammatory cytokines. METHODS Search Strategy The preferred reporting items for systematic reviews and meta-analysis[20] guidelines were followed in this systematic review. From March to June 2021, an [article search was performed using electronic databases PubMed and Scopus](#). The terms "(Quercetin) AND (inflammation OR inflammatory) AND (microRNA OR miRNA OR miR OR IL OR IL OR TNF OR "tumor necrosis factor" OR COX OR cyclooxygenase OR prostaglandin E2 [PGE] OR prostaglandin)" were used to search in both databases. In PubMed and Scopus, the search category was set to "All Fields" and "Title, Abstract, Keywords," respectively. In addition, the range of publication years was limited to only show articles published from 2011 to 2021. Study Selection After removing duplicates using the Mendeley software, all obtained articles were screened based on their titles and abstracts to ensure they met all of the following inclusion

criteria: (1) [Studies that used in vitro or in vivo](#) study designs, (2) studies that used quercetin or quercetin-derived forms as the interventions, and (3) studies that reported anti-inflammatory effects of quercetin or its derivatives using lipopolysaccharide (LPS)- induced models and reported the observation of the following markers: miRNAs and/or inflammatory mediators. Then, [selected articles were subjected to a full-text analysis, excluding articles that met any of the](#) following [exclusion criteria](#): (1) Studies that evaluated the effects of plant extracts, (2) studies that evaluated the effects of quercetin or its derivatives with the addition of other compounds (encapsulation, combination, and inflammatory enzyme promotor/inhibitor), (3) narrative review articles, (4) inaccessible full-articles, (5) non-English articles, and (6) articles were retracted from publication. In addition, previous narrative review articles were read to search for additional original articles by searching manually from the citations and reference list. However, the narrative review articles were not included in the study. Furthermore, the quality of the included articles was assessed based on Joanna Briggs Institute's (JBI's) Critical Appraisal Checklists for Quasi- Experimental Studies.[21] Data Extraction The following data parameters were extracted from included articles: Citation (Author and year), type of intervention (quercetin or its derivatives), study design (in vitro/ex vivo or in vivo), dosages, cell line/animal model with LPS-induced, effects on inflammatory mediator's expressions, effects on miRNAs expressions. [Data extracted from included articles were comprised in](#) tables. [RESULTS Study Selection The study selection was](#) carried out [as](#) shown [in Figure 1](#). There were 2964 articles identified, of which 1007 were from PubMed, and 1957 were from Scopus. The Mendeley software eliminated 947 duplicate publications, leaving 2017 articles for the title and abstract screening. Following the inclusion Figure 1: Flow Chart of study selection in this study. criteria, 1904 articles were excluded during the title and abstract screening phase, while 90 were processed for full- text screening after passing the title and abstract screening procedure. Based on the exclusion criteria, 43 out of 90 articles were excluded from the study. After reading the relevant narrative review articles, no additional original articles needed to be included in the study. At the end of the process, 47 articles that met the eligibility criteria were assessed for their quality using JBI's Critical Appraisal Checklist for Quasi- Experimental Studies. This systematic review included all 47 articles that scored "yes" to at least five of the nine questions on the checklist. Characteristics of the Study The characteristics of the included studies are comprised in Tables 1 and 2. There were 47 articles in total, with 29 in vitro/ex vivo studies, 12 in vivo studies, and six studies that used in vivo animal models to complement and confirm the results of in vitro/ex vivo experiments. Out of 47 articles, 29 studies reported the effects of quercetin aglycone, and 18 reported the effects of quercetin derivatives, but only five studies compared the effects of quercetin to its derivatives. The quercetin derivatives used in the included studies are isorhamnetin, hyperoside, rutin, quercitrin, tamarixetin, quercetin-3-glucuronide, and quercetin pivaloyl ester. Isorhamnetin is the most frequently used quercetin derivative in the included studies. All included studies reported the effects on inflammatory mediators, namely IL, TNF- α , cyclooxygenase 2 (COX-2), and PGE2. However, only eight studies reported the effects on miRNAs. Among the eight studies, two used quercetin derivatives as the intervention, and one used an in vivo study design. Articles employing different samples and models of inflammation [did not allow quantitative estimates of quercetin effects](#). [Hence, performing a meta-analysis was discarded](#). [Effects of Quercetin and the Derivatives on Inflammatory Mediators and miRNAs](#) The extracted data of this systematic review show that in vitro/ex vivo and in vivo administration of quercetin can inhibit LPS induction and reduce the expressions of IL-1 α , IL-1 β , IL-2, IL6, IL-8, IL-12,

TNF- α , COX-2, and PGE2[22-54] as shown in Figure 2. Interestingly, opposing results can be found regarding the effect of quercetin on IL-10 expression. Although quercetin administration in vivo increased IL-10 expression in LPS-induced mice,[55] quercetin administration in vitro decreased IL-10 expression in LPS-induced RAW 264.7 cells.[52] In addition to the parent compound, quercetin derivatives can modulate the expressions of inflammatory mediators. Figure 2 also shows that expressions of various inflammatory mediators, such as IL-1 β , IL6, IL-8, IL-12, TNF- α , COX-2, and PGE2, decreased due to quercetin derivatives [22,24,36,44,56-65] except for the expression of IL-10 which upregulated after tamarixetin administration. [64] This systematic review also collected data on [the effects of quercetin and its derivatives on](#) miRNAs expressions. In addition, the role of miRNAs on inflammatory mediator's regulations was investigated and shown in Figure 3. The included studies show that in vitro/ex vivo administration of quercetin reduced the expressions of [bta-miR-24-2](#), [bta-miR-146a](#), [bta-miR-181c](#), [mmu-miR-155](#), [hsa-miR-221](#), and increased the expressions of [bta-let-7e](#), [bta-miR-17](#), [hsa-miR-124](#), and [mmu-miR-369-3p](#), causing the expressions of TNF- α and IL-6 to decrease.[22,28,31,33,47] Expressions of TNF- α , IL-1 β , and IL-6 are down-regulated under conditions of down-regulated [bta-miR-24-2](#), [bta-miR-146a](#), [bta-miR-181c](#), and [mmu-miR-155](#) as well as up-regulated [bta-let-7e](#) and [bta-miR-17](#) expressions.[22,28] In vivo administration of quercetin increased [mmu-miR-122](#) expression by 68% and [mmu-miR-125b](#) by 48%, causing a decrease in IL-6 expression.[23] Tamarixetin could increase the [mmu-miR-146a](#), [mmu-miR-155](#), and [mmu-miR-187](#) expressions, which upregulated IL-10 and down-regulated TNF- α , IL-6, and IL-12p70 expressions.[64] Isorhamnetin could decrease [mmu-miR-155](#) expression, causing down-regulation of TNF- α , IL-1 β , and IL-6.[22] DISCUSSION Quercetin has known to have anti-inflammatory bioactivities. This systematic review was conducted to summarize information on the effects of quercetin and its derivatives on several inflammatory markers, such as miRNAs and inflammatory mediators, as well as examine the roles of miRNAs on inflammatory mediators from in vivo and in vitro/ex vivo studies. This systematic review did not include clinical or human studies because, according to the authors' knowledge, no studies have reported the anti-inflammatory Table 1: Summary of in vitro/ex vivo studies about the effects of quercetin and its derivatives on inflammatory mediators and miRNAs

First author, year, citations	Quercetin type	Dose/s	Cell line and model	Expression of inflammatory mediators	Expression of miRNAs	JBIC's critical appraisal score
Chang et al., 2013[14]	Quercetin	15, 30, and 60 μ M	RAW 264.7 stimulated with 100 ng/mL LPS	TNF- α , IL-1 β \downarrow ~ -	7/9	7/9
Chen et al., 2018[15]	Quercetin	1, 2.5; 2.5; and 5 μ g/mL	IPEC-J2 stimulated with 10 μ g/mL LPS	IL-6, IL-8 \downarrow -	7/9	7/9
Chuammitri et al., 2015[16]	Quercetin	50 μ M	Bovine neutrophil stimulated with 100 ng/mL LPS	TNF- α , IL-1 β \downarrow -	7/9	7/9
Chuammitri et al., 2017[17]	Quercetin	50 μ M	Bovine neutrophil stimulated with 100 ng/mL LPS	TNF- α , IL-1 β , IL-6 \downarrow	bta-miR-24-2 , bta-miR-146a , bta-miR-181c , bta-miR-let-7e , bta-miR-17 \uparrow	7/9
Dicarolo et al., 2019[18]	Quercetin	25 μ M	WT and UC organoids stimulated with 1 μ M LPS	TNF- α \downarrow -	7/9	7/9
Endale et al., 2013[19]	Quercetin	2.5; 5; 10; and 20 μ M	5, 10, and 20 μ M RAW 264.7 stimulated with 100 ng/mL LPS	TNF- α , IL-1 β , IL-6, COX-2 \downarrow ~	TNF-α , IL-1β , IL-6 , PGE2 \downarrow ~ -	7/9
Galleggiante et al., 2019[3]	Quercetin	25 μ M	BMDC stimulated with 1 μ g/mL LPS	TNF- α , IL-6 \downarrow	mmu-miR-369-3p \uparrow	7/9
Guo et al., 2012[20]	Quercetin	5, 10, 15, 20, and 50 μ M	RAW 264.7 stimulated with 100 ng/mL LPS	COX-2 \downarrow ~ -	7/9	7/9
Guo et al., 2020[21]	Quercetin	20 μ M	HK-2 stimulated with 2 μ g/mL LPS	TNF- α , IL-1 β \downarrow	hsa-miR-124 \uparrow	7/9
Gutierrez-venegaz et al., 2017[22]	Quercetin	10 μ M	H9c2 stimulated with 1 μ g/mL LPS	COX-2 \downarrow -	7/9	7/9
Kang et al., 2020[23]	Quercetin	1 μ g/mL	SHSY-5Y stimulated with 100 ng/mL LPS	BV2 stimulated with 100 ng/mL LPS	TNF- α , IL-1 β , IL-6 \downarrow -	7/9

et al., 2017[24] Quercetin 6,25; 12,5; and 25 μ M RAW 264.7 stimulated with 1 μ g/mL LPS • IL-6 \downarrow ~ • TNF- α , COX-2# - 7/9 Takashima et al., 2014[25] Quercetin 10 μ M BALF [stimulated with 5 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow - 7/9 Veith et al., 2017[26] Quercetin 1, 3, and 30 μ M IPF patients' blood plasma stimulated with LPS TNF- α , IL-8 \downarrow ~ - 7/9 Wang et al., 2019[27] Quercetin 40 μ M WI-38 stimulated with LPS TNF- α , IL-6 \downarrow hsa-miR-221 \downarrow 7/9 Wang et al., 2020[28] Quercetin 100 μ M HOK stimulated with 100 ng/mL LPS - hsa-miR-22 \downarrow 7/9 Xiao et al., 2020[29] Quercetin 5, 10, and 20 μ M WI-38 stimulated with 100 ng/mL LPS IL-6, IL-8 \downarrow ~ - 7/9 Xiong et al., 2019[30] Quercetin 5, 10, and 20 μ M HGF [stimulated with 1 \$\mu\$ g/mL LPS](#) IL-8 \downarrow ~ [TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#), - 7/9 Xue et al., 2017[31] Quercetin 20 μ M [RAW 264.7 stimulated with 500 ng/mL LPS](#) IL-10, COX-2 \downarrow IL-1 α , IL-1 β , IL-2, - 7/9 Zhang et al., 2016[32] Quercetin 25, 50, and 100 μ M Human PBMC [stimulated with 10 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow ~ - 7/9 Chen et al., 2021[33] Isorhamnetin 200 μ mol/l BV2 [stimulated with 1 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$](#) \downarrow - 7/9 (Contd...) Table 1: (Continued) First author, year, citations Quercetin Dose/s Cell line and type model Expression of inflammatory mediators Expression of miRNAs JBI's critical appraisal score Chi et al., 2016[34] Isorhamnetin 2,5; 5; and 10 μ g/mL RAW 264.7 [stimulated with 1 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow ~ Kim et al., 2018[35] Isorhamnetin 50, 100, and 200 μ M BV2 stimulated with 100 ng/mL LPS PGE2 \downarrow ~ TNF- α , IL-1 β , COX-2, Li et al., 2016[36] Isorhamnetin 0.25; 0.5; and 1 nM RAW 264.7 [stimulated with 4 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow ~ Qi et al., 2018[37] Isorhamnetin 10, 20, and 40 μ M HGF [stimulated with 1 \$\mu\$ g/mL LPS](#) IL-6, IL-8, PGE2 \downarrow ~ Fan et al., 2017[38] Hyperoside 2,5; 5; 10; and 20 μ M 20 μ M BV2 stimulated with 100 ng/mL LPS Primary microglial cells stimulated with 100 ng/mL LPS TNF- α , IL-1 β \downarrow ~ TNF- α , IL-1 β \downarrow Jin et al., 2016[39] Hyperoside 10, 50, 100 μ mol/l Human FLS [stimulated with 1 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow ~ Zhou et al., 2018[40] Hyperoside 10, 20, and 50 μ mol/l HUVEC [stimulated with 1 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow ~ Lee et al., 2012[41] Rutin 2,5; 5; 25; 50; and 100 μ M HUVEC [stimulated with 100 ng/mL LPS](#) TNF- α \downarrow ~ Li et al., 2016[42] Quercitrin 0.1–0.5 mmol RAW 264.7 [stimulated with 10 \$\mu\$ g/mL LPS TNF- \$\alpha\$, IL-6](#) \downarrow ~ Park et al., 2018[43] Tamarixetin 6,25; 12,5; and 25 μ M 25 μ M BMDC stimulated with 50 ng/mL LPS • TNF- α , IL-6, IL-12p70 \downarrow ~ • IL-10 \uparrow ~ - Tang et al., 2019[44] Boesch-Saadatmandi et al., 2011[45] Park et al., 2016[46] Mrvova et al., 2015[47] Quercetin Quercitrin Quercetin Isorhamnetin Quercetin -3-glucuronide Quercetin Quercetin-3-O - β -D- Glucuronide Quercetin pivaloyl ester Quercetin 0,03–3 μ g/mL 0,045– 4,5 μ g/mL 10 μ mol/l 10 and 50 μ M 10, 50, and 100 μ M 10 and 25 μ mol/l RAW 264.7 stimulated with 2 μ g/mL LPS [RAW 264.7 stimulated with 10 ng/mL LPS](#) [RAW 264.7 stimulated with 200 ng/mL LPS](#) BV-2 stimulated with 10 μ g/mL LPS [TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow [TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) \downarrow [TNF- \$\alpha\$, IL-1 \$\beta\$, IL-6](#) # PGE2 \downarrow [TNF- \$\alpha\$](#) , COX-2, • COX-2, PGE2 \downarrow with lower extent than quercetin • TNF- α # TNF- α \downarrow with more profound effect than quercetin - - - - - mmu-miR-146a, mmu-miR-155, mmu-miR-187 \uparrow - mmu-miR-155 \downarrow mmu-miR-155# - - 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 \uparrow = up-regulated, \downarrow = down-regulated, * = not statistically significant, # = unchanged, ~ = in a dose-dependent manner, RAW 264.7: Murine macrophages, IPEC-J2: Intestinal porcine enterocyte cells-jejunum 2, WT: wild type, UC: Ulcerative colitis, BV2: Microglia cell, BMDC: Bone marrow dendritic cell, SHSY-5Y: Human neuroblastoma cell, FLS: Fibroblast-like synoviocyte, HK-2: Human kidney 2, H9c2: Rat cardiomyoblast, HUVEC: Human umbilical vein endothelial, HGF: Human gingival fibroblast, BALF: Bronchoalveolar lavage fluid, IPF: Idiopathic pulmonary fibrosis, WI-38: Human embryonic lung fibroblast, HOK: Human oral keratinocyte, PBMC: Peripheral blood mononuclear cell effects of quercetin on miRNAs in humans. Therefore, the authors narrowed this systematic review to only reviewed in vivo and in vitro/ex vivo studies that use LPS to induce the inflammatory

models. Although various cells and animals were used, the inflammatory models of all studies used LPS to induce inflammatory conditions into cell lines or animals. LPS is an endotoxin that can trigger an inflammatory response.[66] The pathway of inflammation induction by LPS in experimental animals is similar to that in humans, where the presence of an LPS protein-binding complex attached to the CD14 and Paramabodhi, [et al.: Effects of quercetin and its derivatives on](#) MicroRNAs Table 2: Summary of in vivo studies about the effects of quercetin and its derivates on inflammatory mediators and miRNAs Citations Quercetin Dose/s Animal and model Expression of Expression type inflammatory of miRNAs mediators JBI's Critical Appraisal Score Boesch- Saadatmandi et al., 2011[45] Boesch- Saadatmandi et al., 2012[48] Chang et al., 2013[14] Huang et al., 2015[49] Lee et al., 2020[50] Li et al., 2020[51] Lin et al., 2020[52] Takashima et al., 2014[25] Tiboc-Schnell et al., 2020[53] Wang et al., 2018[54] Wei et al., 2018[55] Yu et al., 2013[56] Chi et al., 2016[34] Li et al., 2016[36] Yang et al., 2016[57] Khajevand-Khazaei et al., 2018[58] Park et al., 2018[43] Liao et al., 2015[59] Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Quercetin Isorhamnetin Isorhamnetin Rutin Tamarixetin Quercetin Quercetin-3 - glucuronide 0,1 mg/g diet 0,2 and 2 mg/g diet 10 and 100 mg/ kg BW, 10 weeks 1, 10, 50, and 100 [mg/kg BW, single dose 50 mg/kg BW](#) 10, 50, and 100 mg/kg BW Not mentioned 30, 90, and 150 mg/kg BW 10 µM 80 mg/kg BW 25 and [50 mg/kg BW](#) 50 [mg/kg BW 0,5](#); 1; and 2 [mg/kg BW](#) 30 and 60 [mg/kg BW](#) 6, 12, and 24 nM 60 [mg/kg BW](#) 50 and [200 mg/kg BW](#) 1 [mg/kg BW 0,06](#) and 0,15 µmol Female C57BL/6 mice Female C57BL/6J mice Male C57BL/6J mice administered 10 mg/kg BW LPS Sprague-Dawley rats administered 100 µg/kg BW LPS Male Sprague-Dawley rat administered 5 µL LPS Pregnant rat administered 1 µg/kg BW LPS Pregnant BALB/c mice administered 50 µg/kg BW LPS Mice administered 1,25 µg LPS Female Wistar rat administered 5 and 10 µg LPS Male C57/B6 mice administered 2 mg/kg LPS Male BALB/c mice administered 20 mg/kg BW LPS Male New Zealand white rabbits administered 100 µg/kg LPS Male BALB/c mice administered 20 mg/kg BW LPS Male BALB/c mice administered 10 µg LPS Male BALB/c mice administered 3 mg/kg BW LPS Female C57BL/6 mice administered 10 mg/kg BW LPS BALB/c mice administered 10 mg/kg BW LPS Female BALB/c mice administered 8 mg/kg BW LPS TNF-α ↓ IL-6 ↓ ~ TNF-α, IL-1β # TNF-α, IL-1β ↓ ~ TNF-α, IL-6 ↓ • IL-1β, IL-6, COX-2 ↓ • TNF-α ↓ * TNF-α, IL-6 ↓ • IL-6, IL-1β, IL-12, COX-2 ↓ • TNF-α ↓ * • IL-10, IL-13 # TNF-α, IL-1β, IL-6 ↓ • TNF-α, IL-1β, IL-6 ↓ • IL-1α, IL-10, COX-2 ↓ * [TNF-α, IL-1β, IL-6 ↓ TNF-α, IL-1β ↓ TNF-α ↓ ~ TNF-α, IL-1β, IL-6 ↓ ~ TNF-α, IL-1β, IL-6 ↓ ~ TNF-α, IL-1β, COX-2 ↓ COX-2 ↓ ~ TNF-α, IL-6, • TNF-α, IL-6 ↓ • IL-10 ↑ IL-10 ↑ IL-10 ↑ *](#) - mmu-miR- 122, mmu-miR- 125b ↑ ~ - - - - - 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 7/9 ↑ = up-regulated, ↓ = down-regulated, * = not statistically significant, # = unchanged, ~ = [in a dose-dependent manner](#) Figure 2: The extracted data [of](#) this systematic review of LPS administration Figure 3: Role of miRNAs on inflammatory mediator's regulations TLR4 receptors then proceeds with signal transduction of signaling pathways that stimulate [inflammatory cells, such as monocytes, macrophages](#), polymorphonuclear, [and](#) endothelial cells to produce inflammatory cytokines, such as TNF, IL-1, and IL-6.[67] The most frequently used cell is RAW 264.7, the murine macrophage, presumably because macrophage cells are the typical cells that become the source of inflammatory cytokines production.[14,68] In addition, several studies are using human cell lines. In general, there were no differences in the results of the effects of quercetin or its derivatives between studies using human cells and animal cells, presumably because mammalian cell lines are able to produce complex proteins through post-translational modification, such as glycosylation, with

the same mechanism in humans so that they have similar expression systems.[69] There were no differences in inflammatory mediators between animal cells and human cells. However, the different types of miRNAs were seen in the extracted data because miRNAs sequences differ between various species, which is hypothesized to be the case.[70,71] Based on the data obtained in this systematic review, quercetin and its derivatives down-regulate the inflammatory mediators, such as IL-1 α , IL-1 β , IL-2, IL6, IL-8, IL-12, TNF- α , COX-2, and PGE2. However, there is a discrepancy in IL-10 expression due to differences in experimental design between in vitro and in vivo. It has been reviewed and known that IL-10 expression is regulated in a contextualized manner, meaning that the regulation mechanism of IL-10 expression depends on various factors, such as the stimulus, location, and cell type. Factors regarding IL-10 production under local or systemic conditions, tissue specificity, and individual genetic variation also need to be considered in looking at IL-10 regulation. These factors may influence the strength and duration of IL-10 signaling.[72] In addition, IL-10 can stimulate the immune response, including inflammation. However, in some contexts, it can reduce the occurrence of the immune response.[73] Assuming IL-10 as an anti-inflammatory cytokine, its expression is expected to increase when suppressing the inflammatory response. IL-10 has been known to have pleiotropic action as a cytokine synthesis inhibitory factor.[73] IL-10 overexpression has been reported to potentially ameliorate inflammatory bowel disease in a study using an animal model of colitis.[74] IL-10 has also been studied for its beneficial effects on rheumatoid arthritis.[75] Altogether, these suggest that the [effects of quercetin and its derivatives](#) administration in vitro [and in vivo](#) on IL-10 expression remain unclear and need further investigation. Concerning the quercetin administration strategies, the time of quercetin administration affects the inflammatory mediator's regulation. TNF- α and IL-1 β expressions decreased when administered acutely with quercetin but had no effect when given chronically. TNF- α and IL-1 β cytokines formed immediately within the inflammatory response, which causes a short therapeutic window for treatment. Therefore, acute administration of quercetin to treat inflammation is more effective and efficient than chronic administration.[24] [There is much controversy regarding quercetin's purported toxic or even mutagenic properties.](#) Regarding the safety of [quercetin](#), it was reported that quercetin has mutagenicity and genotoxicity in vitro. However, quercetin was reported consistently as not mutagenic/carcinogenic in vivo.[76,77] Although it is believed that administration of quercetin at a typical dosage could unlikely cause any adverse effects, oral quercetin administration reported [gastrointestinal effects such as nausea and rare reports of headache and mild tingling of the extremities. Oral quercetin is generally well tolerated. Intravenous quercetin has been associated with nausea, vomiting, diaphoresis, flushing, and dyspnea. Quercetin has been shown to cause chromosomal mutations in certain bacteria in test tube studies.](#) Nevertheless, [the significance of this finding for humans is unclear because of the lack of the availability of long-term safety data. Quercetin should be avoided by pregnant women and nursing mothers.](#)[78] Based on the type of derivative, data indicate that isorhamnetin, rutin, hyperoside, quercitrin, and tamarixetin can affect the expressions of inflammatory mediators with similar effects to quercetin. The data show that isorhamnetin and tamarixetin, but not [quercetin-3-glucuronide and quercetin-3-O- \$\beta\$ -glucuronide](#), could significantly reduce the expressions of inflammatory genes. Isorhamnetin and tamarixetin are members of methylated quercetin. The data suggest that quercetin methylation does not change the biological properties of quercetin. In contrast, glucuronidation, which masks essential [hydroxyl groups of the quercetin molecule](#), would change [and](#) decrease [the](#) biological properties of

its parent compound.[22] Hyperoside, quercitrin, rutin, [quercetin-3-glucuronide, and quercetin-3-O-β-glucuronide](#) are quercetin glycosides. In general, quercetin glycosides should exhibit more excellent anti-inflammatory and immune-enhancement effects than other forms of quercetin.[13] Nevertheless, this systematic review demonstrated that one quercetin glycoside compound could have different bioactivities than other quercetin glycosides. This difference agrees with the previous review[9] and is most likely because quercetin glycosides have absorption variation depending on the sugar types and the sugar group's conjugation sites. Furthermore, one study reported on quercetin pivaloyl ester, a synthetic quercetin derivative, which can reduce TNF-α expression with a more significant reduction effect than quercetin. It was hypothesized that quercetin pivaloyl ester has a more efficient permeability across membranes, resulting in higher bioavailability. [41] According to the discussion above, the molecular structure of quercetin and its derivatives may alter their permeability, metabolism, and bioavailability, all of which impact their chemical, physical, and biological properties. The current systematic review has demonstrated that the bioactivities of quercetin derivatives in modulating inflammatory mediators depend on the types and structures of the compounds examined. Although the biological function of miRNAs has not been fully elucidated, there is a growing body of evidence indicating that the miRNAs pathways are a novel mechanism of genes regulation in normal and pathologic conditions, suggesting that research into miRNAs biogenesis and function could provide new insights into gene functional studies and drug development.[79] Based on the data obtained in this systematic review, quercetin and its derivatives can increase or decrease miRNAs expressions. The ability of quercetin or its derivatives to modulate miRNAs expressions is presumably because polyphenols, including quercetin, can modulate miRNAs transcription by influencing transcription factors c-Myc and p53, which are miRNAs gene promoters.[17,80] The p53 protein is an activator of miRNAs transcription promoters, while Myc can be an activator or suppressor of different miRNAs transcriptional promoters.[81] Furthermore, the data also suggest that miRNAs play a role in regulating the expressions of inflammatory mediators. A single miRNA can either positively or negatively regulate multiple targets. A positive regulator indicates that the increase of miRNA will cause the inflammatory mediator to increase, whereas the decrease of miRNA will cause the inflammatory mediator to decrease. Meanwhile, a negative regulator indicates that upregulation or downregulation of miRNA will have an opposite effect on the inflammatory mediator expressions. MiRNAs regulate their target depending on 3' Untranslated Region (UTR), leading to decreased gene expression through translational inhibition and/or mRNA degradation. On the other hand, miRNAs that interact with 5'UTR will stimulate or activate gene transcription and protein translation.[82] Interestingly, the opposite results regarding [the effects of quercetin and its derivatives on](#) miR-146a expression [have been](#) reported. Downregulation of bta-miR-146a has been reported following in vivo administration of quercetin;[28] meanwhile, mmu-miR-146a increased after in vitro administration of tamarixetin.[64] There is also conflicting result found in the included studies relating to [the effects of quercetin and its derivatives on](#) miR-155 expression. Tamarixetin was reported to increase the expression of mmu-miR-155, causing an increase in IL-10 expression so that it can ultimately suppress the expressions of other pro-inflammatory cytokines.[64] However, in another study, quercetin and isorhamnetin were reported to downregulate mmu-miR-155 expression, associated with inhibition of NF-κB activation, thereby providing an anti-inflammatory effect.[22] The discrepancies in miR-146a expression may be due to the different sequences between bta-miR-146a and mmu-miR-146a. It is also assumed that the differences between quercetin, isorhamnetin, and

tamarixetin bioactivities give different results on the expressions of miR-146a and miR-155. Anti-inflammatory mechanisms involving quercetin and its derivatives on miR- 146a and miR-155 expressions remain unclear; consequently, there needs to be more research to understand their role in the treatment of inflammatory conditions. This systematic review has a limitation; it discussed in vivo and in vitro studies of various inflammatory conditions using various types of cells or animal models induced by LPS but did not discuss the association of cellular signaling pathways. Therefore, further investigations need to discuss [the effects of quercetin and its derivatives on other inflammation](#) models and the involvement of cellular signaling pathways in anti-inflammatory mechanisms. In addition, further studies regarding [the effects of quercetin and its derivatives on IL-10, miR-146a, and miR-155 expressions in inflammatory conditions](#) are needed. To the authors' knowledge, [this systematic review is the first](#) to illustrate [that quercetin](#) and its derivatives have anti- inflammatory actions by reducing or enhancing the miRNAs expressions and discuss how miRNAs may act as either positive or negative regulators of inflammatory mediators expressions.

CONCLUSION
This systematic review concludes that in vivo and in vitro/ex vivo administration of quercetin and its derivatives suppressed inflammatory responses by down-regulating inflammatory mediators expressions unless the expression of IL-10 is inconsistent. The bioactivities of quercetin derivatives in modulating inflammatory mediators are highly dependent on their types and structures. Quercetin and its derivatives can upregulate the anti-inflammatory and down-regulate the pro- inflammatory miRNAs. Moreover, miRNAs act as a positive or negative regulator that causes a decrease in the expressions of inflammatory mediators under inflammatory conditions.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.

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