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

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

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, Study Program of Pharmacy, Diponegoro University, Jl. Prof. H. Soedarto S.H., Semarang 50275, Indonesia.
E-mail: widyandani.sasikirana@live.undip.ac.id

Received: January 06, 2022
Accepted: July 16, 2022
Published: March 29, 2023

ABSTRACT

Quercetin has been known to have anti-inflammatory effects. Information regarding the anti-inflammatory effects of quercetin or its derivatives on inflammatory mediators and microRNAs (miRNAs) is abundant and varied. However, a comprehensive understanding of its pharmacological actions at the cellular and molecular levels needs to be studied. Therefore, quercetin and its derivatives were studied in this systematic review to investigate how they affect the expressions of miRNAs and inflammatory mediators and their respective roles in the mechanisms of anti-inflammatory actions. A literature search in PubMed and Scopus databases was carried out 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

Inflammation 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

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-ɣ, and IL-6, and is resolved by anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, IFN-α, and TGF-β.[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 derivates), 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

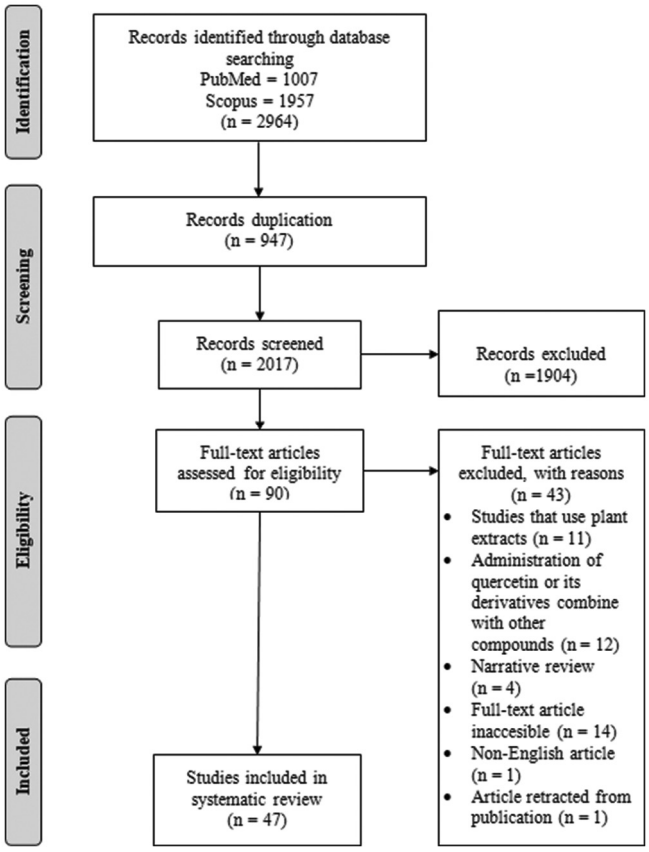

Figure 1: Flow Chart of study selection in this study.

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 PGE_2. 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-1α, IL-1β, IL-2, IL6, IL-8, IL-12, TNF-α, COX-2, and PGE_2[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 246.7 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-1β, IL6, IL-8, IL-12, TNF-α, COX-2, and PGE_2, 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-1β, 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-1β, 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 derivates on inflammatory mediators and miRNAs

First author, year, citations	Quercetin type	Dose/s	Cell line and model	Expression of inflammatory mediators	Expression of miRNAs	JBI's critical appraisal score
Chang *et al.*, 2013[14]	Quercetin	15, 30, and 60 μM	RAW 264.7 stimulated with 100 ng/mL LPS	TNF-α, IL-1β ↓∼	-	7/9
Chen *et al.*, 2018[15]	Quercetin	1,25; 2,5; and 5 μg/mL	IPEC-J2 stimulated with 10 μg/mL LPS	IL-6, IL-8 ↓	-	7/9
Chuammitri *et al.*, 2015[16]	Quercetin	50 μM	Bovine neutrophil stimulated with 100 ng/mL LPS	TNF-α, IL-1β ↓	-	7/9
Chuammitri *et al.*, 2017[17]	Quercetin	50 μM	Bovine neutrophil stimulated with 100 ng/mL LPS	TNF-α, IL-1β, IL-6 ↓	bta-miR-24-2, bta-miR-146a, bta-miR-181c↓bta-miR-Let-7e bta-miR-17 ↑	7/9
Dicarlo *et al.*, 2019[18]	Quercetin	25 μM	WT and UC organoids stimulated with 1 μM LPS	TNF-α ↓	-	7/9
Endale *et al.*, 2013[19]	Quercetin	2,5; 5; 10; and 20 μM 5, 10, and 20 μM	RAW 264.7 stimulated with 100 ng/mL LPS	TNF-α, IL-1β, IL-6, COX-2 ↓∼ TNF-α, IL-1β, IL-6, PGE_2 ↓∼	-	7/9
Galleggiante *et al.*, 2019[3]	Quercetin	25 μM	BMDC stimulated with 1 μg/mL LPS	TNF-α, IL-6 ↓	mmu-miR-369–3p ↑	7/9
Guo *et al.*, 2012[20]	Quercetin	5, 10, 15, 20, and 50 μM	RAW 264.7 stimulated with 100 ng/mL LPS	COX-2 ↓∼	-	7/9
Guo *et al.*, 2020[21]	Quercetin	20 μM	HK-2 stimulated with 2 μg/mL LPS	TNF-α, IL-1β ↓	hsa-miR-124 ↑	7/9
Gutierrez-venegaz *et al.*, 2017[22]	Quercetin	10 μM	H9c2 stimulated with 1 μg/mL LPS	COX-2 ↓	-	7/9
Kang *et al.*, 2020[23]	Quercetin	1 μg/mL	SHSY-5Y stimulated with 100 ng/mL LPS BV2 stimulated with 100 ng/mL LPS	TNF-α, IL-1β, IL-6 ↓	-	7/9
Lee *et al.*, 2017[24]	Quercetin	6,25; 12,5; and 25 μM	RAW 264.7 stimulated with 1 μg/mL LPS	• IL-6 ↓∼ • TNF-α, COX-2#	-	7/9
Takashima *et al.*, 2014[25]	Quercetin	10 μM	BALF stimulated with 5 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓	-	7/9
Veith *et al.*, 2017[26]	Quercetin	1, 3, and 30 μM	IPF patients' blood plasma stimulated with LPS	TNF-α, IL-8 ↓∼	-	7/9
Wang *et al.*, 2019[27]	Quercetin	40 μM	WI-38 stimulated with LPS	TNF-α, IL-6 ↓	hsa-miR-221 ↓	7/9
Wang *et al.*, 2020[28]	Quercetin	100 μM	HOK stimulated with 100 ng/mL LPS	-	hsa-miR-22 ↓	7/9
Xiao *et al.*, 2020[29]	Quercetin	5, 10, and 20 μM	WI-38 stimulated with 100 ng/mL LPS	IL-6, IL-8 ↓∼	-	7/9
Xiong *et al.*, 2019[30]	Quercetin	5, 10, and 20 μM	HGF stimulated with 1 μg/mL LPS	TNF-α, IL-1β, IL-6, IL-8 ↓∼	-	7/9
Xue *et al.*, 2017[31]	Quercetin	20 μM	RAW 264.7 stimulated with 500 ng/mL LPS	IL-1α, IL-1β, IL-2, IL-10, COX-2↓	-	7/9
Zhang *et al.*, 2016[32]	Quercetin	25, 50, and 100 μM	Human PBMC stimulated with 10 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Chen *et al.*, 2021[33]	Isorhamnetin	200 μmol/l	BV2 stimulated with 1 μg/mL LPS	TNF-α, IL-1β ↓	-	7/9

(Contd...)

Table 1: *(Continued)*

First author, year, citations	Quercetin type	Dose/s	Cell line and model	Expression of inflammatory mediators	Expression of miRNAs	JBI's critical appraisal score
Chi *et al.*, 2016[34]	Isorhamnetin	2,5; 5; and 10 μg/mL	RAW 264.7 stimulated with 1 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Kim *et al.*, 2018[35]	Isorhamnetin	50, 100, and 200 μM	BV2 stimulated with 100 ng/mL LPS	TNF-α, IL-1β, COX-2, PGE_2 ↓∼	-	7/9
Li *et al.*, 2016[36]	Isorhamnetin	0.25; 0.5; and 1 nM	RAW 264.7 stimulated with 4 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Qi *et al.*, 2018[37]	Isorhamnetin	10, 20, and 40 μM	HGF stimulated with 1 μg/mL LPS	IL-6, IL-8, PGE_2↓∼	-	7/9
Fan *et al.*, 2017[38]	Hyperoside	2,5; 5; 10; and 20 μM	BV2 stimulated with 100 ng/mL LPS	TNF-α, IL-1β ↓∼	-	7/9
		20 μM	Primary microglial cells stimulated with 100 ng/mL LPS	TNF-α, IL-1β ↓	-	
Jin *et al.*, 2016[39]	Hyperoside	10, 50, 100 μmol/l	Human FLS stimulated with 1 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Zhou *et al.*, 2018[40]	Hyperoside	10, 20, and 50 μmol/l	HUVEC stimulated with 1 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Lee *et al.*, 2012[41]	Rutin	2,5; 5; 25; 50; and 100 μM	HUVEC stimulated with 100 ng/mL LPS	TNF-α ↓∼	-	7/9
Li *et al.*, 2016[42]	Quercitrin	0.1–0.5 mmol	RAW 264.7 stimulated with 10 μg/mL LPS	TNF-α, IL-6 ↓∼	-	7/9
Park *et al.*, 2018[43]	Tamarixetin	6,25; 12,5; and 25 μM	BMDC stimulated with 50 ng/mL LPS	• TNF-α, IL-6, IL-12p70 ↓∼ • IL-10 ↑∼	-	7/9
		25 μM		-	mmu-miR-146a, mmu-miR-155, mmu-miR-187 ↑	
Tang *et al.*, 2019[44]	Quercetin Quercitrin	0,03–3 μg/mL 0,045–4,5 μg/mL	RAW 264.7 stimulated with 2 μg/mL LPS	TNF-α, IL-1β, IL-6 ↓	-	7/9
Boesch-Saadatmandi *et al.*, 2011[45]	Quercetin Isorhamnetin	10 μmol/l	RAW 264.7 stimulated with 10 ng/mL LPS	TNF-α, IL-1β, IL-6 ↓	mmu-miR-155↓	7/9
	Quercetin -3-glucuronide			TNF-α, IL-1β, IL-6 #	mmu-miR-155#	
Park *et al.*, 2016[46]	Quercetin	10 and 50 μM	RAW 264.7 stimulated with 200 ng/mL LPS	TNF-α, COX-2, PGE_2 ↓	-	7/9
	Quercetin-3-O -β-D-Glucuronide	10, 50, and 100 μM		• COX-2, PGE_2↓with lower extent than quercetin • TNF-α #		
Mrvova *et al.*, 2015[47]	*Quercetin pivaloyl ester* Quercetin	10 and 25 μmol/l	BV-2 stimulated with 10 μg/mL LPS	TNF-α ↓ with more profound effect than quercetin	-	7/9

↑ = up-regulated, ↓ = 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 umblical vein endothelial, HGF: Human gingival fibroblast, BALF: Bronchoalveolal 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

Table 2: Summary of *in vivo* studies about the effects of quercetin and its derivates on inflammatory mediators and miRNAs

Citations	Quercetin type	Dose/s	Animal and model	Expression of inflammatory mediators	Expression of miRNAs	JBI's Critical Appraisal Score
Boesch-Saadatmandi *et al*., 2011[45]	Quercetin	0,1 mg/g diet	Female C57BL/6 mice	TNF-α ↓	-	7/9
Boesch-Saadatmandi *et al*., 2012[48]	Quercetin	0,2 and 2 mg/g diet	Female C57BL/6J mice	IL-6 ↓∼	mmu-miR-122, mmu-miR-125b ↑∼	7/9
Chang *et al*., 2013[14]	Quercetin	10 and 100 mg/kg BW, 10 weeks 1, 10, 50, and 100 mg/kg BW, single dose	Male C57BL/6J mice administered 10 mg/kg BW LPS	TNF-α, IL-1β # TNF-α, IL-1β↓∼	-	7/9
Huang *et al*., 2015[49]	Quercetin	50 mg/kg BW	Sprague-Dawley rats administered 100 μg/kg BW LPS	TNF-α, IL-6 ↓	-	7/9
Lee *et al*., 2020[50]	Quercetin	10, 50, and 100 mg/kg BW	Male *Sprague-Dawley* rat administered 5 μL LPS	• IL-1β, IL-6, COX-2 ↓ • TNF-α ↓*	-	7/9
Li *et al*., 2020[51]	Quercetin	Not mentioned	Pregnant rat administered 1 μg/kg BW LPS	TNF-α, IL-6 ↓	-	7/9
Lin *et al*., 2020[52]	Quercetin	30, 90, and 150 mg/kg BW	Pregnant BALB/c mice administered 50 μg/kg BW LPS	• IL-6, IL-1β, IL-12, COX-2 ↓ • TNF-α ↓* • IL-10, IL-13 #	-	7/9
Takashima *et al*., 2014[25]	Quercetin	10 μM	Mice administered 1,25 μg LPS	TNF-α, IL-1β, IL-6 ↓	-	7/9
Tiboc-Schnell *et al*., 2020[53]	Quercetin	80 mg/kg BW	Female Wistar rat administered 5 and 10 μg LPS	• TNF-α, IL-1β, IL-6 ↓ • IL-1α, IL-10, COX-2 ↓*	-	7/9
Wang *et al*., 2018[54]	Quercetin	25 and 50 mg/kg BW	Male C57/B6 mice administered 2 mg/kg LPS	TNF-α, IL-1β, IL-6 ↓	-	7/9
Wei *et al*., 2018[55]	Quercetin	50 mg/kg BW	Male BALB/c mice administered 20 mg/kg BW LPS	TNF-α, IL-1β ↓	-	7/9
Yu *et al*., 2013[56]	Quercetin	0,5; 1; and 2 mg/kg BW	Male *New Zealand* white rabbits administered 100 μg/kg LPS	TNF-α ↓∼	-	7/9
Chi *et al*., 2016[34]	Isorhamnetin	30 and 60 mg/kg BW	Male BALB/c mice administered 20 mg/kg BW LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Li *et al*., 2016[36]	Isorhamnetin	6, 12, and 24 nM	Male BALB/c mice administered 10 μg LPS	TNF-α, IL-1β, IL-6 ↓∼	-	7/9
Yang *et al*., 2016[57]	Isorhamnetin	60 mg/kg BW	Male BALB/c mice administered 3 mg/kg BW LPS	TNF-α, IL-1β, COX-2 ↓	-	7/9
Khajevand-Khazaei *et al*., 2018[58]	Rutin	50 and 200 mg/kg BW	Female C57BL/6 mice administered 10 mg/kg BW LPS	TNF-α, IL-6, COX-2 ↓∼	-	7/9
Park *et al*., 2018[43]	Tamarixetin	1 mg/kg BW	BALB/c mice administered 10 mg/kg BW LPS	• TNF-α, IL-6 ↓ • IL-10 ↑	-	7/9
Liao *et al*., 2015[59]	Quercetin *Quercetin-3 -glucuronide*	0,06 and 0,15 μmol	Female BALB/c mice administered 8 mg/kg BW LPS	IL-10 ↑ IL-10 ↑*	-	7/9

↑ = up-regulated, ↓ = down-regulated, * = not statistically significant, # = unchanged, ∼ = in a dose-dependent manner

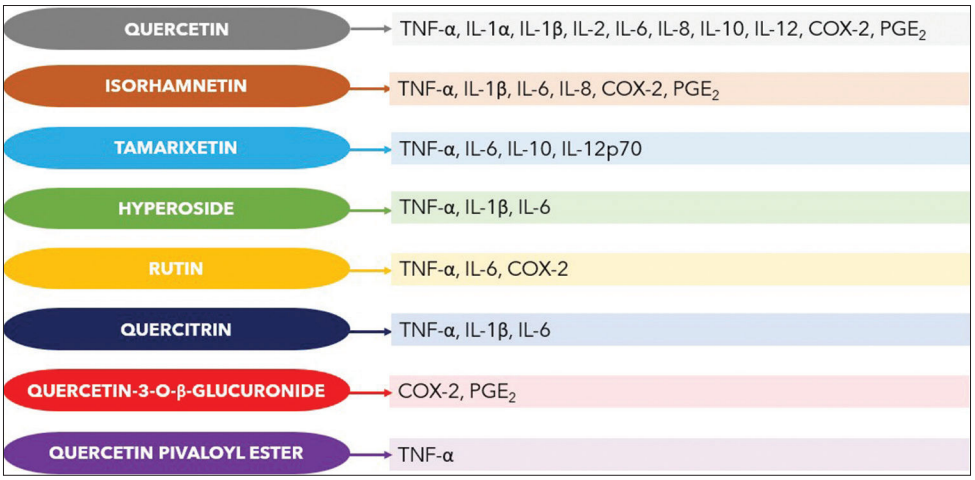

Figure 2: The extracted data of this systematic review of LPS administration

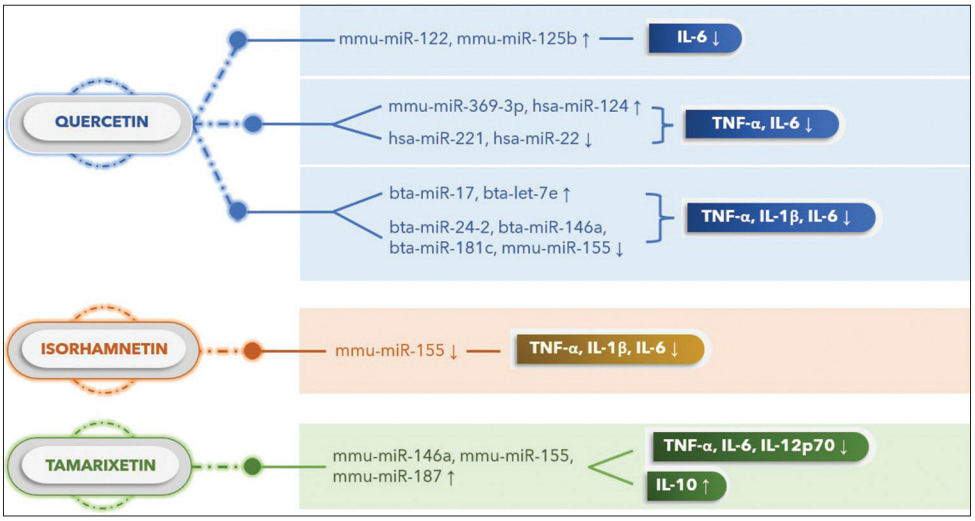

Figure 3: Role of miRNAs on inflammatory mediator's regulations

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-1α, IL-1β, IL-2, IL6, IL-8, IL-12, TNF-α, COX-2, and PGE_2. 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-1β expressions decreased when administered acutely with quercetin but had no effect when given chronically. TNF-α and IL-1β 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-β-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.

REFERENCES

1. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: Importance of NOD2 and NALP3 in interleukin-1beta generation. Clin Exp Immunol 2007;147:227-35.
2. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, *et al*. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2018;9:7204-18.
3. Carullo G, Cappello AR, Frattaruolo L, Badolato M, Armentano B, Aiello F. Quercetin and derivatives: Useful tools in inflammation and pain management. Chimia (Aarau) 2016;71:643.
4. Sugimoto MA, Sousa LP, Pinho V, Perretti M, Teixeira MM. Resolution of inflammation: What controls its onset? Front Immunol 2016;7:160.
5. De Cássia da Silveira e Sá R, Andrade LN, de Sousa DP. A review on anti-inflammatory activity of monoterpenes. Molecules 2013;18:1227-54.
6. Pahlavani N, Sedaghat A, Moghaddam AB, Kiapey SS, Navashenaq JG, Jarahi L, *et al.* Effects of propolis and melatonin on oxidative stress, inflammation, and clinical status in patients with primary sepsis: Study protocol and review on previous studies. Clin Nutr ESPEN 2019;33:125-31.
7. Hadi V, Pahlavani N, Malekahmadi M, Nattagh-Eshtivani E, Navashenaq JG, Hadi S, *et al*. *Nigella sativa* in controlling Type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases: Molecular aspects. J Res Med Sci 2021;26:20.
8. Zeng Y, Li Y, Yang J, Pu X, Du J, Yang X, *et al.* Therapeutic role of functional components in alliums for preventive chronic disease in human being. Evid Based Complement Alternat Med 2017;2017:9402849.
9. Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, *et al*. Quercetin, inflammation and immunity. Nutrients 2016;8:167.
10. Khan F, Niaz K, Maqbool F, Hassan FI, Abdollahi M, Venkata KC, *et al*. Molecular targets underlying the anticancer effects of quercetin: An update. Nutrients 2016;8:529.
11. Batiha GE, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, *et al*. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin. Foods 2020;9:374.
12. Kordkheyli VA, Tarsi AK, Mishan MA, Tafazoli A, Bardania H, Zarpou S, *et al*. Effects of quercetin on microRNAs: A mechanistic review. J Cell Biochem 2019;120:12141-55.
13. Wang D, Sun-Waterhouse D, Li F, Xin L, Li D. MicroRNAs as molecular targets of quercetin and its derivatives underlying their biological effects: A preclinical strategy. Crit Rev Food Sci Nutr 2019;59:2189-201.
14. Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed. Philadelphia, PA: Elsevier Saunders; 2013.
15. Harper KA, Tyson-Capper AJ. Complexity of COX-2 gene regulation. Biochem Soc Trans 2008;36:543-5.
16. Hirschberger S, Hinske LC, Kreth S. MiRNAs: Dynamic regulators of immune cell functions in inflammation and cancer. Cancer Lett 2018;431:11-21.
17. Kim DH, Khan H, Ullah H, Hassan ST, Šmejkal K, Efferth T, *et al*. MicroRNA targeting by quercetin in cancer treatment and chemoprotection. Pharmacol Res 2019;147:104346.
18. Chakraborty C, Sharma AR, Sharma G, Lee SS. The interplay among miRNAs, major cytokines, and cancer-related inflammation. Mol Ther Nucleic Acids 2020;20:606-20.
19. Yoshimura A, Mori H, Ohishi M, Aki D, Hanada T. Negative regulation of cytokine signaling influences inflammation. Curr Opin Immunol 2003;15:704-8.
20. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:
21. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Systematic reviews of effectiveness. In: Joanna Briggs Institute Reviewer's Manual. South Australia: Joanna Briggs Institute; 2017. p. 3.
22. Boesch-Saadatmandi C, Loboda A, Wagner AE, Stachurska A, Jozkowicz A, Dulak J, *et al*. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: Role of miR-155. J Nutr Biochem 2011;22:293-9.
23. Boesch-Saadatmandi C, Wagner AE, Wolffram S, Rimbach G. Effect of quercetin on inflammatory gene expression in mice liver *in vivo* - role of redox factor 1, miRNA-122 and miRNA-125b. Pharmacol Res 2012;65:523-30.
24. Chang YC, Tsai MH, Sheu WH, Hsieh SC, Chiang AN. The therapeutic potential and mechanisms of action of quercetin in relation to lipopolysaccharide-induced sepsis *in vitro* and *in vivo*. PLoS One 2013;8:e80744.
25. Chen F, Hu M, Shen Y, Zhu W, Cao A, Ni B, *et al*. Isorhamnetin promotes functional recovery in rats with spinal cord injury by abating oxidative stress and modulating M2 macrophages/microglia polarization. Eur J Pharmacol 2021;895:173878.
26. Chen ZG, Xu GR, Yuan QL, Chen HY, Lei HY, Su JM. Quercetin inhibits porcine intestinal inflammation *in vitro*. Trop J Pharm Res 2018;17:1947-52.
27. Chuammitri P, Amphaiphan C, Nojit P. *In vitro* modulatory effects of quercetin on bovine neutrophil effector functions. Thai J Vet Med 2015;45:63-72.
28. Chuammitri P, Srikok S, Saipinta D, Boonyayatra S. The effects of quercetin on microRNA and inflammatory gene expression in lipopolysaccharide-stimulated bovine neutrophils. Vet World 2017;10:403-10.
29. Dicarlo M, Teti G, Verna G, Liso M, Cavalcanti E, Sila A, *et al*. Quercetin exposure suppresses the inflammatory pathway in intestinal organoids from Winnie mice. Int J Mol Sci 2019;20:5771.

30. Endale M, Park SC, Kim S, Kim SH, Yang Y, Cho JY, *et al*. Quercetin disrupts tyrosine-phosphorylated phosphatidylinositol 3-kinase and myeloid differentiation factor-88 association and inhibits MAPK/AP-1 and IKK/NF-κB-induced inflammatory mediators production in RAW 264.7 cells. Immunobiology 2013;218:1452-67.
31. Galleggiante V, De Santis S, Liso M, Verna G, Sommella E, Mastronardi M, *et al*. Quercetin-induced miR-369-3p suppresses chronic inflammatory response targeting C/EBP-β. Mol Nutr Food Res 2019;63:e1801390.
32. Guo C, Hou GQ, Li XD, Xia X, Liu DX, Huang DY, *et al*. Quercetin triggers apoptosis of lipopolysaccharide (LPS)-induced osteoclasts and inhibits bone resorption in RAW264.7 cells. Cell Physiol Biochem 2012;30:123-36.
33. Guo S, Sun J, Zhuang Y. Quercetin alleviates lipopolysaccharide-induced inflammatory responses by up-regulation miR-124 in human renal tubular epithelial cell line HK-2. Biofactors 2020;46:402-10.
34. Gutiérrez-Venegas G, Torras-Ceballos A, Gómez-Mora JA, Fernández-Rojas B. Luteolin, quercetin, genistein and quercetagetin inhibit the effects of lipopolysaccharide obtained from *Porphyromonas gingivalis* in H9c2 cardiomyoblasts. Cell Mol Biol Lett 2017;22:19.
35. Huang R, Zhong T, Wu H. Quercetin protects against lipopolysaccharide-induced acute lung injury in rats through suppression of inflammation and oxidative stress. Arch Med Sci 2015;2:427-32.
36. Kang S, Piao Y, Kang YC, Lim S, Pak YK. Qi-activating quercetin alleviates mitochondrial dysfunction and neuroinflammation *in vivo* and *in vitro*. Arch Pharm Res 2020;43:553-66.
37. Lee B, Yeom M, Shim I, Lee H, Hahm DH. Protective effects of quercetin on anxiety-like symptoms and neuroinflammation induced by lipopolysaccharide in rats. Evid Based Complement Alternat Med 2020;2020:4892415.
38. Lee HN, Shin SA, Choo GS, Kim HJ, Park YS, Kim BS, *et al*. Anti-inflammatory effect of quercetin and galangin in LPS-stimulated RAW264.7 macrophages and DNCB-induced atopic dermatitis animal models. Int J Mol Med 2017;41:888-98.
39. Li Q, Yin L, Si Y, Zhang C, Meng Y, Yang W. The bioflavonoid quercetin improves pathophysiology in a rat model of preeclampsia. Biomed Pharmacother 2020;127:110122.
40. Lin X, Peng Q, Zhang J, Li X, Huang J, Duan S, *et al*. Quercetin prevents lipopolysaccharide-induced experimental preterm labor in mice and increases offspring survival rate. Reprod Sci 2020;27:1047-57.
41. Mrvová N, Škandík M, Kuniaková M, Račková L. Modulation of BV-2 microglia functions by novel quercetin pivaloyl ester. Neurochem Int 2015;90:246-54.
42. Park JY, Lim MS, Kim SI, Lee HJ, Kim SS, Kwon YS, *et al*. Quercetin-3-O-β-D-glucuronide suppresses lipopolysaccharide-induced JNK and ERK phosphorylation in LPS-challenged RAW264.7 cells. Biomol Ther (Seoul) 2016;24:610-5.
43. Takashima K, Matsushima M, Hashimoto K, Nose H, Sato M, Hashimoto N, *et al*. Protective effects of intratracheally administered quercetin on lipopolysaccharide-induced acute lung injury. Respir Res 2014;15:150.
44. Tang J, Diao P, Shu X, Li L, Xiong L. Quercetin and quercitrin attenuates the inflammatory response and oxidative stress in LPS-induced RAW264.7 cells: *In vitro* assessment and a theoretical model. Biomed Res Int 2019;2019:7039802.
45. Tiboc-Schnell CN, Filip GA, Man SC, Decea N, Moldovan R, Opris R, *et al*. Quercetin attenuates naso-sinusal inflammation and inflammatory response in lungs and brain on an experimental model of acute rhinosinusitis in rats. J Physiol Pharmacol 2020;71:4.
46. Veith C, Drent M, Bast A, van Schooten FJ, Boots AW. The disturbed redox-balance in pulmonary fibrosis is modulated by the plant flavonoid quercetin. Toxicol Appl Pharmacol 2017;336:40-8.
47. Wang C, Qu Z, Kong L, Xu L, Zhang M, Liu J, *et al*. Quercetin ameliorates lipopolysaccharide-caused inflammatory damage via down-regulation of miR-221 in WI-38 cells. Exp Mol Pathol 2019;108:1-8.
48. Wang XF, Song SD, Li YJ, Hu ZQ, Zhang ZW, Yan CG, *et al*. Protective effect of quercetin in LPS-induced murine acute lung injury mediated by cAMP-Epac pathway. Inflammation 2018;41:1093-103.
49. Wei X, Meng X, Yuan Y, Shen F, Li C, Yang J. Quercetin exerts cardiovascular protective effects in LPS-induced dysfunction *in vivo* by regulating inflammatory cytokine expression, NF-κB phosphorylation, and caspase activity. Mol Cell Biochem 2018;446:43-52.
50. Xiao Y, Zhou L, Zhang T, Qin C, Wei P, Luo L, *et al*. Anti-fibrosis activity of quercetin attenuates rabbit tracheal stenosis via the TGF-β/AKT/mTOR signaling pathway. Life Sci 2020;250:117552.
51. Xiong G, Ji W, Wang F, Zhang F, Xue P, Cheng M, *et al*. Quercetin inhibits inflammatory response induced by LPS from *Porphyromonas gingivalis* in human gingival fibroblasts via suppressing NF- κ B signaling pathway. Biomed Res Int 2019;2019:6282635.
52. Xue F, Nie X, Shi J, Liu Q, Wang Z, Li X, *et al*. Quercetin inhibits LPS-induced inflammation and ox-LDL-induced lipid deposition. Front Pharmacol 2017;8:40.
53. Yu PX, Zhou QJ, Zhu WW, Wu YH, Wu LC, Lin X, *et al*. Effects of quercetin on LPS-induced disseminated intravascular coagulation (DIC) in rabbits. Thromb Res 2013;131:e270-3.
54. Zhang M, Lin JM, Li XS, Li J. Quercetin ameliorates LPS-induced inflammation in human peripheral blood mononuclear cells by inhibition of the TLR2-NF-κB pathway. Genet Mol Res 2016;15:2.
55. Liao YR, Lin JY. Quercetin intraperitoneal administration ameliorates lipopolysaccharide-induced systemic inflammation in mice. Life Sci 2015;137:89-97.
56. Chi G, Zhong W, Liu Y, Lu G, Lü H, Wang D, *et al*. Isorhamnetin protects mice from lipopolysaccharide-induced acute lung injury via the inhibition of inflammatory responses. Inflamm Res 2016;65:33-41.
57. Fan HH, Zhu LB, Li T, Zhu H, Wang YN, Ren XL, *et al*. Hyperoside inhibits lipopolysaccharide-induced inflammatory responses in microglial cells via p38 and NFκB pathways. Int Immunopharmacol 2017;50:14-21.
58. Jin XN, Yan EZ, Wang HM, Sui HJ, Liu Z, Gao W, *et al*. Hyperoside exerts anti-inflammatory and anti-arthritic effects in LPS-stimulated human fibroblast-like synoviocytes *in vitro* and in mice with collagen-induced arthritis. Acta Pharmacol Sin 2016;37:674-86.
59. Khajevand-Khazaei MR, Mohseni-Moghaddam P, Hosseini M, Gholami L, Baluchnejadmojarad T, Roghani M. Rutin, a quercetin glycoside, alleviates acute endotoxemic kidney injury in C57BL/6 mice via suppression of inflammation and up-regulation of antioxidants and SIRT1. Eur J Pharmacol 2018;833:307-13.
60. Li Y, Chi G, Shen B, Tian Y, Feng H. Isorhamnetin ameliorates LPS-induced inflammatory response through downregulation of NF-κB signaling. Inflammation 2016;39:1291-301.
61. Li W, Li H, Zhang M, Wang M, Zhong Y, Wu H, *et al*. Quercitrin ameliorates the development of systemic lupus erythematosus-like disease in a chronic graft-versus-host murine model. Am J Physiol Renal Physiol 2016;311:F217-26.
62. Lee W, Ku SK, Bae JS. Barrier protective effects of rutin in LPS-induced inflammation in *vitro* and *in vivo*. Food Chem Toxicol 2012;50:3048-55.
63. Yang B, Li XP, Ni YF, Du HY, Wang R, Li MJ, *et al*. Protective effect of isorhamnetin on lipopolysaccharide-induced acute lung injury in mice. Inflammation 2016;39:129-37.
64. Park HJ, Lee SJ, Cho J, Gharbi A, Han HD, Kang TH, *et al*. Tamarixetin exhibits anti-inflammatory activity and prevents bacterial sepsis by increasing IL-10 production. J Nat Prod 2018;81:1435-43.
65. Qi F, Sun JH, Yan JQ, Li CM, Lv XC. Anti-inflammatory

effects of isorhamnetin on LPS-stimulated human gingival fibroblasts by activating Nrf2 signaling pathway. Microb Pathog 2018;120:37-41.
66. Mayeux PR. Pathobiology of lipopolysaccharide. J Toxicol Environ Health 1997;51:415-35.
67. Da browski MP, Wanda S. Immunostimulatory effects of lipopolysaccharide. Cent Eur J Immunol 2011;36:85-6.
68. Grossman SC, Porth CM. Porth's Pathophysiology. 9th ed. United States: Wolters Kluwer Health; 2014.
69. Dumont J, Euwart D, Mei B, Estes S, Kshirsagar R. Human cell lines for biopharmaceutical manufacturing: History, status, and future perspectives. Crit Rev Biotechnol 2016;36:1110-22.
70. Guo L, Chen F. A challenge for miRNA: Multiple isomiRs in miRNAomics. Gene 2014;544:1-7.
71. Guo L, Zhao Y, Zhang H, Yang S, Chen F. Close association between paralogous multiple isomiRs and paralogous/orthologues miRNA sequences implicates dominant sequence selection across various animal species. Gene 2013;527:624-9.
72. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol 2012;32:23-63.
73. Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. J Exp Med 2020;217:1.
74. Cardoso A, Gil Castro A, Martins AC, Carriche GM, Murigneux V, Castro I, *et al*. The dynamics of interleukin-10-afforded protection during dextran sulfate sodium-induced colitis. Front Immunol 2018;9:400.
75. Galeazzi M, Bazzichi L, Sebastiani GD, Neri D, Garcia E, Ravenni N, *et al*. A phase IB clinical trial with Dekavil (F8-IL10), an immunoregulatory 'armed antibody' for the treatment of rheumatoid arthritis, used in combination wIh methotrexate. Isr Med Assoc J 2014;16:666.
76. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol 2007;45:2179-205.
77. Okamoto T. Safety of quercetin for clinical application (review). Int J Mol Med 2005;16:275-8.
78. Lakhanpal P, Rai DK. Quercetin: A versatile flavonoid. Int J Med Update 2007;2:22-37.
79. Liu Z, Sall A, Yang D. MicroRNA: An emerging therapeutic target and intervention tool. Int J Mol Sci 2008;9:978-99.
80. Milenkovic D, Jude B, Morand C. miRNA as molecular target of polyphenols underlying their biological effects. Free Radic Biol Med 2013;64:40-51.
81. Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. Nat Rev Genet 2010;11:597-610.
82. Breving K, Esquela-Kerscher A. The complexities of microRNA regulation: Mirandering around the rules. Int J Biochem Cell Biol 2010;42:1316-29.